

determine whether the survival advantage seen with NALIRIFOX would remain significant in the subset of study participants lacking DDR mutations.

Notably, outcomes in the PASS-01 population were numerically poorer for both arms as compared with other studies. This potentially reflects the effect of removing patients with better prognosis and DDR-mutant tumors and replacing them with patients more likely to have poor-prognosis basal-subtype disease.¹³ In PASS-01, patients with basal subtype had inferior progression-free survival compared with those with classical subtype, as expected (2.7 vs 5.7 months; $P = .03$). New treatment paradigms are needed to address basal disease.

An alternative hypothesis that could explain the divergent results of PASS-01 and GENERATE, as compared with NAPOLI-3, is that we have wrongly assumed that NALIRIFOX is just an equivalent derivative regimen to mFFX. NALIRIFOX led to better outcomes than GnP, but mFFX failed to do so. Perhaps we should recalibrate and consider that NALIRIFOX may be superior to mFFX and endeavor to determine if this is true. A head-to-head study could address whether there is sufficient improvement in benefit to justify the cost difference.

Select randomized trials of first-line therapy in mPDAC are summarized in the Table.^{1,2,7,10,11}

Table. Randomized Trials of First-Line Therapy in mPDAC

Study	Intervention	Comparator	Date	Phase	Pls	ICOG PS	Age (y)	Liver mets (% of pop)	mOS (months; 95% CI; P value)	mPFS (months; 95% CI; P value)	Comments
PRODIGE-4	FOLFIRINOX	Gem	2011	III	342	0.1	65.6	17.6/27.7	11.6/8.4 (p = .001)	6.4/2.2 (p = .001)	Intermediate durability across
FFACT ^a	GnP	Gem	2013	III	485	0.1	66.0	10/16	10.6/7.7 (p = .001)	5.5/2.7 (p = .005)	—
NAPOLI-3 ^b	NALIRIFOX	GnP	2013	III	777	0.1	62.8/60.2	10/10	11.5/8.2 (p = .001)	7.8/5.0 (p = .001)	Intermediate overall survival in 2017 patients data
ACCORD-14 ^c	S-1/ROX	GnP	2014	III	323	0.1	66.0/65.0	8.7/5.9	8.7/7.2 (p = .001)	8.6/6.0 (p = .001)	Interimly superior results
PASS-01 ^c	mFFX	GnP	2014	III	334	0.1	62.0	15/10	8.4/7.7 (p = .001)	4.5/3.2 (p = .001)	Interimly superior results

^aGnP versus S-1/ROX (HR 1.23, 95% CI [0.98, 1.56]) and GnP versus mFFX (HR 1.27, 95% CI [1.01, 1.61]).

^bGnP versus S-1/ROX (HR 0.96, 95% CI [0.77, 1.20]) and GnP versus mFFX (HR 1.06, 95% CI [0.86, 1.32]).

^cData are still maturing.

Abbreviations: C, comparator; DDR, DNA damage repair; Gem, gemcitabine; GnP, gemcitabine/nab-paclitaxel; I, intervention; mets, metastases; mFFX, modified FOLFIRINOX; mOS, median overall survival; mPDAC, metastatic pancreatic ductal adenocarcinoma; mPFS, median progression-free survival; pop, population; PS, performance status; S-1/ROX, S-1/irinotecan/oxaliplatin.

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The Bigger Picture

Choosing the most efficacious first-line regimen for each patient matters. A total of 44% of patients in PASS-01 were unable to receive second-line treatment, underscoring that second chances are frequently unavailable even for patients with good initial performance status. The data collectively emphasize the need for biomarker-driven approaches to choosing first-line therapy. We await new treatment breakthroughs in the field that might finally push mOS for patients with mPDAC beyond 1 year.

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Patents, Royalties, Other Intellectual Property (Inst.): Licensing fee from mouse model

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Author Bios

Dr. Nebojsa Skorupan is a medical oncologist and clinical investigator at the National Cancer Institute Center for Cancer Research, where he focuses on early-phase clinical trials in gastrointestinal cancers.

Dr. Christine Alewine is a medical oncologist and translational researcher at the National Cancer Institute Center for Cancer Research specializing in pancreatic cancer.

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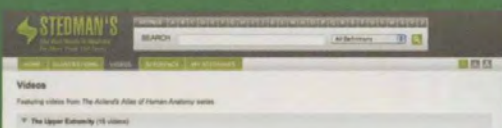
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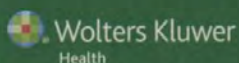
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trau·ma·top·a·thy (traw'mă-top'ă-thē) Any pathologic condition resulting from violence or wounds. [*traumato-* + *G. pathos*, suffering]

trau·ma·top·ne·a (traw'mă-top'nē-ă) Passage of air in and out through a wound of the chest wall. SYN *traumatopnoea*. [*traumato-* + *G. pnoē*, breath]

traumatopnoea [Br.] SYN *traumatopnea*.

trav·el·er's di·ar·rhe·a (trav'el-ērz dī'ă-rē-ă) Of sudden onset, often accompanied by abdominal cramps, vomiting, and fever, this digestive disorder occurs sporadically in travelers usually during the first week of a trip; most commonly caused by strains of enterotoxigenic *Escherichia coli*. SYN *traveller's diarrhoea*.

trav·el·ing wave the·o·ry (trav'el-ing wāv thē'ōr-ē) Generally held theory that a wave travels from the base to the apex of the basilar membrane of the cochlea in response to acoustic stimulation, and that the site of maximal displacement of the basilar membrane depends on the frequency of the stimulating tone, with higher frequencies causing maximal displacement near the base and lower frequencies causing maximal displacement near the apex. SYN *travelling wave theory*.

traveller's diarrhoea [Br.] SYN *traveler's diarrhea*.

travelling wave theory [Br.] SYN *traveling wave theory*.

tra·verse (tră-vērs') COMPUTED TOMOGRAPHY One complete linear movement of the gantry across the object being scanned.

Treach·er Col·lins syn·drome (trēch'ēr kol'inz sin'drōm) Mandibulofacial dysostosis characterized by bone abnormalities of structures formed from the first pharyngeal arch, including downward sloping palpebral fissures, depressed cheek bones, deformed pinnae, a receding chin, and a large, fishlike mouth with dental abnormalities. Atresia of the external acoustic meatus (auditory canal), defects of the external acoustic meatus and ossicles, and cleft palate are most common. SYN *mandibulofacial dysostosis*.

treat (trēt) To manage a disease by medicinal, surgical, or other measures; to care for a patient medically or surgically. [Fr. *traiter*, fr. L. *tracto*, to drag, handle, perform]

treat·ment (trēt'mēnt) Medical or surgical management of a patient. SEE ALSO *therapy*, *therapeutics*.

tre·ble in·crease at low lev·els (trē'bl in'krēs lō lev'ēlz) A hearing aid signal-processing strategy to increase gradually the amplification of high-frequency sounds at low levels.

tre·ha·lose (trē-hă'lōs) A natural disaccha-

ride occurring in some plants and in trehala, a mannalike Asian food consisting of beetle larvae; a food additive and sweetener. [*trēhala*, fr. Turk. *tigala*, + *-ose*]

Tré·lat stools (trā-lah' stūlz) Stools that look as if stippled with eggwhite that are also streaked with blood, as occurs in association with proctitis.

tre·ma·cam·ra (trē'mă-kam'ră) The extracellular part of the cell surface adhesion molecule ICAM-1 involved in rhinovirus attachments to mucosal cells.

Trem·a·to·da (trēm'ă-tō'dă) A class in the phylum Platyhelminthes (the flatworms) consisting of flukes with a leaf-shaped body and two muscular suckers, and an acelomate parenchyma-filled body cavity. Flukes of interest to human or veterinary medicine are members of the order Digenea, with complete life cycles involving embryonic multiplication in a mollusk as their first intermediate host. [*G. trēmatōdēs*, full of holes, fr. *trēma*, a hole, + *eidos*, appearance]

trem·a·tode, trem·a·toid (trēm'ă-tōd, -toyd) 1. Common name for a fluke of the class Trematoda. 2. Relating to a fluke of the class Trematoda.

trem·or (trēm'ōr) 1. Repetitive, often regular, oscillatory movements caused by alternate, or synchronous, but irregular contraction of opposing muscle groups; usually involuntary. 2. Minute ocular movement occurring during fixation on an object. SYN *trepidation* (1). [L. a shaking]

trem·u·lous (trēm'yū-lūs) Characterized by tremor.

trench fe·ver (trench fē'vēr) An uncommon rickettsial fever caused by *Bartonella quintana* and transmitted by the louse *Pediculus humanus*; first appeared as an epidemic during trench warfare in World War I (1914–1918); characterized by the sudden onset of chills and fever, myalgia (especially of the back and legs), headache, and general malaise that typically lasts 5 days but may recur.

trench·foot (trench'fut) SYN *immersion foot*.

trench mouth (trench mowth) SYN *necrotizing ulcerative gingivitis*.

Tren·de·len·burg op·er·a·tion (tren-del'en-burg op-ēr-ă'shūn) A pulmonary embolectomy.

Tren·de·len·burg po·si·tion (tren-del'en-burg pō-zish'ūn) A supine position on the operating table, which is inclined at varying angles so that the pelvis is higher than the head; used during and after operations in the pelvis or for shock.

Tren·de·len·burg sign, Tren·del·en·burg gait (tren'del'en-burg sīn, gāt) A physi-

Appendix STEIN01

Keywords: metastatic pancreatic cancer; locally advanced pancreatic cancer; FOLFIRINOX

Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer

Stacey M Stein^{1,7}, Edward S James^{1,7}, Yanhong Deng², Xiangyu Cong², Jeremy S Kortmansky¹, Jia Li^{1,3}, Carol Staugaard¹, Doddamane Indukala⁴, Ann Marie Boustani⁴, Vatsal Patel⁴, Charles H Cha⁵, Ronald R Salem⁵, Bryan Chang⁶, Howard S Hochster¹ and Jill Lacy^{*,1}

¹Department of Medicine, Section of Medical Oncology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA;

²Yale School of Public Health, 300 George Street, New Haven, CT 06510, USA; ³VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA; ⁴Department of Diagnostic Radiology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA; ⁵Department of Surgery, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA and ⁶Department of Therapeutic Radiology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA

Background: Modifications of FOLFIRINOX are widely used despite the absence of prospective data validating efficacy in metastatic disease (metastatic pancreatic cancer (MPC)) or locally advanced pancreatic cancer (LAPC). We conducted a multicentre phase II study of modified FOLFIRINOX in advanced pancreatic cancer to assess the impact of dose attenuation in MPC and efficacy in LAPC.

Methods: Patients with untreated MPC or LAPC received modified FOLFIRINOX (irinotecan and bolus 5-fluorouracil reduced by 25%). Adverse events (AEs) were compared with full-dose FOLFIRINOX. Response rate (RR), median progression-free survival (PFS) and median overall survival (OS) were determined.

Results: In total, 31 and 44 patients with LAPC and MPC were enrolled, respectively. In MPC, efficacy of modified FOLFIRINOX was comparable with FOLFIRINOX with RR 35.1%, OS 10.2 months (95% CI 7.65–14.32) and PFS 6.1 months (95% CI 5.19–8.31). In LAPC, efficacy was notable with RR 17.2%, resection rate 41.9%, PFS 17.8 months (95% CI 11.0–23.9) and OS 26.6 months (95% CI 16.7, NA). Neutropenia ($P < 0.0001$), vomiting ($P < 0.001$) and fatigue ($P = 0.01$) were significantly decreased. [¹⁸F]-Fluorodeoxyglucose positron emission tomography imaging response did not correlate with PFS or OS.

Conclusions: In this first prospective study of modified FOLFIRINOX in MPC and LAPC, we observed decreased AEs compared with historical control patients. In MPC, the efficacy appears comparable with FOLFIRINOX. In LAPC, PFS and OS were prolonged and support the continued use of FOLFIRINOX in this setting.

Pancreatic ductal carcinoma is a highly lethal malignancy with a five-year survival rate of just 6% in the United States (Rahib *et al*, 2014). The incidence of pancreatic cancer is increasing, and in the absence of meaningful advances in prevention or treatment, it is projected that pancreatic cancer will emerge as the second leading

cause of cancer-related deaths in the United States by 2030 (Rahib *et al*, 2014). While surgical resection may be curative, the cure rate is only 5%. Furthermore, up to 80% of patients have unresectable disease at the time of diagnosis due to distant metastases or vascular involvement (Malik *et al*, 2012). Between 1997 and 2010,

*Correspondence: Professor J Lacy; E-mail: jill.lacy@yale.edu

⁷These two authors contributed equally to this work.

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the median survival of patients with metastatic and locally advanced pancreatic cancer (LAPC) enrolled into multiple prospective clinical trials was consistently less than 7 and 11 months, respectively. During this period, gemcitabine remained the standard of care for advanced pancreatic cancer, as multiple randomised phase III trials were unable to demonstrate improved survival with gemcitabine-based combinations compared with gemcitabine monotherapy. In LAPC, the addition of radiotherapy to gemcitabine-based therapy did not convincingly improve outcomes (Hong, 2012).

In 2010, FOLFIRINOX was introduced into clinical practice and heralded as a significant advance in the treatment of metastatic pancreatic cancer (MPC) based on the results of the PRODIGE 4/ACCORD 11 trial. In this randomised prospective phase III study comparing FOLFIRINOX with gemcitabine in patients with MPC with a good performance status, FOLFIRINOX was associated with an unprecedented overall survival (OS) of 11.1 months compared with 6.8 months with gemcitabine, as well as significant improvements in progression-free survival (PFS) and response rate (RR) (Conroy *et al*, 2011; Gourgou-Bourgade *et al*, 2013). Moreover, the FOLFIRINOX regimen was associated with an improvement in quality-of-life measures compared with single-agent gemcitabine (Gourgou-Bourgade *et al*, 2013). However, the significant toxicities of FOLFIRINOX reported in the PRODIGE 4/ACCORD 11 trial, including neutropenia, fatigue, diarrhoea and vomiting, have tempered enthusiasm for the widespread use of FOLFIRINOX in full doses in community and academic practices. Despite the absence of prospective data regarding efficacy and tolerability, use of *ad hoc* modifications of FOLFIRINOX has been reported retrospectively by several institutions (Marsh *et al*, 2015), and ongoing trials with FOLFIRINOX in combination with novel agents often incorporate modifications that have not been piloted or studied.

Given its efficacy in MPC, FOLFIRINOX is now widely used for LAPC. Published experience with this regimen in the locally advanced setting, however, has been confined to retrospective reviews (Hosein *et al*, 2012; Faris *et al*, 2013; Khushman *et al*, 2015). Although the retrospective data are promising, prospective studies with FOLFIRINOX in LAPC have not yet been reported.

To assess the tolerability of FOLFIRINOX in our practice at Smilow Cancer Hospital, we retrospectively analysed all patients with advanced pancreatic cancer treated with FOLFIRINOX at our institution between June 2010 and July 2011 (Gunturu *et al*, 2013). Our analysis suggested that modest initial dose attenuations of bolus 5-fluorouracil (5FU) and/or irinotecan were associated with excellent tolerability, while efficacy appeared to be comparable with previously reported data (Conroy *et al*, 2011). Based on our institution's experience, we conducted a prospective phase II open label study to evaluate the efficacy and tolerability of FOLFIRINOX using upfront dose reductions of the 5FU bolus (25%) and irinotecan (25%) in patients with advanced pancreatic cancer. Herein, we report the final analysis of the efficacy and toxicity of modified FOLFIRINOX in both LAPC and MPC.

MATERIALS AND METHODS

Design. We conducted a phase II open label single arm multi-institutional study at Yale's Smilow Cancer Hospital (New Haven, CT, USA), the Smilow Cancer Hospital Care Centers (our regional community-based clinics), the VA Connecticut Healthcare System West Haven Campus (West Haven, CT, USA) and Bridgeport Hospital (Bridgeport, CT, USA) from November 2011 through January 2014. The primary objective of this study was to determine the PFS in patients with MPC and LAPC treated with a dose-attenuated modification of FOLFIRINOX. Secondary objectives

were to determine objective response rate according to RECIST, OS, and toxicities and to correlate early changes in glucose metabolism using [^{18} F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning with PFS and OS. The study is registered on the clinical trial web site of the National Cancer Institute (ClinicalTrials.gov identifier: NCT01523457).

Patient selection. Patients with pathologically confirmed, measurable or non-measurable assessable MPC or LAPC (including unresectable and borderline resectable) were eligible for inclusion in this study. Patients were determined to have locally advanced unresectable or borderline resectable disease by the investigators (RRs, CHC) using the imaging criteria established by the National Comprehensive Cancer Network (NCCN) (Callery *et al*, 2009; Tempero *et al*, 2010). No prior therapy of any type for advanced disease was allowed. Prior adjuvant chemotherapy or radiotherapy for resected pancreatic adenocarcinoma was allowed if more than 6 months had elapsed since completion of prior therapy and registration. Additional inclusion criteria were as follows: age 18 or older, ECOG performance status of 0 or 1, no prior oxaliplatin or irinotecan therapy, and adequate haematological, renal and liver function (absolute neutrophil count $\geq 1500/\mu\text{l}$, platelet count $\geq 100\,000/\mu\text{l}$, haemoglobin $\geq 9\text{ g dl}^{-1}$, creatinine $<1.5 \times \text{ULN}$ or estimated GFR $>30\text{ ml min}^{-1}$, bilirubin $<1.5 \times \text{ULN}$, and AST and ALT $<3 \times \text{ULN}$). Patients were excluded if they had grade ≥ 2 peripheral sensory neuropathy, chronic diarrhoea, significant cardiac disease, any serious coexisting medical conditions, or were pregnant or breastfeeding.

All patients provided informed consent. The protocol was approved by institutional review boards at all participating institutions. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Treatment. Patients were treated with modified FOLFIRINOX every 2 weeks as follows: oxaliplatin 85 mg m^{-2} infused over 120 min, immediately followed by folinic acid 400 mg m^{-2} infused over 120 min with the addition, after 30 min, of irinotecan 135 mg m^{-2} infused over 90 min, followed by 5FU 300 mg m^{-2} IV bolus, followed by 2400 mg m^{-2} continuous infusion for 46 h (25% reduction in bolus 5FU and irinotecan doses). All patients received pegylated filgrastim with each cycle on day 3 or 4 in the absence of severe leukocytosis. All patients routinely received palonosetron, aprepitant and dexamethasone for emesis prophylaxis. Protocol-specified treatment modifications or delays for treatment-related adverse events were mandated (Conroy *et al*, 2011). If treatment was held for any treatment-related toxicities for ≥ 3 weeks, protocol therapy was discontinued.

Assessments. Patients were evaluated for toxicities at the start of each cycle with history, physical examination, performance status, complete blood count and metabolic panel. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. computed tomograph (CAT) scans were obtained after every four cycles. Tumour response was determined according to RECIST 1.1 by independent radiology review. [^{18} F]-Fluorodeoxyglucose positron emission tomography scans were obtained at baseline and after two cycles. Metabolic response was categorised into four groups based on % change in summed SUVs at maximum five sites (including primary when possible): significant response, $\geq 50\%$ decrease; mild response, $<50\%$ to $\geq 25\%$ decrease; stable disease $<25\%$ decrease to $\geq 25\%$ increase; progression of disease, $>25\%$ increase.

Duration of treatment and follow-up. The duration of study treatment was 12 cycles in the MPC cohort and eight cycles in the LAPC cohort. Patients who completed the study treatment phase without disease progression in both cohorts were allowed to enter a post-study treatment phase and continue treatment per protocol guidelines until progression at the discretion of the treating

physician. Treatment during the study or post-study phase was discontinued for unacceptable toxicity, progression of disease, treating physician's discretion, patient's unwillingness to continue protocol treatment for personal reasons, or pursuit of alternative therapies in the LAPC cohort (surgical resection or radiotherapy). Oxaliplatin was permanently discontinued for grade 3 sensory neuropathy persisting between treatments, and treatment was continued without oxaliplatin. Surgery was pursued in patients deemed candidates for R0 resection during or after study treatment as determined by the investigators (RRS, CHC). Patients were followed for PFS and OS.

Statistics. Toxicities in both the LAPC and MPC cohorts were compared with the historical control group of patients with metastatic disease treated with standard FOLFIRINOX as reported by Conroy *et al* (2011). For comparison of patient characteristics and response rate with the historical control group, we included only those patients with MPC. One sample median test (one sample Wilcoxon signed-rank test) for continuous variables and Fisher's exact test for categorical variables were used to compare patient characteristics. Fisher's exact test was used to compare the proportion of grade 3 and 4 adverse events. Progression-free survival and OS in the MPC and LAPC cohorts were summarised using Kaplan–Meier curves. Associations of metabolic response by FDG-PET imaging to PFS and OS were analysed by log-rank test and Fisher's exact test. *P*-value of <0.05 was considered statistically significant. Analyses were conducted using SAS 9.3 (Cary, NC, USA).

RESULTS

Patient characteristics and drug delivery. Between November 2011 and March 2014, 75 patients, including 44 with MPC and 31 with LAPC, were enrolled. The demographics and disease characteristics of the 37 evaluable patients in the MPC cohort in this study and the historical control group treated with standard FOLFIRINOX are shown in Table 1. There were no significant differences in age, sex, performance status, CA19-9 level, pancreatic tumor location or presence of biliary stent in our MPC cohort compared with the historical control group (Conroy *et al*, 2011). Significantly more patients in our MPC cohort had peritoneal metastases (37.8% vs 19.4%, *P*=0.010), and there were fewer patients with liver metastases (54.1% vs 87.6%, *P*<0.0001). Median number of cycles in the MPC cohort was 9 (range 1–46). Twenty-one patients in the MPC cohort did not complete 12 cycles due to progression of disease (*n*=16), treatment delay for unresolved grade >1 diarrhoea (*n*=1) or infection (*n*=3) and patient preference (*n*=1). The median relative dose intensities of bolus 5FU, infusional 5FU, bolus plus infusional 5FU combined, irinotecan and oxaliplatin were 88.9%, 90.9%, 89.7%, 88.9% and 88.9%, respectively. The percentage of patients who received full doses of bolus 5FU, infusional 5FU, irinotecan and oxaliplatin for all cycles were 70.3%, 75.7%, 59.5% and 59.5%, respectively.

The demographics and disease characteristics for the LAPC cohort are shown in Table 2. Median number of cycles in the LAPC cohort was 8 (range 4–21). In 13 patients who underwent surgical resection, the median number of preoperative FOLFIRINOX cycles was 8 (range 4–12) and the median number of combined pre- and postoperative cycles was 10 (range 6–13). Treatment was discontinued prior to completing eight cycles in 15 patients, including four who went on to surgery, five who had treatment delays for unresolved infection (*n*=2) or grade >1 toxicities (*n*=3), four with stable disease who opted to receive chemoradiation and two who declined further treatment. No patients in the LAPC cohort discontinued study treatment due to progression of disease. The median relative dose intensities of bolus

Table 1. Patient and disease characteristics of the MPC cohort

Characteristics	MPC cohort (n = 37)	Historical (n = 171)	P-value ^a
Age, median (range)	62 (50–77)	61 (25–76)	0.75 ^b
Male, n (%)	21 (56.8)	106 (62)	0.58 ^c
ECOG PS, n (%)			0.47 ^c
0	17 (46.0)	64 (37.4)	
1	20 (54.0)	106 (62.0)	
Pancreatic tumour location, n/total no. (%) ^d			
Head	17/31 (54.8)	67/165 (40.6)	0.58 ^c
Body	14/31 (45.2)	98/165 (59.4)	
Metastatic sites, n/total no. (%)			
Liver	20/37 (54.1)	149/170 (87.6)	<0.0001 ^c
Peritoneal	14/37 (37.8)	33/170 (19.4)	0.010 ^c
Lung	12/37 (32.4)	33/170 (19.4)	0.059 ^c
Lymph node	15/37 (40.5)	49/170 (28.8)	0.145 ^c
Level of CA19.9, n/total no. (%)			0.85 ^{**}
Normal	4/37 (10.8)	24/164 (14.6)	0.23 ^c
Elevated, < 59 × ULN	18/37 (48.7)	72/164 (43.9)	
Elevated, ≥ 59 × ULN	15/37 (40.5)	68/164 (41.5)	
Biliary stent, n/total no. (%)			
Yes	9/37 (24.3)	27 (15.8)	0.23 ^c
No	28/37 (75.7)	144 (84.2)	

^aComparison between evaluable patients in the MPC cohort and the historical control group treated with standard FOLFIRINOX as reported by Conroy *et al*.
^bP-value from one sample median test (signed-rank test).
^cP-value is based on Fisher exact test for count.
^dSix patients had prior pancreatic resection.

Table 2. Patient and disease characteristics of the LAPC cohort

Characteristics	LAPC cohort (n = 31)
Age, median (range)	63 (46–79)
Male, n (%)	20 (64.5)
ECOG PS, n (%)	
0	15 (48)
1	16 (52)
Pancreatic tumour location, n (%)	
Head	27 (87)
Body	4 (13)
Unresectable vs Borderline resectable, n (%)	
Unresectable	20 (64.5)
Borderline	11 (35.5)
Level of CA19.9, n (%)	
Normal	3 (9.6)
Elevated, <59 × ULN	24 (77.4)
Elevated, ≥59 × ULN	4 (12.9)
Biliary stent, n (%)	
Yes	17 (54.8)
No	14 (45.2)

5FU, infusional 5FU, bolus plus infusional 5FU combined, irinotecan and oxaliplatin were 88.9%, 90.4%, 88.9%, 88.9% and 88.9%, respectively, in the LAPC cohort. The percentage of patients who received full doses of bolus 5FU, infusional 5FU, irinotecan and oxaliplatin for all cycles were 74.2%, 83.9%, 67.7% and 67.7%, respectively.

Efficacy in the MPC cohort. Seven of 44 patients with MPC were excluded from efficacy analysis due to voluntary withdrawal from

the study for reasons unrelated to disease progression or toxicity prior to completing four cycles to reach the first efficacy assessment (one patient was not treated, and three and four patients received one and two cycles, respectively). At the time of this analysis, 29 patients had expired and eight patients were alive. Three patients remained on treatment. The objective RR by independent radiology review in evaluable patients was 35.1% and was not significantly different from the response rate in evaluable patients in the FOLFIRINOX-treated historical control group (36.3%, $P=0.82$) (Table 3). Similarly, the RR of 30.2% for all treated patients (including invaluable patients) did not differ from the RR in the intent-to-treat FOLFIRINOX-treated historical control group (30.1%, $P=0.93$). The disease control rate was not significantly different from the historical control group (86.5% v 82.2%).

The PFS rates at 6, 12 and 18 months were 54%, 14% and 9%, respectively (Table 4 and Figure 1). The median PFS was 6.1 months (95% CI 5.19–8.31) (Table 4 and Figure 1). The OS rates at 6, 12 and 18 months were 81%, 38% and 22%, respectively, in the MPC cohort (Table 4). The median OS was 10.2 months (95% CI 7.65–14.32). Three patients (8%) have survived for more than 3 years (Table 4, Figure 1).

Efficacy in the LAPC cohort. Two of 31 patients with LAPC were excluded from efficacy analysis because they did not complete four cycles to reach the first efficacy assessment (one due to cholecystitis with abscess and one due to cerebrovascular accident). Nineteen patients remained alive and 12 patients had not had disease progression at the time of the analysis. The response rate was 17.2% with 100% having disease control (Table 3). The PFS rates at 6, 12 and 18 months were 97%, 69% and 62%, respectively (Table 4). The median PFS was 17.8 months (95% CI 11.0–23.9) (Table 4 and Figure 1). The OS rates at 6, 12 and 18 months were 100%, 86% and 62%, respectively (Table 4). The median OS was 26.6 months (95% CI 16.7, NA) (Table 4 and Figure 1).

In patients with stable or responding disease, 11 received chemoradiotherapy, 7 underwent surgery and 6 received chemoradiotherapy followed by surgery. Thirteen patients in the LAPC cohort (41.9%) had surgical resection; seven patients initially had borderline resectable and six had unresectable disease. All patients who underwent surgery had R0 resections. The post-treatment

pathologic stages (and preoperative treatment) were as follows: ypT0N0 stage 0, one patient (chemotherapy); ypT1N0 stage I, two patients (chemotherapy, $n=1$; chemotherapy followed by chemoradiotherapy, $n=1$); ypT3N0, six patients (chemotherapy, $n=3$; chemotherapy followed by chemoradiotherapy, $n=3$); and ypT3N1 stage IIB, four patients (chemotherapy, $n=2$; chemotherapy followed by chemoradiotherapy, $n=2$). At the time of the analysis, 10 of 13 patients who underwent surgery were alive, and 6 had no evidence of recurrent disease.

Metabolic response by FDG-PET imaging. We performed an exploratory analysis of the association between early metabolic response by FDG-PET imaging and PFS and OS. In the metastatic cohort, eight patients were excluded from this analysis due to negative baseline FGD-PET scan or failure to obtain the follow-up scan. Among the 29 patients who were evaluated with baseline and follow-up FDG PET scans after two cycles, 24 patients (83%) had a metabolic response, including 14 patients (48%) with significant response and 10 patients (34%) with mild response. Two patients had stable disease and three patients had progression of disease. In the LAPC cohort, six patients were not evaluable. Of the 23 patients who were evaluable, 12 patients (52%) had a metabolic response, including eight major responses (35%) and four (17%) minor responses. Ten patients had stable disease and one patient had progression of disease.

There was no statistical association between metabolic response (combined significant and mild response) and either PFS or OS for either cohort (for metastatic cohort: P -values of 0.55 and 0.27 based on Fisher's exact test for count, 0.42 and 0.42 based on log-rank test; for locally advanced cohort: P -values of 0.37 and 0.68 based on Fisher's exact test for count, 0.44 and 0.43 based on log-rank test). Similarly, there was no statistical association between significant metabolic response and PFS or OS for either cohort (for metastatic cohort: P -values of 0.60 and 0.65 based on Fisher's exact test for count, 0.88 and 0.69 based on log-rank test; for locally advanced cohort: P -values of 0.18 and 0.22 by Fisher's exact test for count, 0.19 and 0.09 based on log-rank test).

Second-line chemotherapy. In the MPC cohort, three patients remained on study treatment, 21 patients received second-line chemotherapy with gemcitabine ($n=5$) or gemcitabine-based regimen ($n=16$) and 13 patients did not receive second-line therapy. In the LAPC cohort, 16 of 18 patients who had progression of disease received second-line chemotherapy with gemcitabine-based chemotherapy ($n=11$) or re-introduction of FOLFOX ($n=1$), FOLFIRI ($n=1$) or FOLFIRINOX ($n=1$); two patients did not receive second-line chemotherapy.

Adverse events. One of 75 patients did not receive treatment and was excluded from toxicity analysis. Treatment-related grade 3 and 4 adverse events observed in our study and in the historical control group treated with standard FOLFIRINOX are summarised in Table 5. As we did not observe differences in the spectrum or incidence of toxicities between the MPC and LAPC patients, we combined these cohorts for a sample size of 74 patients. There were no treatment-related deaths or non-haematologic grade 4 toxicities attributed to modified FOLFIRINOX. Grade 3 and 4 treatment-related adverse events were as follows: diarrhoea, 16.2% (grade 3

Table 3. Response in LAPC and MPC cohorts				
	LAPC cohort (n = 29)	MPC cohort (n = 37)	Historical (n = 146)	P-value ^a
Response, n (%)				
CR	0 (0)	0 (0)	1 (0.7)	
PR	5 (17.2)	13 (35.1)	53 (36.3)	
SD	24 (82.7)	19 (51.5)	66 (45.2)	
PD	0 (0)	5 (13.5)	26 (17.8)	
CR + PR	5 (17.2)	13 (35.1)	54 (37.0)	0.87 ^b
CR + PR + SD	29 (100)	32 (86.5)	120 (82.2)	0.67 ^b
^a Comparison between evaluable patients in the MPC cohort and historical control group treated with standard FOLFIRINOX as reported by Conroy <i>et al</i> .				
^b P-value is based on Fisher exact test for count.				

Table 4. Progression-free and overall survival in MPC and LAPC cohorts								
	Overall survival				Progression-free survival			
	Median OS	6 mo	12 mo	18 mo	Median PFS	6 mo	12 mo	18 mo
Metastatic (37 pts)	10.2 mo	81%	38%	22%	6.1 mo	54%	14%	9%
LAPC (29 pts)	26.6 mo	100%	86%	62%	17.8 mo	97%	69%	62%

Abbreviations: mo, months; Pts, patients.

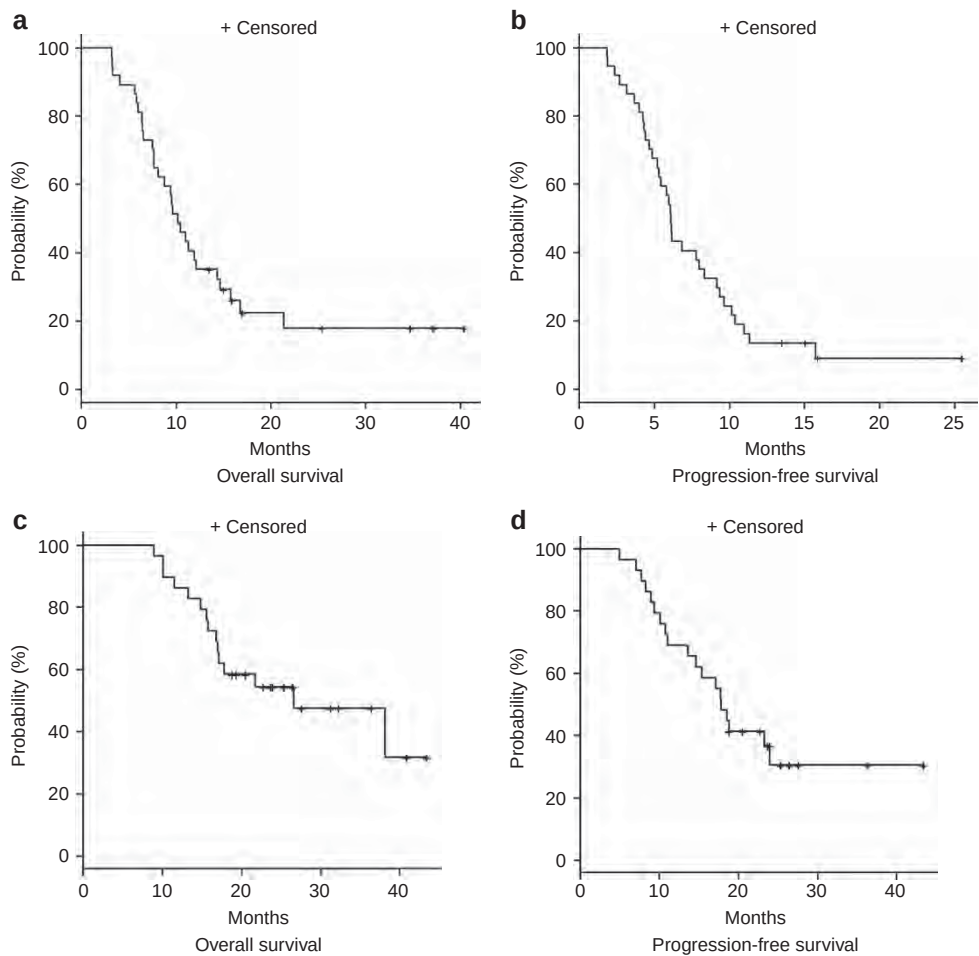


Figure 1. The Kaplan–Meier curve for overall survival and progression-free survival in the metastatic cohort (A, B) and in the locally advanced cohort (C, D).

Table 5. Grade 3/4 adverse events in MPC and LAPC cohorts and historical control			
Adverse event	MPC & LAPC (N = 74) no. of pts/total no. (%)	Historical (N = 171) no. of pts/total no. (%)	P-value ^a
Haematologic			
Neutropenia	9/74 (12.2)	75/164 (45.7)	<0.0001
Thrombocytopenia	7/74 (9.5)	15/165 (9.1)	0.83
Anaemia	4/74 (5.4)	13/166 (7.8)	0.66
Febrile neutropenia	3/74 (4.1)	9/166 (5.4)	0.79
Nonhaematologic			
Diarrhoea	12/74 (16.2)	21/165 (12.7)	0.38
Fatigue	9/74 (12.2)	39/165 (23.6)	0.02
Alanine aminotransferase (ALT) increased	3/74 (4.1)	12/165 (7.3)	0.37
Thromboembolic event	3/74 (4.1)	11/166 (6.6)	0.48
Peripheral sensory neuropathy	2/74 (2.7)	15/166 (9.0)	0.06
Vomiting	2/74 (2.7)	24/166 (14.5)	0.001
^a P-value is based on Fisher's exact test.			
^a Comparison between MPC and LAPC cohorts and the historical control group treated with standard FOLFIRINOX as reported by Conroy <i>et al.</i>			

only); neutropenia and fatigue, 12.2%; thrombocytopenia, 9.5%; anaemia, 5.4%; ALT elevated, thromboembolism and febrile neutropenia, 4.1%; vomiting and peripheral neuropathy, 2.7%.

The incidence of grade 3 or 4 neutropenia (12.2% *vs* 45.7%, $P < 0.0001$), vomiting (2.7% *vs* 14.5%, $P = 0.001$) and fatigue (12.2% *vs* 23.6%, $P = 0.02$) was significantly decreased in our study compared with the historical control group treated with standard FOLFIRINOX (Conroy *et al.*, 2011). There was a nonsignificant trend towards a lower incidence of peripheral sensory neuropathy (2.7% *vs* 9.0%, $P = 0.06$).

DISCUSSION

FOLFIRINOX has been heralded as a major advance in the treatment of advanced pancreatic cancer and is now widely used in patients with both metastatic and LAPC. However, the toxicities associated with standard FOLFIRINOX have prompted widespread use of *ad hoc* modifications of this regimen in academic centres and community practices. Although single institution retrospective experiences suggest that modest dose attenuations improve tolerability while maintaining efficacy, prospective data validating comparable efficacy and diminished toxicity have not previously been reported. Moreover, there are no prospective data regarding the efficacy of FOLFIRINOX in patients with non-metastatic locally advanced disease.

We report the results of our prospective multiinstitutional phase II open label study to evaluate the efficacy and tolerability of modified FOLFIRINOX using upfront dose reductions of the 5FU bolus (25%) and irinotecan (25%) in patients with advanced pancreatic cancer. The rationale for these specific dose reductions was based on a retrospective review of all patients treated with

FOLFIRINOX at our institution between June 2010 and July 2011 (Gunturu *et al*, 2013). In our retrospective analysis, the majority of patients received attenuated doses of bolus 5FU and irinotecan with the first and subsequent cycles, and the median relative dose intensity of bolus 5FU and irinotecan was lower than those reported in the FOLFIRINOX-treated group reported by Conroy *et al* (2011). Our findings suggested that upfront dose attenuations of bolus 5FU and irinotecan improved tolerability without compromising efficacy and provided the rationale for the dose attenuations utilised in this trial (Gunturu *et al*, 2013).

We have now shown in this prospective study that the efficacy of modified FOLFIRINOX with upfront dose attenuations of bolus 5FU and irinotecan is comparable with standard FOLFIRINOX in patients with MPC. In addition, we have demonstrated a notable PFS, OS and resection rate in patients with LAPC. Moreover, the patient characteristics of our MPC cohort were similar to the patient characteristics treated with standard FOLFIRINOX. Of note, the incidence of peritoneal carcinomatosis, which confers a particularly poor prognosis in MPC (Takahara *et al*, 2015), was significantly higher in our MPC patients compared with the historically control group (37% vs 19.4%, $P = 0.010$).

Gemcitabine with nab-paclitaxel is emerging as an alternative to FOLFIRINOX in the initial treatment of MPC based on its superior efficacy compared with gemcitabine (Von Hoff *et al*, 2013; Goldstein *et al*, 2015). The recent updated analysis of the phase III MPACT trial reported an OS of 8.7 months with 4% of patients surviving long term (more than 3 years) (Goldstein *et al*, 2015). Thus, the OS of 10.2 months in our patient population treated with modified FOLFIRINOX, with 8% of patients surviving more than 3 years, is at least comparable with gemcitabine with nab-paclitaxel.

In this first prospective study of FOLFIRINOX in LAPC, the efficacy of this regimen is noteworthy. Both categories of locally advanced disease, unresectable and borderline, were included in this study, as the approach to their management in recent years has converged with widespread use of upfront chemotherapy. Although FOLFIRINOX is clearly superior to gemcitabine in MPC, there are limited prospective data regarding efficacy and tolerability of FOLFIRINOX in LAPC. In the initial phase II trial of FOLFIRINOX in advanced pancreatic cancer only 11 patients had locally advanced disease with RR 7% and median OS 15.7 months (Conroy *et al*, 2005). The PFS and OS of 17.8 and 26.6 months, respectively, in our study surpass previously published reports from randomised trials with chemotherapy or chemoradiotherapy. For example, in the GEMCORP/GISCAD trial comparing gemcitabine with gemcitabine/oxaliplatin, OS in the LAPC cohort was just 10.3 months in both arms (Louvvet *et al*, 2005). In the ECOG trial comparing conventional gemcitabine, gemcitabine FDR and gemcitabine/oxaliplatin in advanced pancreatic cancer, the PFS and OS were 5.4 and 9.2 months, respectively, in the LAPC cohort, with no difference between any of the regimens (Poplin *et al*, 2009). In the LAP-07 study, which examined the role of radiation following induction gemcitabine with or without erlotinib in LAPC, OS was 11.9 and 13.6 months, respectively (Hammel *et al*, 2013). Remarkably, the PFS and OS in LAPC in our study trial exceeded that reported for patients with resectable pancreatic cancer undergoing adjuvant gemcitabine (OS 22.8 months) (Oettle *et al*, 2013) or 5FU (23.6 months) (Neoptolemos *et al*, 2010). Although our study was not designed to compare the outcomes of patients with borderline resectable vs locally advanced unresectable disease, we observed longer survival in the borderline cohort (82% vs 50% at 18 months).

Thirteen patients with LAPC (41.9%) on our study went on to subsequent R0 resection; six of these patients had radiation after modified FOLFIRINOX and before surgery. The outcome of patients who underwent surgery was noteworthy. Median OS has not been reached (median follow-up 24 months). Ten patients were alive at the time of the analysis, and 82% were alive at 18 months. Given the small number of patients who received FOLFIRINOX only vs

FOLFIRINOX and radiotherapy prior to surgery, we are unable to draw any conclusions about the impact of preoperative radiation after modified FOLFIRINOX. In the LAP-07 study, radiation after induction gemcitabine was not superior to continuing gemcitabine in the patients with LAPC who had not progressed on gemcitabine (OS 15.3 and 16.5 months, respectively) (Hammel *et al*, 2013). Studies examining the role of radiation in LAPC patients who have received a FOLFIRINOX regimen have not yet been published, and the benefit of radiation in this setting remains unknown.

Modified FOLFIRINOX was well tolerated in both cohorts. We observed no treatment-related deaths or non-haematologic grade 4 toxicities. Compared with standard FOLFIRINOX, we observed a significantly lower incidence of grade 3 and 4 neutropenia, vomiting and fatigue with modified FOLFIRINOX. Although we observed no incidents of grade 4 diarrhoea, we did not observe a lower overall incidence of grade 3 and 4 diarrhoea compared with standard FOLFIRINOX as reported by Conroy *et al* (2011). The improved tolerability of modified FOLFIRINOX may be related to the dose modifications, routine use of growth factor support and the routine inclusion of aprepitant in the antiemetic regimen.

In this study, we explored the utility of early metabolic response by FGD-PET imaging in predicting outcome as early metabolic response has been shown to correlate with survival in other solid tumours (Ott *et al*, 2006; Day *et al*, 2011). The response rate by FDG-PET imaging was high in the MPC cohort (83%), and there was no correlation between metabolic response (either $\geq 50\%$ or $\geq 25\%$ decrease in SUV) and PFS or OS in this cohort. Similarly, although the response rate by FGD-PET imaging was lower in the LAPC cohort (52%), we were unable to demonstrate a correlation between metabolic response and either PFS or OS in patients with locally advanced disease. Given the small sample size of our study, further studies of the utility of serial metabolic imaging in pancreatic cancer may be warranted. However, our results suggest that the use of FGD-PET imaging for response assessment in pancreatic cancer is not justified in routine clinical practice.

We acknowledge that observations from single-arm phase II results should be considered with caution, given the limitations of sample size, possible enrollment bias and patient selection. In addition, the composition of the LAPC cohort was heterogeneous with inclusion of patients with borderline resectable disease. Also, some patients subsequently received radiation, and this study was not designed to assess the impact of radiation in this patient population. Our findings are reassuring, albeit not definitive, that the modifications of FOLFIRINOX used in this study do not appear to impact efficacy in MPC and are associated with a favourable outcome in LAPC.

CONCLUSIONS

In this first prospective study to evaluate the tolerability and efficacy of a dose-attenuated FOLFIRINOX in MPC and LAPC, the RR in MPC is not significantly different from the RR reported by Conroy *et al* using standard FOLFIRINOX. Progression-free survival and OS were also comparable. When given with pegylated filgrastim and aprepitant, modified FOLFIRINOX is associated with significantly less neutropenia, vomiting and fatigue compared with standard FOLFIRINOX. The results of our study suggest that the modifications of FOLFIRINOX used in this prospective trial do not negatively impact efficacy in patients with MPC while improving tolerability. Thus, incorporation of these modifications, with routine use of pegylated filgrastim, can be considered an option for patients similar to those treated at our institution, when balancing toxicity and efficacy.

In this first prospective trial of a FOLFIRINOX regimen in LAPC, the efficacy of this regimen is noteworthy and supports the continued use of this regimen in locally advanced disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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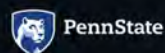
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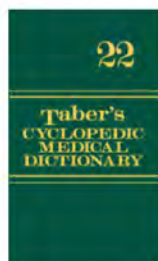
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Revised Trauma Score (RTS)

Glasgow Coma Scale (GCS)	Systolic Blood Pressure (SBP)	Respiratory Rate (RR)	Coded Value
13–15	>89	10–29	4
9–12	76–89	>29	3
6–8	50–75	6–9	2
4–5	1–49	1–5	1
3	0	0	0
RTS = 0.9368 GCS _c + 0.7326 SBP _c + 0.2908 RR _c coded values × revised score coefficient			

SOURCE: From Champion, HR, et al: J Trauma 29:623–629, 1989.

traumat-, wound] Prefixes meaning *trauma*, wound.

traumatology (traw-mă-töl'ō-jē) [Gr. *trauma*, wound, + *logos*, word, reason] The branch of surgery dealing with wounds and their care.

traumatopathy (traw'mă-töp'ă-thē) [" + *pathos*, disease, suffering] A pathological state caused by trauma.

traumatopnea (traw'mă-töp-nē'ă) [" + *pnoia*, breath] The passage of air in and out of a wound in the chest wall.

travel [ME. *travaillen*, to travail, to journey] 1. To move from place to place, e.g., from one country to another. 2. The act of moving among different places or countries. Travel to some locations presents health risks, such as deep venous thrombosis, diarrhea, geographically specific infections (e.g., malaria), injury, insomnia, rashes, colds, and influenza.

tray (trā) A flat surface with raised edges.

impression t. In dentistry, a receptacle with raised edges for carrying impression material and supporting it in contact with the surfaces to be recorded until the impression material sets or hardens.

trazodone (trăz'ō-dōn) A triazolopyridine and antidepressant. It is administered orally to treat major depression and may be used as an adjunct to psychotherapy. SYN: *Desyrel*.

TRCHII *tanned red cell hemagglutination immunoassay*.

Treacher Collins syndrome (trē'chēr-kōl'inz) [Edward Treacher Collins, Brit. ophthalmologist, 1862–1919] Mandibulofacial dysostosis.

treadmill (trēd'mil) A conveyor belt for walking or running in place; the speed of movement and angle of inclination can be varied during tests of cardiopulmonary health and conditioning. SEE: *exercise tolerance test*.

treatment (trēt'mēnt) [ME. *treten*, to handle] 1. Medical, surgical, dental, or psychiatric management of a patient. 2. Any specific procedure used for the cure or the amelioration of a disease or pathological condition. SEE: *therapy*. Particular treatments are listed under the first word. SEE: e.g., *conservative*

treatment; *legally mandated treatment*; *radiation treatment*.

treatment burden The deterioration in a patient's health that may be caused by exposure to medications, radiation therapy, surgery, or other forms of therapy.

treatment card In dentistry, a specially formatted card or file summarizing a patient's dental care. SEE: *dental chart*.

tree (trē) A structure that resembles a tree.

bronchial t. The right or left primary bronchus with its branches and their terminal arborizations.

decision t. A graphic analysis of the decisions or choices available to a health care manager or provider. The graph includes estimates of the probabilities of all the events that may result from each selection or choice. SEE: *decision analysis*.

tracheobronchial t. The trachea, bronchi, and their branches.

tree nut Any of several nuts, e.g., almonds, cashews, filberts or pecans, that grow on shrubs or trees. They are among the most common sources of food allergy.

Treg (treg) A regulatory T cell.

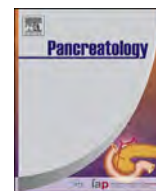
trehalase (trē-hā'lās) The enzyme that cleaves the bond between glucose molecules in the disaccharide, trehalose.

trehalose (trē-hā'lōs) A disaccharide containing two linked glucose molecules. It is less sweet than sucrose, but can be used as a source of glucose. SYN: *mycose*.

Trematoda (trēm'ă-tō-dă) [Gr. *trematodes*, pierced] A class of flatworms, commonly called flukes, and belonging to the phylum Platyhelminthes. It includes two orders: Monogenea, which are external or semixternal parasites having direct development with no asexual multiplication, and Digenea, internal parasites with asexual generation in their life cycle. The Digenea usually require two or more hosts, the hosts alternating. SEE: *fluke*.

trematode (trēm'ă-tōd) A parasitic flatworm belonging to the class Trematoda. SEE: *cercaria*; *fluke*. **trematodiasis** (trēm-tō-dī-ă-sis) Infection with a trematode.

Appendix TAKEDA01



Improved prognosis of pancreatic cancer patients with peritoneal metastasis

Tsuyoshi Takeda^a, Takashi Sasaki^{a,*}, Takafumi Mie^a, Takaaki Furukawa^a, Yuto Yamada^a, Akiyoshi Kasuga^a, Masato Matsuyama^a, Masato Ozaka^a, Naoki Sasahira^a

^a Department of Hepato-Biliary-Pancreatic Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

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ABSTRACT

Background: Peritoneal metastasis is one of the most important poor prognostic factors in advanced pancreatic cancer (PC). Whether the prognosis of PC with peritoneal metastasis has improved with the advent of gemcitabine plus nab-paclitaxel (GnP) and modified FOLFIRINOX (mFFX) is uncertain. The aim of this study was to evaluate the improvements in treatment outcomes of PC with peritoneal metastasis. **Methods:** We retrospectively investigated consecutive PC patients with peritoneal metastasis treated with chemotherapy at our institution between 2010 and 2019. We compared the clinical characteristics and survival outcomes according to the period of diagnosis (group A, 2010–2014; group B, 2015–2019) and chemotherapy regimen. We also examined the prognostic factors for overall survival (OS).

Results: Among 180 patients included (GnP 88; mFFX 14; other regimens 78), distant metastasis was confined to the peritoneum in 89 patients. Although group B had a worse performance status compared to group A, median OS was significantly longer in group B. GnP and mFFX showed a significantly higher objective response rate and disease control rate in addition to longer progression free survival and OS compared to other regimens. The administration of GnP or mFFX, performance status, and neutrophil to lymphocyte ratio ≥ 5 were identified as independent prognostic factors for OS. Furthermore, the amount of ascites and extent of peritoneal metastasis were significantly associated with OS in patients with distant metastasis confined to the peritoneum.

Conclusions: The prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of GnP and mFFX.

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in Japan with a dismal prognosis [1]. Surgical resection with negative margins is the only chance for long-term survival, however the majority of patients are diagnosed at an advanced stage [2]. Peritoneal metastasis, defined as the presence of cancer cells that have spread or metastasized to the peritoneal cavity, has been considered as one of the most important poor

prognostic factors in metastatic PC [3]. Peritoneal metastasis often leads to severe complications such as intestinal obstruction, massive ascites, and malnutrition, resulting in reduced performance status (PS) and impaired quality of life [4]. Consequently, patients with peritoneal metastasis are usually underrepresented in most clinical trials and the efficacy of chemotherapy in these patients has not been well established. Furthermore, it has been reported that the prognosis of PC patients with peritoneal metastasis has not improved over time despite the advances in chemotherapy for metastatic PC [4,5].

Gemcitabine monotherapy has long been the standard first-line chemotherapy for metastatic PC [6]. Many randomized clinical trials have been conducted to develop a more effective regimen than gemcitabine alone. Gemcitabine plus erlotinib demonstrated a significant improvement in prognosis compared to gemcitabine alone, however the median survival difference between the two regimens was only two weeks [7]. Recently, FOLFIRINOX (FFX) and

* Corresponding author. Department of Hepato-Biliary-Pancreatic Medicine, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31, Ariake, Koto, Tokyo, 135-8550, Japan.

E-mail addresses: tsuyoshi.takeda@jfcrr.or.jp (T. Takeda), sasakit-tyk@umin.ac.jp (T. Sasaki), takafumi.mie@jfcrr.or.jp (T. Mie), takaaki.furukawa@jfcrr.or.jp (T. Furukawa), yuto.yamada@jfcrr.or.jp (Y. Yamada), akiyoshi.kasuga@jfcrr.or.jp (A. Kasuga), masato.matsuyama@jfcrr.or.jp (M. Matsuyama), masato.ozaka@jfcrr.or.jp (M. Ozaka), naoki.sasahira@jfcrr.or.jp (N. Sasahira).

Abbreviations

PC	pancreatic cancer
PS	performance status
mFFX	modified FOLFIRINOX
GnP	gemcitabine plus nab-paclitaxel
CT	computed tomography
PET	positron emission tomography
ECOG	Eastern Cooperative Oncology Group
BMI	body mass index
CEA	carcinoembryonic antigen
CA19-9	carbohydrate antigen 19-9
mGPS	modified Glasgow prognostic score
CRP	C-reactive protein
NLR	neutrophil to lymphocyte ratio
OS	overall survival
PFS	progression free survival
HR	hazard ratio
CI	confidence interval

gemcitabine plus nab-paclitaxel (GnP) have been shown to significantly improve the prognosis of metastatic PC patients with a good PS and are considered as first-line treatment [8,9]. However, it still remains uncertain whether these two regimens have similar

beneficial effects on PC patients presenting with peritoneal metastasis.

Therefore, we conducted this retrospective study to evaluate the improvements in treatment outcomes and examine the prognostic factors for advanced PC patients with peritoneal metastasis.

Patients and methods*Patients*

Consecutive patients diagnosed with metastatic or recurrent PC who received first-line chemotherapy at our institution between January 2010 and December 2019 were identified from our prospectively maintained database. Recurrent PC patients who had received neoadjuvant therapy were excluded from this study because we intended to evaluate the efficacy of first-line chemotherapy in chemotherapy-naïve PC patients. Each patient underwent a computed tomography (CT) for tumor staging. Magnetic resonance imaging and/or positron emission tomography (PET)/CT were also performed at the discretion of the physician. Although the diagnosis of peritoneal metastasis was confirmed by the presence of peritoneal nodules detected on CT or PET/CT in most of the patients, peritoneal metastasis was also confirmed by laparoscopy or laparotomy in cases with negative findings on CT in some of the patients. Since modified FFX (mFFX) and GnP became commercially available in December 2013 and December 2014, respectively, in Japan, we divided the study population into two groups: group A,

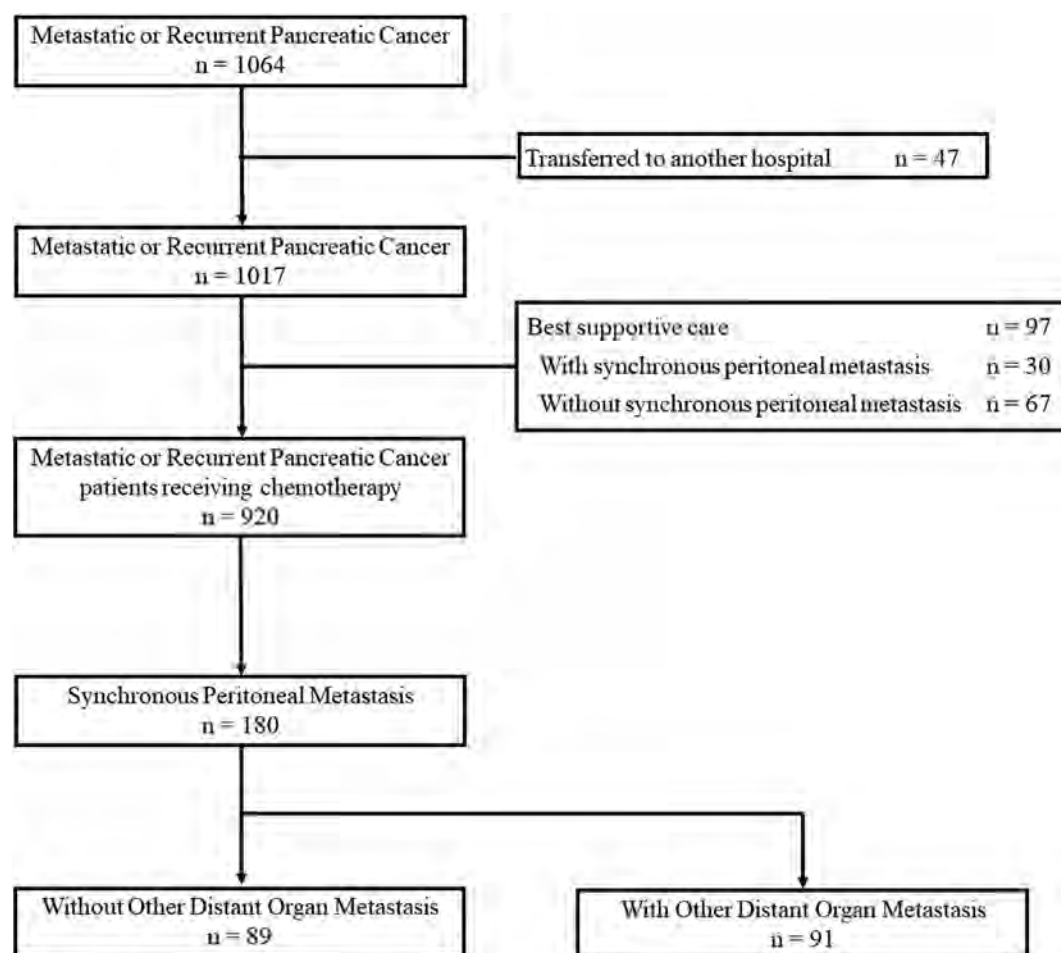


Fig. 1. Patients flowchart.

Table 1
Patient characteristics according to the period of diagnosis.

	n = 180	Period of diagnosis		P value
		Group A (n = 60)	Group B (n = 120)	
Age, years	67 (37–88)	68 (37–80)	67 (39–88)	0.490
Sex, Male	88 (49%)	32 (53%)	56 (47%)	0.432
BMI, kg/m ²	20.6 (15.0–30.5)	20.7 (17.6–28.5)	20.6 (15.0–30.5)	0.419
Disease status				1.000
Metastatic	152 (84%)	51 (85%)	101 (84%)	
Recurrent	28 (16%)	9 (15%)	19 (16%)	
Tumor location [n = 152]				0.251
Head	25 (16%)	11 (22%)	14 (14%)	
Body or tail	127 (84%)	40 (78%)	87 (86%)	
ECOG PS				0.021
0	119 (66%)	47 (78%)	72 (60%)	
1	56 (31%)	11 (18%)	45 (38%)	
2	5 (3%)	2 (3%)	3 (3%)	
Amount of ascites ^a				0.262
None or Small	131 (73%)	41 (68%)	90 (75%)	
Moderate	39 (22%)	17 (28%)	22 (18%)	
Massive	10 (6%)	2 (3%)	8 (7%)	
Extent of peritoneal metastasis ^b				0.528
P1	91 (51%)	28 (47%)	63 (53%)	
P2/P3	89 (49%)	32 (53%)	57 (48%)	
Metastatic sites other than the peritoneum				
Liver	68 (38%)	22 (37%)	46 (38%)	0.872
Lung	15 (8%)	3 (5%)	12 (10%)	0.392
Distant lymph node	37 (21%)	15 (25%)	22 (18%)	0.330
mGPS				0.548
0	116 (64%)	41 (68%)	75 (63%)	
1	32 (18%)	8 (13%)	24 (20%)	
2	32 (18%)	11 (18%)	21 (18%)	
NLR [n = 176]	3.2 (1.0–46.5)	3.0 (1.1–23.0)	3.2 (1.0–46.5)	0.601
CEA, ng/mL	6.4 (0.7–16984.4)	7.7 (0.8–1306.1)	5.8 (0.7–16984.4)	0.909
CA19-9, IU/mL	1411 (2–50000)	1013 (2–50000)	2122 (2–50000)	0.801
Regimen of chemotherapy				< 0.001
GnP	88 (49%)	0	88 (73%)	
mFFX	14 (8%)	2 (3%)	12 (10%)	
Gemcitabine plus S-1	3 (2%)	3 (5%)	0	
Gemcitabine plus erlotinib	1 (1%)	1 (2%)	0	
Gemcitabine monotherapy	63 (35%)	44 (73%)	19 (16%)	
S-1 monotherapy	5 (3%)	4 (7%)	1 (1%)	
Investigational new drug	6 (3%)	6 (10%)	0	

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions).

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

^a Evaluated by computed tomography; none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity.

^b Evaluated by computed tomography or positron emission tomography: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; P3, numerous metastatic nodules throughout the peritoneal cavity.

patients who started chemotherapy between 2010 and 2014; and group B, patients who started chemotherapy between 2015 and 2019. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institution (Institutional Review Board number: 2020-1279). All patients provided informed consent for chemotherapy.

Treatment

Before mFFX and GnP became commercially available in our institution, most of the patients received gemcitabine monotherapy (gemcitabine, 1000 mg/m², on days 1, 8, and 15, every 4 weeks) or S-1 monotherapy (S-1, 40 mg, 50 mg, 60 mg on the basis of body surface area, orally administered twice daily for 4 weeks followed by 2 weeks rest), while the other patients received gemcitabine plus erlotinib (n = 1), gemcitabine plus S-1 (n = 3), or investigational new drugs (n = 6).

After mFFX and GnP became commercially available in our institution, we basically administered either of the following

regimens considering the patients' age, Eastern Cooperative Oncology Group (ECOG) PS and comorbidities: (1) GnP (gemcitabine, 1000 mg/m², nab-paclitaxel, 125 mg/m², on days 1, 8, and 15 every 4 weeks), (2) mFFX (oxaliplatin 85 mg/m², leucovorin, 400 mg/m², irinotecan, 150 mg/m², infusional 5-FU, 2400 mg/m², every 2 weeks), (3) gemcitabine monotherapy or (4) S-1 monotherapy. Treatment delay and dose reduction were performed based on toxicity and physician/patient discretion, and treatment was continued until disease progression, intolerable toxicity, or patient refusal. Radiologic tumor response was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. Treatment-related adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Data collections and outcome measurements

We retrieved data on pretreatment clinical characteristics including age, sex, body mass index (BMI), primary tumor location,

Table 2
Patient characteristics and treatment efficacy according to the chemotherapy regimen.

	GnP or mFFX (n = 102)	Other regimens (n = 78)	P value
Age, years	66 (39–83)	70 (37–88)	< 0.001
Sex, Male	47 (46%)	41 (53%)	0.452
BMI, kg/m ²	21.0 (15.0–30.5)	20.6 (15.1–28.5)	0.573
Disease status			0.061
Metastatic	91 (89%)	61 (78%)	
Recurrent	11 (11%)	17 (22%)	
Tumor location [n = 152]			0.383
Head	13 (14%)	12 (20%)	
Body or tail	78 (86%)	49 (80%)	
ECOG PS			0.108
0	61 (60%)	58 (74%)	
1	38 (37%)	18 (23%)	
2	3 (3%)	2 (3%)	
Amount of ascites ^a			0.435
None or Small	78 (76%)	53 (68%)	
Moderate	19 (19%)	20 (26%)	
Massive	5 (5%)	5 (6%)	
Extent of peritoneal metastasis ^b			1.000
P1	52 (51%)	39 (50%)	
P2/P3	50 (49%)	39 (50%)	
Metastatic sites other than the peritoneum			
Liver	41 (40%)	27 (35%)	0.535
Lung	10 (10%)	5 (6%)	0.588
Distant lymph node	21 (21%)	16 (21%)	1.000
mGPS			0.119
0	60 (59%)	56 (72%)	
1	23 (23%)	9 (12%)	
2	19 (19%)	13 (17%)	
NLR [n = 176]	3.4 (1.0–46.5)	3.0 (1.0–23.0)	0.098
CEA, ng/mL	6.0 (0.7–16984.4)	6.6 (0.8–1306.1)	0.990
CA19-9, IU/mL	2122 (2–50000)	1091 (2–50000)	0.866
Best tumor response			< 0.001
Complete response	0	0	
Partial response	29 (28%)	4 (5%)	
Stable disease	45 (44%)	33 (42%)	
Progressive disease	27 (26%)	33 (42%)	
Not evaluable	1 (1%)	8 (10%)	
Objective response rate	28%	5%	< 0.001
Disease control rate	73%	47%	< 0.001

Continuous variables are expressed as median (range) and categorical variables are expressed as absolute numbers (proportions).

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

^a Evaluated by computed tomography: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity.

^b Evaluated by computed tomography or positron emission tomography: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; P3, numerous metastatic nodules throughout the peritoneal cavity.

metastatic site, ECOG PS, amount of ascites, extent of peritoneal metastasis, laboratory data, and serum tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA 19-9]). The amount of ascites was evaluated by CT and was categorized according to the Japanese Classification of Gastric Carcinoma [10]: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity. The extent of peritoneal metastasis was evaluated by CT or PET/CT and was classified using criteria modified from the Japanese Classification of Gastric Carcinoma [10]: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; and P3, numerous metastatic nodules throughout the peritoneal cavity. Since the difference between P2 and P3 is ambiguous, we combined the category into P2/P3 with reference to a previous study [11]. Modified Glasgow prognostic score (mGPS) [12] was calculated as follows: C-reactive protein (CRP) $\leq$ 1 mg/dL, 0 point; CRP $>$ 1 mg/dL and albumin $\geq$ 3.5 g/dL, 1 point; CRP $>$ 1 mg/dL and albumin $<$ 3.5 g/dL, 2 points. Neutrophil to lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count [13]. Overall

survival (OS) was defined as the time from treatment initiation until death from any cause or the last follow up. Progression free survival (PFS) was defined as the time from treatment initiation until disease progression, death from any cause, or the last follow up. The follow-up data was confirmed until December 31, 2020.

First, we compared the clinical and treatment characteristics according to the period of diagnosis (group A vs. group B). Second, we compared PFS and OS according to the chemotherapy regimen (GnP or mFFX vs. other regimens). Finally, we examined the prognostic factors for OS in PC patients with peritoneal metastasis.

Statistical analysis

Continuous variables are presented as median (range), and were compared using Mann-Whitney *U* test or Kruskal-Wallis test as appropriate. Categorical variables are described as absolute numbers (proportions), and were analyzed using χ^2 test or Fisher's exact test as appropriate. PFS and OS were estimated using the Kaplan-Meier method and the Kaplan-Meier curves were compared by the log-rank test. Multivariate analysis was conducted using the cox proportional hazards model to identify prognostic

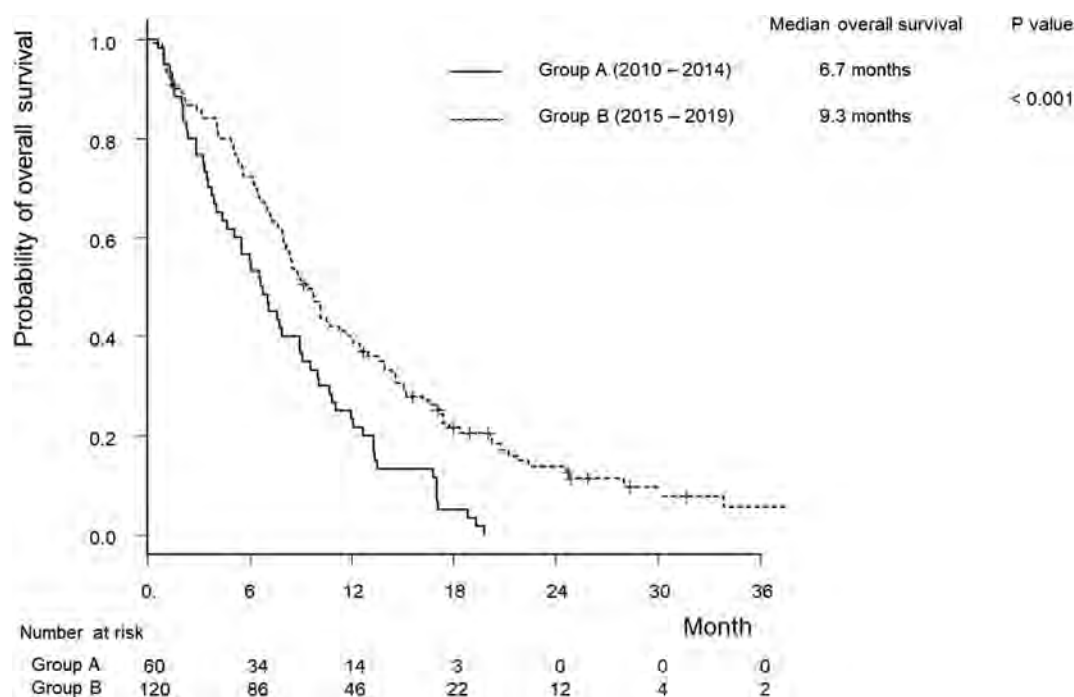


Fig. 2. Kaplan-Meier curves of overall survival according to the period of diagnosis.

factors for OS. Statistical tests were two-sided and a P value < 0.05 was considered statistically significant. Statistical analysis was carried out using the EZR software version 1.40 [14].

Results

Patient characteristics

A total of 1064 consecutive patients were diagnosed as metastatic or recurrent PC at our institution between January 2010 and December 2019. Forty-seven patients were transferred to another hospital and 97 patients received best supportive care, and the remaining 920 patients received palliative chemotherapy at our institution. Among them, 180 patients (20%) were diagnosed with synchronous peritoneal metastasis and were included in this study; the peritoneum was the only site of metastasis in 89 patients, whereas the remaining 91 patients presented with distant organ metastasis other than the peritoneum (Fig. 1). Of the 180 patients, the diagnosis of peritoneal metastasis was confirmed by CT or PET/CT in 157 patients and by laparoscopy or laparotomy in 23 patients. The predominant site of distant organ metastasis other than the peritoneum was the liver (38%), followed by distant lymph node (21%) and lung (8%). During the follow-up period, 2 patients were continuing first-line chemotherapy, 12 patients were transferred to another hospital without disease progression, and the remaining 166 patients discontinued first-line chemotherapy. The reasons for first-line chemotherapy discontinuation were disease progression in 142 (86%), deterioration of general condition in 17 (10%), unacceptable toxicity in 5 (including 3 interstitial pneumonia, 1 peripheral neuropathy, and 1 acute kidney injury), and patients' decision in 2. The details of disease progression consisted of exacerbation of peritoneal metastasis in 65 (including 8 cases of ileus and 2 cases of gastrointestinal perforation due to peritoneal metastasis), exacerbation of the primary tumor or other metastatic sites in 43, exacerbation of malignant ascites in 19, rapid increase in tumor markers in 14, and death in 1.

Patient characteristics according to the period of diagnosis (group A vs. group B) are shown in Table 1. Although patients in group B had a worse PS ($p = 0.021$) and received a higher rate of combination chemotherapy using GnP or mFFX compared to patients in group A (83% vs. 3%, $p < 0.001$), other parameters such as the amount of ascites, the extent of peritoneal metastasis, metastatic site other than the peritoneum, mGPS, NLR, and tumor markers were not significantly different between the two groups.

On the other hand, patient characteristics and treatment efficacy according to the chemotherapy regimen (GnP or mFFX vs. other regimens) are illustrated in Table 2. Although patients who received GnP or mFFX were significantly younger compared to those who received other regimens (66 years vs. 70 years, $p < 0.001$), other parameters were well-balanced between the two groups. Regarding treatment efficacy, the objective response rate (28% vs. 5%, $p < 0.001$) and disease control rate (73% vs. 47%, $p < 0.001$) were significantly higher in patients receiving GnP or mFFX compared to patients receiving other regimens.

Survival outcomes

Kaplan-Meier curves of OS according to the period of diagnosis are illustrated in Fig. 2. Median OS was significantly longer in group B compared to group A (9.3 months vs. 6.7 months, $p < 0.001$). This finding indicates that the prognosis of PC with peritoneal metastasis has significantly improved over time.

Kaplan-Meier curves of PFS and OS according to the chemotherapy regimen (GnP or mFFX vs. other regimens) are shown in Fig. 3. Median PFS (6.1 months vs. 3.4 months, $p < 0.001$) and OS (10.1 months vs. 6.8 months, $p < 0.001$) were significantly longer in patients receiving GnP or mFFX compared to patients receiving other regimens.

Cox proportional hazards regression analysis for OS are shown in Table 3. Combination chemotherapy using GnP or mFFX (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.22–0.46; $p < 0.001$), ECOG PS of 0 (HR, 0.51; 95%CI, 0.33–0.78; $p = 0.002$), and NLR ≥ 5

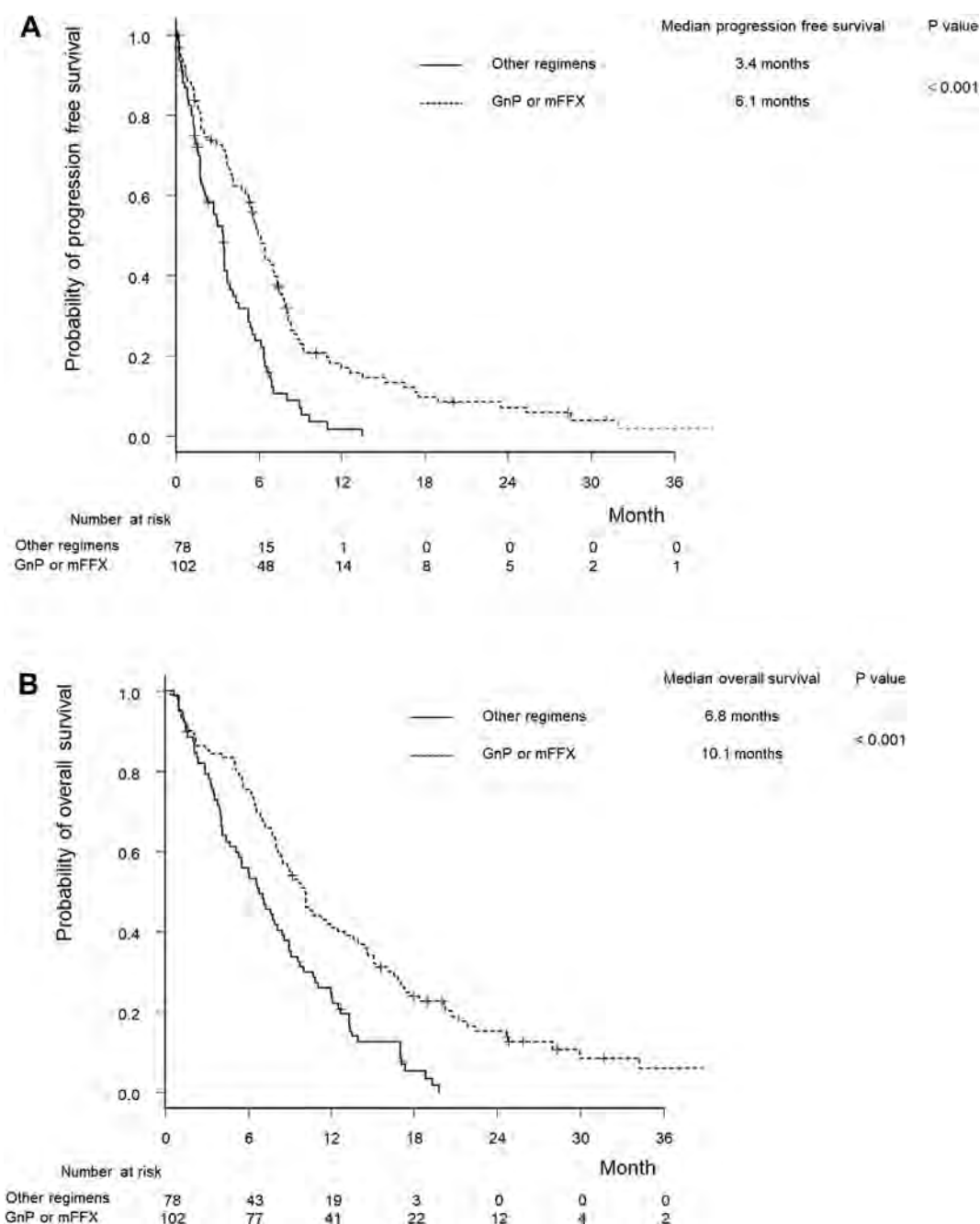


Fig. 3. Kaplan-Meier curves of (A) progression free survival and (B) overall survival according to the chemotherapy regimen. GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

(HR, 1.68; 95%CI, 1.05–2.70; $p = 0.032$) were identified as independent prognostic factors for OS in PC patients presenting with peritoneal metastasis.

Subgroup analysis of patients with distant metastasis confined to the peritoneum

Kaplan-Meier curves of OS according to the amount of ascites and the extent of peritoneal metastasis are illustrated in Fig. 4. Median OS of patients with large volume of ascites (6.4 months vs. 12.4 months, $p = 0.003$) and advanced peritoneal metastasis (6.9 months vs. 15.2 months, $p = 0.001$) was significantly shorter compared to patients with small volume of ascites and limited

peritoneal metastasis. These findings suggest that patients with small volume of ascites and limited peritoneal metastasis could expect long-term survival and are good candidates for aggressive combination chemotherapy.

Subgroup analysis of patients who received recent combination chemotherapy (GnP or mFFX)

Patient characteristics and treatment efficacy according to the regimen of recent combination chemotherapy (GnP vs. mFFX) are illustrated in Supplementary Table 1. First, patients who received mFFX were significantly younger compared to patients receiving GnP (62 years vs. 67 years, $p = 0.028$). Second, the incidence of liver

Table 3
Cox proportional hazards regression analysis for overall survival.

		Univariate			Multivariate		
		HR	95% CI	P value	HR	95% CI	P value
Age, years	≥75	1.17	0.80–1.69	0.420			
Sex	Male	1.00	0.74–1.36	0.999			
Disease status	Metastatic	0.96	0.64–1.46	0.855			
Peritoneum as the sole distant metastatic site	Yes	0.57	0.42–0.78	< 0.001	0.79	0.56–1.11	0.169
Amount of ascites ^a	Moderate/Massive	1.87	1.33–2.65	< 0.001	0.96	0.62–1.48	0.853
Extent of peritoneal dissemination ^b	P2/P3	1.63	1.20–2.23	0.002	1.26	0.87–1.80	0.219
ECOG PS	0	0.46	0.33–0.64	< 0.001	0.51	0.33–0.78	0.002
CEA, ng/mL	≥10	1.43	1.04–1.97	0.028	0.86	0.60–1.23	0.402
CA19-9, IU/mL	≥1000	1.57	1.15–2.16	0.005	1.28	0.89–1.86	0.186
mGPS	0	0.46	0.33–0.63	< 0.001	0.68	0.45–1.03	0.071
NLR	≥5	1.97	1.39–2.79	< 0.001	1.68	1.05–2.70	0.032
Regimen of chemotherapy	GnP or mFFX	0.51	0.37–0.70	< 0.001	0.32	0.22–0.46	<0.001

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; mGPS, modified Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; GnP, gemcitabine plus nab-paclitaxel; mFFX, modified FOLFIRINOX.

^a Evaluated by computed tomography: none, ascites undetected by CT; small, ascites localized in only one area such as the pelvic cavity; moderate, ascites neither small nor massive; and massive, ascites extending throughout the abdominal cavity.

^b Evaluated by computed tomography or positron emission tomography: P1, metastatic nodule(s) limited to one area of the peritoneum; P2, multiple scattered metastatic nodules within the peritoneal cavity; P3, numerous metastatic nodules throughout the peritoneal cavity.

metastasis (44% vs. 14%, $p = 0.041$) was significantly higher and the level of CA19-9 (310 IU/mL vs. 3761 IU/mL, $p = 0.020$) was significantly lower in the mFFX group compared to the GnP group. Third, although the amount of ascites and the extent of peritoneal metastasis were not significantly different between the two groups, mFFX was contraindicated for patients with massive ascites. Finally, the objective response rate and disease control rate were similar between the two groups.

Comparison of treatment-related severe adverse events according to the regimen of recent combination chemotherapy are illustrated in [Supplementary Table 2](#). The incidence of severe hematologic and non-hematologic adverse events was not significantly different between the two groups except for leukopenia (36% vs. 7%, $p = 0.033$).

Kaplan-Meier curves of PFS and OS according to the regimen of recent combination chemotherapy (GnP vs. mFFX) are shown in [Figs1 and Figs2](#). As mentioned above, although there were some differences in patient characteristics favoring patients receiving mFFX, the median PFS (6.0 months vs. 7.5 months, $p = 0.217$) and OS (9.2 months vs. 16.9 months, $p = 0.148$) were not significantly different between the two groups (GnP vs. mFFX).

Discussion

This retrospective study evaluated the improvements in treatment outcomes over time and examined the prognostic factors for advanced PC patients with peritoneal metastasis. We demonstrated that the prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of intensified combination chemotherapy regimens, namely, GnP and mFFX. The objective response rate (28% vs. 5%, $p < 0.001$) and disease control rate (73% vs. 47%, $p < 0.001$) were also significantly higher in patients receiving GnP or mFFX compared to patients receiving other regimens. Furthermore, combination chemotherapy using GnP or mFFX (HR, 0.32; $p < 0.001$), ECOG PS of 0 (HR, 0.51; $p = 0.002$), and NLR ≥ 5 (HR, 1.68; $p = 0.032$) were identified as independent prognostic factors for OS in PC patients presenting with peritoneal metastasis. Taken together, these results suggest that patients with a good ECOG PS could significantly benefit from these two regimens even in the presence of peritoneal metastasis. Subgroup analysis of patients with distant metastasis confined to the peritoneum revealed that median OS of patients with large volume of ascites (6.4 months vs. 12.4 months, $p = 0.003$) and advanced peritoneal

metastasis (6.9 months vs. 15.2 months, $p = 0.001$) was significantly shorter compared to patients with small volume of ascites and limited peritoneal metastasis. To the best of our knowledge, this is one of the largest studies that exclusively focused on the treatment outcomes of PC patients with peritoneal metastasis. The assessment of the extent of peritoneal metastasis was also one of the strengths in this study.

Peritoneal metastasis is one of the most common forms of metastasis in PC. In this study, the incidence of synchronous peritoneal metastasis was 20% (180/920) among advanced PC patients, which was in line with previous studies [3,5]. One study reported that the incidence of synchronous peritoneal metastasis was 22% (88/409) among metastatic PC patients receiving gemcitabine-containing regimen [3], while the other population-based study reported that the incidence of synchronous peritoneal metastasis was 19% (265/1412) among metastatic PC patients with an increasing trend over time (16% [1995–2004] to 22% [2005–2009]) [5]. The increasing trend of the diagnosis of synchronous peritoneal metastasis could be attributed to the improvement in the diagnostic performance of multidetector CT and PET/CT in detecting small peritoneal nodules.

Peritoneal metastasis is often associated with intestinal obstruction, massive ascites, and reduced PS [4,15]. Therefore, it has been regarded as a devastating condition precluding most of the patients from receiving palliative chemotherapy. Indeed, only a minority of patients received palliative chemotherapy in the two retrospective studies focusing on peritoneal metastasis, 29% in one study and 18.5% in the other study, resulting in an extremely poor OS of 6–7 weeks in the entire cohort of each study [4,5]. Recently, several studies reported the improvements in the management of intestinal obstruction and massive ascites [16–21]. These procedures enable the patients to maintain their PS and offer the patients the chance to be candidates for chemotherapy. Furthermore, recent combination chemotherapy regimens, GnP and mFFX, have been shown to significantly improve the prognosis of metastatic PC patients with a good PS [8,9,22]. In this study, we demonstrated that the beneficial effect of GnP and mFFX was also observed in PC patients presenting with peritoneal metastasis. First, the objective response rate (28% vs. 5%, $p < 0.001$) and disease control rate (73% vs. 47%, $p < 0.001$) of these two regimens were significantly higher than those of other regimens. Second, these two regimens showed a somewhat satisfactory median OS of 10.1 months, whereas the other regimens showed a median OS of 6.8 months. Considering

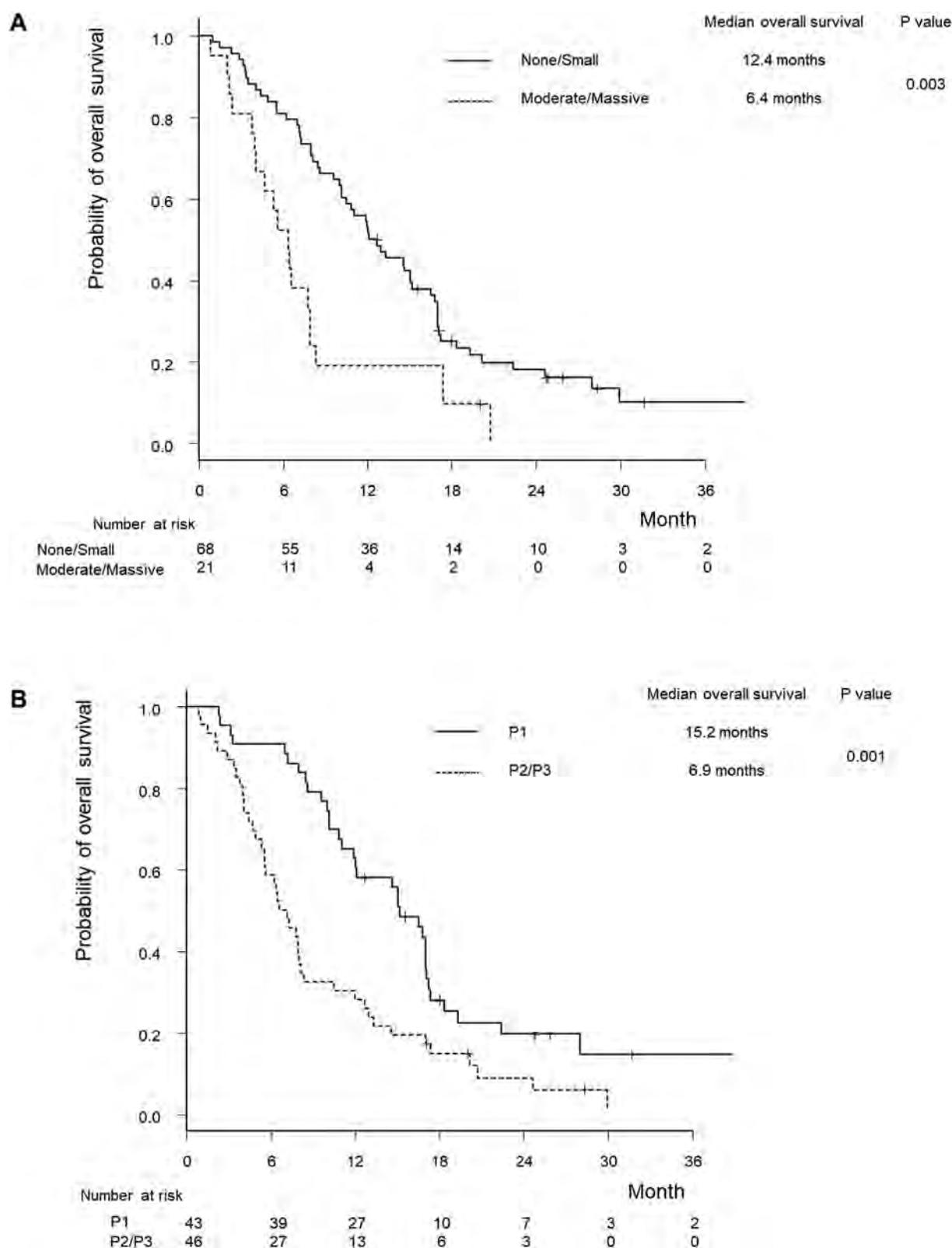


Fig. 4. Kaplan-Meier curves of overall survival according to (A) the amount of ascites and (B) the extent of peritoneal metastasis.

that PC patients with peritoneal metastasis are generally reported to have a poor prognosis, the survival outcomes of these two regimens are encouraging. Third, combination chemotherapy using these two regimens (HR, 0.32; $p < 0.001$) was identified as an independent prognostic factor for OS, together with ECOG PS of 0 and

NLR ≥ 5 . Subgroup analysis of patients with distant metastasis confined to the peritoneum was also conducted in this study. We revealed that the amount of ascites and the extent of peritoneal metastasis were significantly associated with OS. Patients with small volume of ascites and limited extent of peritoneal metastasis

showed a satisfactory median OS of 12.4 months and 15.2 months, respectively.

Although the prognosis of PC with peritoneal metastasis has moderately improved over time with the advent of intensified combination chemotherapy regimens, a novel treatment strategy focusing on peritoneal metastasis is needed to further improve its prognosis. Intraperitoneal chemotherapy has been developed to enhance the activity of antitumor drugs against peritoneal metastasis by maintaining a high drug concentration in the peritoneal cavity. Recently, promising results of intraperitoneal chemotherapy with paclitaxel have been reported in patients with peritoneal metastasis from several malignancies including PC [11,23–26]. The results of a phase II study evaluating the efficacy of intravenous GnP combined with intraperitoneal paclitaxel in PC patients with peritoneal metastasis (JRCTs031180095) is awaited to further validate the benefit of intraperitoneal chemotherapy. In this study, 88 patients received GnP as first-line chemotherapy for PC patients with peritoneal metastasis; the objective response rate, disease control rate, median PFS, and median OS were 28%, 73%, 6 months, and 9.2 months, respectively. As a result, we think that these data could be used as a standard reference for the above-mentioned phase II study evaluating intraperitoneal chemotherapy.

Our study has several limitations. First, this was a retrospective study with a limited sample size from a single institution. However, this is one of the largest studies focusing on PC patients with peritoneal metastasis. Second, since we only included patients who received chemotherapy and excluded patients who received best supportive care, the results of this study cannot be generalized to all PC patients with peritoneal metastasis. Third, the amount of ascites might be affected by factors other than peritoneal metastasis; for example, low albumin levels and/or portal hypertension could also influence the amount of ascites. Finally, the incidence of peritoneal metastasis could be underestimated in this study, because accurate diagnosis of peritoneal metastasis is sometimes difficult despite the improved diagnostic performance of CT and PET/CT.

In conclusion, we demonstrated that the prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of the novel combination chemotherapy regimens (GnP and mFFX). These two regimens showed a satisfactory radiologic tumor response, PFS, and OS, and was identified as an independent prognostic factor for OS. The amount of ascites and extent of peritoneal metastasis were significantly associated with OS in patients with distant metastasis confined to the peritoneum. Furthermore, we consider that the results of this study could serve as a standard reference for future studies evaluating PC patients with peritoneal metastasis.

Declaration of competing interest

The authors declare no conflict of interests.

Acknowledgments

We have no funds and grants in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2021.03.006>.

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Appendix THOTA02

Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer

Is Wishful Thinking Clouding Successful Drug Development for Pancreatic Cancer?

Ramya Thota, MBBS,* Anirban Maitra, MBBS,† and Jordan D. Berlin, MD*

Abstract: Prior phase III trials in advanced pancreatic cancer have been predominantly unsuccessful. In this review, we attempt to understand how past preclinical data were translated into phase III clinical trials in metastatic pancreatic cancer as described in the article. A systematic literature review conducted through the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, from January 1997 to June 2015 using key words—phase III clinical trials, metastatic/advanced pancreatic adenocarcinoma or pancreatic cancer identified 30 randomized controlled trials (RCTs) that met criteria. The trials were limited to RCTs in the first-line treatment of patients with metastatic pancreatic cancer. The success rate of first-line phase III studies in advanced pancreatic cancer was only 13%. In 60% of the RCTs, no preclinical experiments were referenced in biologically cognate pancreatic models. Nine (30%) of the RCTs were designed based on preclinical evidence from in vitro cell lines alone without additional in vivo validation in xenograft models. It remains uncertain how strongly the preclinical data influence the development of clinical regimens but so far the studies developed based on more solid preclinical evidence have been successful.

Key Words: preclinical evidence, metastatic pancreatic cancer, randomized phase III trials

(*Pancreas* 2017;46: 143–150)

Pancreatic cancer is the fourth leading cause of cancer related mortality in the United States and is expected to rise to the second leading within a decade.¹ The majority of the patients with pancreatic cancer have advanced disease at diagnosis with limited treatment options. Despite intensive research efforts over past several decades, the prognosis of advanced pancreatic cancer remains dismal. Even with the newest regimens, median survivals for advanced disease remain less than a year.^{2,3} Therefore, there is an urgent need for the development of new effective drugs to improve the survival of patients with metastatic pancreatic cancer.

From the *Division of Hematology/Oncology, Vanderbilt University, Nashville, TN; and †Sheikh Ahmed Pancreatic Cancer Research Center, Departments of Pathology and Translational Molecular Pathology, MD Anderson Cancer Center, Houston, TX.

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Address correspondence to: Jordan D. Berlin, MD, Division of Hematology/Oncology, Vanderbilt University, Nashville, 2220 Pierce Ave, 777, Nashville, TN 37232 (e-mail: jordan.berlin@vanderbilt.edu).

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Although we have made remarkable progress in understanding the biology of pancreatic cancer, this has not translated into new drug discovery. In fact, the only positive trials in recent years have involved traditional chemotherapy.^{2,3} Drug development in pancreatic cancer has been challenging. At least 1 issue that needs to be better understood is how preclinical data supporting the use of new agents or new combinations failed to result in clinical benefit in randomized phase III clinical trials.

The failure of clinical trials at later stages of drug development results in exposure of already symptomatic patients to unwanted toxicities causing further impairment in quality of life, waste of health care dollars, resources, and delay in development of therapies that may have a better chance of success. Preclinical data are used in the development of agents and regimens, but it remains unclear how informative these data are and how well it truly informs by the time the phase III is developed.

A diverse group of preclinical murine models have been used in cancer research. However, due to complex genetic and molecular heterogeneity in human tumors compared with mice, few, if any, of these animal models can faithfully recapitulate the in vivo pancreatic tumor microenvironment. This analysis was undertaken to better understand how past preclinical data were translated into clinical trials in pancreatic cancer. In this review, we report the preclinical rationale for all the published first-line phase III trials in metastatic pancreatic cancer as described in the article. These data may inform us in methods for improvement for future drug development in advanced pancreatic cancer.

MATERIALS AND METHODS

We conducted a systematic literature review through the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, from January 1997 to June 2015 using key words—phase III clinical trials, metastatic/advanced pancreatic adenocarcinoma or pancreatic cancer. The trials were limited to randomized controlled trials (RCTs) in the first-line treatment of patients with metastatic pancreatic cancer. RCTs in nonmetastatic pancreatic cancer, second-line metastatic pancreatic cancer or nonrandomized trials in metastatic pancreatic cancer were excluded. As a result, we did not include the recent successful phase III NAPOLI-1 trial in the second line setting, which has led to the US Food and Drug Administration approval of a combination liposomal irinotecan (Onivyde) regimen in pancreatic cancer patients that progressed on gemcitabine or gemcitabine-based therapies. Further, to be included, the trial had to be published. Abstract only reports were not included because background data could not be reviewed.

We identified 30 published RCTs that met inclusion criteria. Data collected from the articles included: first author, publication year, chemotherapy regimens, and information on preclinical studies. The preclinical data from published phase III trials were

collected in a systematic manner. First, each published phase III study was carefully reviewed to verify that preclinical rationale was reported. If preclinical data were available, information was collected on the number and type of preclinical models tested (in vitro, cell line–derived xenograft, patient-derived xenograft [PDX], or genetically engineered mouse model [GEMM]) based on the reports referenced in the article. Then each study was

analyzed for evidence of preclinical activity in pancreatic models and if the science for the combination drug therapy and sequencing of the drugs is proven in pancreatic cancer or not was noted. The science for the combination drug therapy was considered fully supported in pancreatic cancer only if evidence for synergy of the drug combinations was tested in pancreatic models specifically. In addition, because preclinical evidence was not always

TABLE 1. Preclinical Evidence Reported in Published Phase III Trials in Metastatic Pancreatic Cancer

Study	Drug	Phase III	Phase II	In Vitro Cell Line	Cell Line–Derived Xenograft		GEMM Model	Patient-Derived Xenograft	
					Hetero	Ortho		Hetero	Ortho
Positive trials									
Von Hoff et al, 2013 ³	Gemcitabine + nab-Paclitaxel	Yes ³	Yes ⁴				Yes ⁵	Yes ⁴	
Conroy et al, 2011 ²	FOLFIRINOX	Yes ²	Yes ⁶	Yes ^{7–10}	Yes ^{10,11}				
Moore et al, 2007 ¹²	Gemcitabine + erlotinib	Yes ¹²	No	Yes ¹³		Yes ¹³			Yes ¹⁴
Burris et al, 1997 ¹⁵	Gemcitabine	Yes ¹⁵	Yes ¹⁶	Yes ¹⁷	Yes ¹⁷				
Negative trials									
Colucci et al, 2002 ¹⁸ GOIM	Gemcitabine + cisplatin	Yes ¹⁸	Yes ^{19,20}	Yes ^{21,22}					
Moore et al, 2003 ²³	BAY 12-9566	Yes ²³	No		Yes ²⁴				
Colucci et al, 2010 ²⁵ GIP-1	Gemcitabine + cisplatin	Yes ²⁵	NA	Yes ^{21,22,26–28}					
Berlin et al, 2002 ²⁹	Gemcitabine + 5-flourouracil	Yes ²⁹	Yes ^{30–33}	Yes ^{34,35}					
Brahmall et al, 2001 ³⁶	Gemcitabine + marimastat	Yes ³⁶	Yes ³⁷	Yes ³⁸	Yes ^{39–42}	Yes ^{38,43}			
Van Custem et al, 2004 ⁴⁴	Gemcitabine + tipifarnib	Yes ⁴⁴	No	Yes ⁴⁵	Yes ⁴⁵				
Rocha Lima et al, 2004 ⁴⁶	Gemcitabine + irinotecan	Yes ⁴⁶	Yes ⁴⁷	Yes ⁴⁸					
Oettle et al, 2005 ⁴⁹	Gemcitabine + pemetrexed	Yes ⁴⁹	Yes ⁵⁰	Yes ⁵¹					
Louvet et al, 2005 ⁵²	Gemcitabine + oxaliplatin	Yes ⁵²	Yes ⁵³	Yes ⁵⁴					
Reni et al, 2005 ⁵⁵	Gemcitabine + epirubicin cisplatin 5-flourouracil	No ⁵⁵	No ⁵⁶						
Hienemann et al, 2006 ⁵⁷	Gemcitabine + cisplatin	Yes ⁵⁷	Yes ^{19,20,58}	Yes ^{27,59,60}	Yes ^{59,60}				
Abou-Alfa et al, 2006 ⁶¹	Gemcitabine + exatecan	Yes ⁶¹	Yes ⁶²	Yes ^{63,64}					
Stathopoulos et al, 2006 ⁶⁵	Gemcitabine + irinotecan	No ⁶⁵	Yes ^{47,66}	Yes ^{21,48,67}					
Hermann et al, 2007 ⁶⁸	Gemcitabine + capecitabine	Yes ⁶⁸	Yes ^{69–71}	Yes ³⁵	Yes ⁷²				
Van Custem et al, 2009 ⁷³	Gemcitabine + erlotinib + bevacizumab	No ⁷³	No ⁷⁴						
Cunningham et al, 2009 ⁷⁵	Gemcitabine + capecitabine	No ⁷⁵	Yes ^{69–71,76}	Yes ³⁵	Yes ⁷²				
Poplin et al, 2009 ⁷⁷	Gemcitabine + oxaliplatin	No ⁷⁷	Yes ⁷⁸	Yes ⁷⁹					
Philip et al, 2010 ⁸⁰	Gemcitabine + cetuximab	Yes ⁸⁰	Yes ⁸¹		Yes ⁸²	Yes ¹³			
Kindler et al, 2010 ⁸³	Gemcitabine + bevacizumab	Yes ⁸³	Yes ⁸⁴		Yes ⁸⁵	Yes ^{85–89}			
Kindler et al, 2011 ⁹⁰	Gemcitabine + axitinib	No ⁹⁰	No ⁹¹						
Gonçalves et al, 2012 ⁹²	Gemcitabine + sorafenib	Yes ⁹²	Yes ⁹³	Yes ⁹⁴	Yes ⁹⁵				
Rougier et al, 2013 ⁹⁶	Gemcitabine + aflibercept	Yes ⁹⁶	No	Yes ⁹⁷	Yes ⁹⁷	Yes ⁹⁷			
Middleton et al, 2014 ⁹⁸	Gemcitabine + capecitabine + GV1001	Yes ⁹⁸		Yes ⁹⁹	Yes ⁹⁹				
Ueno et al, 2013 ¹⁰⁰	Gemcitabine + S-1	No ¹⁰⁰	Yes ^{101,102}	Yes ¹⁰³					
Deplanque et al, 2015 ¹⁰⁴	Gemcitabine + masatinib	Yes ¹⁰⁴	Yes ¹⁰⁵	Yes ¹⁰⁶	Yes ¹⁰⁶				
Fuchs et al, 2015 ¹⁰⁷	Gemcitabine + ganitumumab	Yes ¹⁰⁷	Yes ¹⁰⁸	Yes ¹⁰⁹	Yes ¹⁰⁹				
NA indicates not applicable									

TABLE 2. Detailed Evidence for Preclinical Activity in Various Animal Models

Study	Drug	Target	Tested in		Evidence of Activity Drug Hits the Target	Evidence of Activity Pancreatic Cancer	Synergy Tested and Proven	Sequence or Dosing Schedule Tested	Is the Science for	
			Target Valid Pancreatic Cancer	Pancreatic Models or Others					Other Models Tested	Combination Setup in Pancreatic Cancer
Conroy et al, 2011 ²	FOLFIRINOX		NA	No	Colon, HNSCC, Intestine	No	No	Yes	No	No
Moore et al, 2007 ¹²	Gemcitabine + erlotinib	EGFR	Yes	Yes		Yes	Yes	Yes	No	Yes
Von Hoff et al, 2013 ³	Gemcitabine + nab-paclitaxel	SPARC	Yes	Yes		Yes	Yes	Yes	No	Yes
Colucci et al, 2001 ¹⁸ GOIM	Gemcitabine + cisplatin		NA	No	HNSCC, Ovarian, Colon, NSCLC	NA	No	Yes	Yes	No
Moore et al, 2003 ²³	BAY 12-9566	MMP-2,3,9,13	Yes	No	Colon, Mammary, Melanoma, Lung	No	No	NA	Yes	NA
Colucci et al, 2010 ²⁵ GIP-1	Gemcitabine + cisplatin		NA	No	Ovarian, NSCLC	NA	No	Yes	Yes	No
Berlin et al, 2002 ²⁹	Gemcitabine + 5-flourouracil		NA	No	Colon	NA	No	Yes	Yes	No
Brahmall et al, 2001 ³⁶	Gemcitabine + marimastat	MMP (BB94)	Yes	Yes	Ovarian, Melanoma, Gastric, Lung	No	Yes	No	No	No
Van Cussem et al, 2004 ⁴⁴	Gemcitabine + tipifarnib	Farnesyl transferase	Yes	Yes	Colon, Melanoma	Yes	Yes	No	No	No
Rocha Lima et al, 2004 ⁴⁶	Gemcitabine + irinotecan		NA	No	Breast, SCLC, NSCLC	No	No	Yes	No	No
Oettle et al, 2005 ⁴⁹	Gemcitabine + pemetrexed		NA	No	Colorectal	No	No	Yes	Yes	No
Louvet et al, 2005 ⁵²	Gemcitabine + oxaliplatin		NA	No	Leukemia, Colon	No	No	Yes	Yes	No
Reni et al, 2005 ⁵⁵	Gemcitabine + epirubicin cisplatin 5-flourouracil		NA	No	No	No	No	No	No	No
Hienemann et al, 2006 ⁵⁷	Gemcitabine + cisplatin		NA	No	HNSCC, Ovarian, Colon, NSCLC	No	No	Yes	Yes	No
Abou-Alfa et al, 2006 ⁶¹	Gemcitabine + exatecan		NA	Yes		No	Yes	Yes	Yes	Yes
Stathopoulos et al, 2006 ⁶⁵	Gemcitabine + irinotecan		NA	No	Colorectal	No	No	Yes	No	No
Hermann et al, 2007 ⁶⁸	Gemcitabine + capecitabine		NA	No	Colon	NA	No	No	No	No
Van Cussem et al, 2009 ⁷³	Gemcitabine + erlotinib + bevacizumab	EGFR, VEGF	No	No	No	No	No	No	No	No
Cunningham et al, 2009 ⁷⁵	Gemcitabine + capecitabine		NA	No	Colon	NA	No	No	No	No

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TABLE 2. (Continued)

Study	Drug	Target	Target Valid		Tested in		Evidence of		Synergy or Dosing		Is the Science
			Cancer or Not	Pancreatic	Other Models	Drug Hits	Activity in	Tested and	Proven	Schedule	Setup
Poplin et al, 2009 ⁷⁷	Gemcitabine + oxaliplatin		NA	No	Leukemia, Colon	No	No	Yes	Yes	Yes	No
Philip et al, 2010 ⁸⁰	Gemcitabine + cetuximab	EGFR	Yes	Yes		Yes	Yes	Yes	Yes	No	Yes
Kindler et al, 2010 ⁸³	Gemcitabine + bevacizumab	VEGF	Yes	Yes		Yes	Yes	Yes	Yes	No	Yes
Kindler et al, 2011 ⁹⁰	Gemcitabine + axitinib	VEGF	No	No		No	No	No	No	No	No
Gonçalves et al, 2012 ⁹²	Gemcitabine + sorafenib	VEGFR, PDGF, RAF	Yes	Yes		Yes	Yes	No	No	No	No
Rougier et al, 2013 ⁹⁶	Gemcitabine + aflibercept	VEGF, Trap	Yes	Yes		Yes	Yes	No	No	No	No
Middleton et al, 2014 ⁹⁸	Gemcitabine + capecitabine + GV1001	Telomerase	Yes	No	Mesothelioma	No	No	No	No	No	No
Ueno et al, 2013 ¹⁰⁰	Gemcitabine + S-1		No	Yes	Colon	No	No	Yes	Yes	No	Yes
Deplanque et al, 2015 ¹⁰⁴	Gemcitabine + masitinib	TKI c-Kit, Lyn, Fyn, FGFR3, PDGFR, FAK	Yes	Yes		Yes	Yes	Yes	Yes	No	No
Fuchs et al, 2015 ¹⁰⁷	Gemcitabine + ganitumumab	IGFR	Yes	Yes		Yes	Yes	Yes	Yes	No	No

EGFR indicates epidermal growth factor receptor; FGF, fibroblast growth factor; HNSCC, head and neck squamous cell cancer; NSCLC, non small cell lung cancer; PDGF, placenta derived growth factor; VEGF, vascular endothelial growth factor; NA, not applicable.

reported in the phase III publication, the article for the corresponding and referenced phase II study was reviewed systematically as well to note if any preclinical rationale was reported.

RESULTS

Among the 30 published randomized phase III clinical trials in the first-line in metastatic pancreatic cancer, only 3 studies had true clinical impact. The combination of gemcitabine and erlotinib had a positive trial but did not change practice in a substantive manner due to infrequent adoption by clinicians. The success rate of phase III studies in advanced pancreatic cancer was only 13% in terms of meeting primary endpoint but 10% for practice changing trials. The detailed information on preclinical evidence and models used in each RCT is listed in Tables 1 and 2.

In the studies that reported preclinical rationale, in vitro cell lines or cell line-derived subcutaneous xenograft models were the most commonly used preclinical models (n = 27, 90%). Orthotopic xenograft models were referenced for preclinical experiments in only 5 RCTs (17%). The PDX models and GEMMs were cited in 2 RCTs (7%) and 1 RCT (3%), respectively (Fig. 1).

In 60% of the RCT studies (n = 18), no preclinical experiments were referenced in biologically cognate pancreatic models. The sequence/schedule of the combination therapy was not tested in 22 (73%) studies. Synergy for the combination was reported for 18 (60%) of the phase III studies. Overall, references for the science for the combination drug regimen was referenced in pancreatic cancer models in only 6 (20%) of the studies.

Nine (30%) of the RCTs were designed based on preclinical evidence from in vitro cell lines alone without additional in vivo validation in xenograft models. Common examples of drugs tested in vitro alone were the combination of gemcitabine with 5-fluorouracil, irinotecan, oxaliplatin, S-1, exatecan, and pemetrexed. The cell line-derived subcutaneous xenograft models were reportedly used in 15 (50%) of the 30 phase III studies.

When compared with the negative RCTs, we noted the recent positive RCTs, such as gemcitabine and nab-paclitaxel had extensive preclinical testing done in multiple preclinical models including PDX and GEMMs.

DISCUSSION

The failure rate of phase III clinical trials in advanced pancreatic cancer is high (87%). This analysis was undertaken to see if there might be information gleaned from the use of preclinical models in developing regimens that make it to phase III. There are several difficulties inherent in evaluating the impact of preclinical study on subsequent phase III success rate. First, there are only 4 positive phase III trials in first-line metastatic pancreatic cancer during the 18 years covered in this analysis, of which only 3 (10%) could be considered practice changing.

Second, preclinical data that set the rationale for the drug used or drug combinations may not all be referenced in the articles for many reasons. Article page limit may reduce the amount of introduction in the article where most of the rationale is outlined; for example, the steps between preclinical data and phase III analysis can be myriad and often include phase I and II trials. Therefore, some of the preclinical data may simply not have been included in the articles for sake of brevity. Many of the regimens come from work done within the pharmaceutical industry, and some of the data may be unpublished, limiting the ability to reference the data. Other preclinical data may have only been in abstract form at national or international meetings, limiting the likelihood it will be used as a reference.

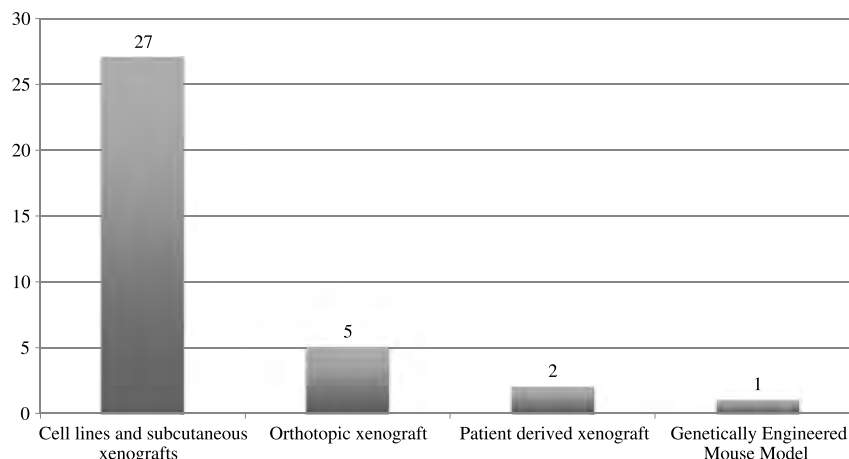


FIGURE 1. Preclinical models used for validation of phase III clinical trials in metastatic pancreatic cancer.

Nonetheless, the reality exists that many of the publications relevant to pancreatic cancer RCTs did not reference preclinical data in pancreatic models. We did not do an analysis of the novel agents to see where in the “life cycle” the pancreatic cancer trial occurred. In other words, when a company decides to bring an agent out of the preclinical realm into clinical development, there are primary targets that “lead off” the pipeline, and thereafter, secondary targets that are either planned later or come from outside leads. The vast majority of preclinical data are developed to establish or refute the rationale in the primary target diseases. The phase III trial may be then undertaken based on early phase clinical evidence, which would logically trump the need for preclinical evidence. In fact, in this analysis, very few, if any of the agents studied were primarily purposed for pancreatic cancer, including gemcitabine that was initially developed in lung cancer primarily, with hopes for effect in colorectal cancer as well.

The authors of this article are unaware of a systematic analysis of how much preclinical evidence is needed to bring an agent into a clinical trial. However, in pancreatic cancer, a State of the Science meeting attempted to define loose guidelines for preclinical evidence. Several conclusions about preclinical models were reached including: older models are flawed; newer models need to be interrogated and to fully test a hypothesis, more than 1 model should be used.¹¹⁰ It is noted that all of the trials that were positive had agents or combinations that were tested in multiple cell lines and/or models. Of the 3 combination trials, 2 of 3 were tested in pancreatic models and all 3 had synergy data presented in the references. This suggests at least that trials with more solid preclinical evidence have been successful even if some of the data are derived in models of other cancers.

The data presented here do show that there is no uniformity in developing the rationale for use of drugs or drug combinations in phase III trials. The clear, but broad recommendations from the 2007 State of the Science meeting were made with regard to developing clinical regimens in pancreatic cancer.¹¹⁰ Those guidelines are as yet untested, but these data suggest they may indicate a better way to move forward. An analysis of published phase II reports may be conducted to analyze if more robust preclinical data before phase II leads to greater likelihood of moving to phase III, but this would be flawed as an accompanying article demonstrates that robust phase II data has not been required to go to phase III trials in the past and, in fact, many studies went to phase III despite negative phase II data.

Finally, it remains uncertain how strongly the preclinical data influences the development of clinical regimens. Is compelling

science the rationale used to justify conducting a pivotal trial, or are many of these studies “trials of convenience”? Irrespective, with the exceptionally low success rate for clinical trials in pancreatic cancer (and, in fact, in most cancers), it is clear that we need to reevaluate how we have been developing our trials and designing our regimens. This article is not meant as any indictment of the past, but instead, it is meant to start that discussion.

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Appendix UNDEVIA02

PHARMACOKINETIC VARIABILITY OF ANTICANCER AGENTS

Samir D. Undevia, Gonzalo Gomez-Abuin and Mark J. Ratain

Abstract | The translation of advances in cancer biology to drug discovery can be complicated by pharmacokinetic variation between individuals and within individuals, and this can result in unpredictable toxicity and variable antineoplastic effects. Previously unrecognized variables (such as genetic polymorphisms) are now known to have a significant impact on drug disposition. How can the pharmacokinetic variability of anticancer agents be reduced? This will require the understanding of correlations between pharmacokinetics and treatment outcomes, the identification of relevant patient parameters, mathematical modelling of individual and population pharmacokinetics, and the development of algorithms that will tailor doses to the individual patient.

ABSORPTION

The process by which a drug leaves its site of administration and enters systemic circulation. Not relevant to intravenously administered agents.

DISTRIBUTION

The process by which a drug distributes into interstitial and intracellular fluids.

METABOLISM

The process by which a drug undergoes biotransformation to a usually inactive (but sometimes active) metabolite.

EXCRETION

The process by which a drug and/or its metabolites are removed from the body.

Cancer Research Center,
The University of Chicago,
5841 South Maryland
Avenue, MC 2115 Chicago,
Illinois 60637, USA.
Correspondence to M.J.R.
e-mail: mratain@medicine.bsd.uchicago.edu
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Pharmacokinetics can be defined as the study of the bodily ABSORPTION, DISTRIBUTION, METABOLISM and EXCRETION (ADME) profile of drugs (FIG. 1) or, put simply, what the body does to the drug. Most anticancer agents have wide interindividual pharmacokinetic variability and a narrow THERAPEUTIC INDEX. Systemic exposure after standard doses of cytotoxic drugs can vary 2–10-fold between patients^{1–3}. Pharmacokinetic parameters of many anticancer drugs are associated with treatment outcome. Therefore, high pharmacokinetic variability can make it difficult to predict how a patient will respond to a drug. Moreover, with decreased predictability comes increased risks of both toxicity and subtherapeutic dosing in the individual patient.

To decrease interindividual pharmacokinetic differences, doses should ideally be tailored to the individual patient (individualized dosing). Traditionally, this has been done by normalizing dose to body surface area (BSA), which is calculated from height and weight. However, studies have shown that this is inadequate⁴. In this review, we discuss the sources of interindividual and intraindividual variation in the pharmacokinetics of anticancer drugs. Several methods for quantifying and accounting for this variability are being explored. We discuss pharmacokinetic and genetic-based methods of dose adjustment and mathematical modelling schemes to guide dosing.

We explore methods of modulating pharmacokinetics using other drugs to reduce variability. Finally, we discuss the impact of pharmacokinetic variability on the design of clinical trials.

The aim of this review is not to catalogue the published pharmacokinetic variability of anticancer agents but instead to focus on concepts and the potential impact of variability on outcome. Most drugs that we refer to in this article are classic cytotoxic agents. The pharmacokinetic data available for these agents are, in general, more extensive than those for the newer, so-called ‘targeted’ agents, by virtue of the long history of use, so we use these here to illustrate the concepts of pharmacokinetic variability. However, the concepts apply to all anticancer agents, past, present and future, regardless of their mechanisms of action.

Quantifying pharmacokinetic variability

The pharmacokinetic profile of a drug is described by several numerical parameters (BOX 1) and whether or not the pharmacokinetics are linear or non-linear (BOX 2). Often, the reported pharmacokinetic data of anticancer agents consist simply of the mean values of these parameters with their standard deviations at each dose level evaluated. However, because it is the interindividual variability in these parameters that is important when understanding differences in patient

Summary

- The field of pharmacokinetics attempts to describe the bodily disposition of drugs in terms of numerical parameters that are calculated from plasma concentrations obtained at time points after drug administration. These parameters can be correlated with treatment outcomes such as toxicity and efficacy.
- Anticancer drugs can have considerable interindividual pharmacokinetic variability, which, given the narrow therapeutic index of these drugs, results in unpredictable clinical effects.
- There are many potential sources of pharmacokinetic variation, including interindividual differences in absorption, distribution, metabolism and excretion of anticancer drugs.
- A considerable amount of research is currently directed towards defining genetic polymorphisms in drug-disposition pathways that explain observed interindividual pharmacokinetic variability.
- Tailoring doses of anticancer drug to the individual patient will decrease interpatient pharmacokinetic variability and reduce the risks of severe toxicity and subtherapeutic treatment.
- Individualized dosing strategies currently being examined in the research setting are promising, although few are used in routine clinical practice.

outcomes, the COEFFICIENT OF VARIATION (CV) is the single best descriptor of pharmacokinetic variability. The 'spread' of a parameter is estimated by calculating the variance and standard deviation, and the CV provides a relative measure of data dispersion with reference to the mean. A high CV means the pharmacokinetics in an individual patient are unpredictable.

Once pharmacokinetic variability is recognized, the next step is to identify the many potential sources of the variation. Here, we systematically consider each of the steps of ADME of drugs (BOX 3).

Drug absorption

Most anticancer agents are administered intravenously or orally. Intravenous administration of drug is the most direct route and results in rapid and complete BIOAVAILABILITY, so that the prescriber is assured that the patient is receiving the desired dose. By contrast, the bioavailability of oral drugs is subject to absorption barriers and the FIRST-PASS EFFECT. As a result, oral agents characteristically have far greater

pharmacokinetic variability than intravenous agents. This is best demonstrated by anticancer agents that can be administered by either route. In a study of etoposide, an epipodophyllotoxin used in testicular and lung cancers, the CV of the AREA UNDER THE CURVE (AUC; see BOX 1) for oral versus intravenous administration was 58% and 28%, respectively⁵. High pharmacokinetic variability can limit the use of oral agents when cure is the goal and subtherapeutic dosing is unacceptable. Etoposide is uniformly administered intravenously when used for testicular cancer, a curable malignancy even when metastatic, to ensure adequate drug exposure.

Absorption from the gut is governed by absorptive surface area, transit time through the gut, blood flow to the site of absorption, and gastric and intestinal pH^{6,7}. Because these factors can vary between patients and within a patient, they are all potential sources of pharmacokinetic variability. In addition, anticancer drugs are subject to intestinal transport and metabolism.

Intestinal drug transport and P-glycoprotein. P-glycoprotein (P-gp), a drug-efflux pump encoded by *ABCB1*, confers a multidrug-resistance phenotype to cancer cells by actively extruding drugs out of tumour cells^{8–12}. It is also expressed in the intestinal epithelium, where it might impede the oral uptake of anticancer drugs^{13,14}. Studies have shown that the absorption of oral paclitaxel, a taxane used to treat breast and lung cancers, is substantially increased in P-gp-knockout mice compared with wild-type mice, and that P-gp knockouts have a 6-fold higher AUC^{14,15}. Concomitant administration of P-gp inhibitors increases the oral bioavailability of paclitaxel in murine models^{16–20}. As we discuss below, this strategy has also been explored in human trials.

These observations indicate that variation in P-gp activity can lead to variation in drug pharmacokinetics, and recent research has focused on the differential expression of P-gp due to POLYMORPHISMS in *ABCB1* (REFS 21–24). In a study of 461 white volunteers, the allelic frequency of the 3435C>T (C to T change at nucleotide 3,435) polymorphism was 0.54, and 29% of the participants were homozygotes²⁵. This

THERAPEUTIC INDEX

Conceptual description of the ratio of the toxic dose to the therapeutic dose of a drug, describing the dose range over which a drug is therapeutic but not unacceptably toxic.

COEFFICIENT OF VARIATION

The ratio of the standard deviation to the mean, multiplied by 100%. A high coefficient of variation means high interindividual variability.

BIOAVAILABILITY

The fraction of an administered dose that reaches systemic circulation.

FIRST-PASS EFFECT

The decrease in bioavailability of an oral drug owing to enteric metabolism, hepatic metabolism and excretion before the drug reaches the systemic circulation.

AREA UNDER THE CURVE (AUC).

The area under the curve in a graph of plasma concentration against time — a measure of drug exposure.

POLYMORPHISM

The presence of two or more alleles with a frequency of at least 1% in the general population at the same gene locus.

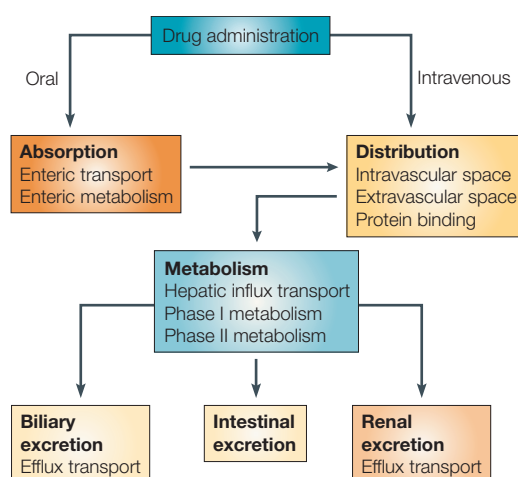


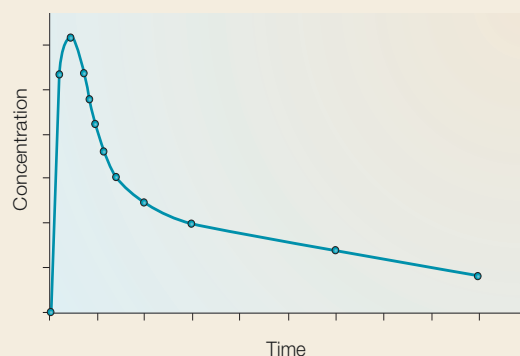
Figure 1 | The process of drug disposition. The process of drug disposition can be divided into four parts — absorption, disposition, metabolism and excretion — and each part has several steps within it. Interindividual and intraindividual differences in these steps are potential sources of pharmacokinetic variability.

Box 1 | The commonly reported pharmacokinetic parameters for anticancer drugs

The minimal data required to characterize a drug's pharmacokinetics are the route of administration, dose administered, dosing interval, plasma drug concentrations, and collection times relative to drug administration. The area under the curve (AUC) in a graph of plasma concentration against time, is a measure of drug exposure (see figure). The measure of the body's ability to remove drug from the blood or plasma, referred to as clearance, is the ratio of dose administered to AUC.

The period of time required for the plasma concentration of a drug to be reduced by one-half is the drug's half-life. For most drugs, half-life is not constant, but initially falls rapidly and then decreases slowly. The initial fall is due to drug distribution to extravascular sites, whereas the slower rate of decrease, representing the terminal half-life, is a function of drug elimination. It is the terminal half-life that determines the dosing interval, with more frequent administration for drugs with short terminal half-lives. As a general rule, the higher the clearance, the shorter the half-life.

The body can be represented as a collection of separate compartments (for example, vascular, interstitial and intracellular) in which a drug distributes at different concentrations. The volume of distribution is the apparent volume required to account for all of the drug in the body if it were present throughout the body in the same concentration as in the plasma. This volume does not have a strict physiological basis but is a proportionality factor between the concentration of drug in the plasma, which is the only compartment accessible to sampling, and the total amount of drug in the body.



polymorphism is correlated with intestinal P-gp protein expression levels and the oral bioavailability of the non-cancer drugs digoxin, used for heart conditions, and phenytoin, an anticonvulsant^{21,23,26}. However, the putative importance of *ABCB1* polymorphisms in anticancer-drug pharmacokinetics remains controversial, with contradictory findings in the published literature and the positive studies consisting of small sample sizes. Nonetheless, this is an emerging area of investigation, as researchers attempt to explain the observed interindividual differences of orally administered drugs. Other intestinal drug-transport proteins that have been described include the products of *ABCC2* and *ABCG2* (REFS 27,28).

Intestinal drug metabolism and CYP3A. As part of the first-pass effect, orally administered drugs are subject to intestinal metabolism. CYP3A is a major subclass of the CYTOCHROME P450 ENZYMES and is located in both the liver and gut. Members of the CYP3A family account for more than 70% of intestinal cytochrome p450 expression^{29,30}. CYP3A4 is localized to the apex of mature enterocytes, adjacent to the microvillus border, and is the predominant P450 enzyme in the intestines^{29–35}. Kolars and colleagues performed an elegant experiment in which they administered cyclosporine, a CYP3A4 substrate, directly into the small bowel of two patients during the anhepatic phase of liver transplantation surgery³⁶. By measuring drug metabolite levels in the portal venous blood, they found that as much as 50% of cyclosporine was metabolized by enterocyte CYP3A4, demonstrating that intestinal metabolism can comprise a significant portion of the overall metabolism of a drug.

The potential for interindividual variability in CYP3A4 activity was shown by a study of 20 patients who underwent small-intestine biopsies³⁷. Investigators found an 11-fold variation in CYP3A4 protein content and an 8-fold variation in mRNA levels. Hepatic CYP3A4 is involved in the metabolism of many different anticancer drugs (for example, the taxanes, etoposide, irinotecan, ifosfamide, imatinib and the *Vinca* alkaloids). Therefore, CYP3A4 polymorphisms might have important consequences for the pharmacokinetics of oral agents. However, for anticancer agents, a statistically significant correlation between genetic variation in CYP3A4 and drug pharmacokinetics has not yet been described.

Although CYP3A4 and CYP3A5 have overlapping substrate specificity, the relative importance of CYP3A5 in intestinal metabolism of anticancer drugs is less clear. Although an early study of small-intestinal CYP3A expression reported its presence in most of the 20 patients examined³⁷, a more recent study of 10 human small intestines failed to detect any CYP3A5 protein³⁸. At the very least, this indicates that CYP3A5 expression in the small bowel is variable. As a result, oral agents that are significantly metabolized by this enzyme in the gut might display interpatient variation in bioavailability.

Drug distribution

Following absorption or intravenous administration, a drug distributes from the intravascular space to its target in the extravascular space. Most drugs bind to plasma proteins, such as albumin and α_1 -acid glycoprotein. The amount of drug that moves to the extravascular space depends, in part, on how much drug is bound — protein-bound drug is not free to

CYTOCHROME P450 ENZYMES
A family of haeme-containing intracellular oxidizing enzymes that are responsible for the first phase of metabolism of many drugs.

Box 2 | **Linear versus non-linear pharmacokinetics**

Drugs have either linear or non-linear pharmacokinetics. Linear pharmacokinetics means that the area under the curve (AUC) is directly proportional to dose. Therefore, a doubling of the dose results in a doubling of the AUC. Other characteristics of linear pharmacokinetics are a half-life that is independent of concentration and a clearance that is independent of dose and dosing interval. Therefore, AUC is not affected by changes in the administration interval. For example, the AUC after a 75 mg/m² dose equals the total AUC for three daily doses of 25 mg/m². The AUC would be the same if the 75 mg/m² were given continuously over 72 hours.

Non-linear pharmacokinetics commonly implies that some aspect of the pharmacokinetic behaviour of the drug is saturable^{132,133}. This can be due to saturation of drug transport or metabolic systems and is recognized by a decrease in drug clearance at higher doses. The implication of non-linear pharmacokinetics is that AUC will vary with dose and dosing interval. For example, at higher doses of 5-fluorouracil, used in colorectal cancer, there is saturation of the enzyme that converts it to the inactive dihydrofluorouracil by dihydropyrimidine dehydrogenase^{134–136}, so that a doubling of the dose from 7.5 mg/kg to 15 mg/kg results in a 135% increase in AUC⁷. Therefore, the behaviour of drugs with non-linear pharmacokinetics is not as predictable as that of drugs with linear pharmacokinetics.

distribute and only 'free' drug is pharmacologically active. Because protein binding is usually a saturable process, differences in plasma protein levels between patients will result in variable drug distribution^{39–41}. In cancer patients, malnutrition and hepatic dysfunction due to liver metastases commonly lead to hypoalbuminaemia. For a highly bound drug, the same dose results in higher levels of unbound drug in the hypoalbuminaemic patient than in a patient with normal synthetic function. Alternatively, an inflammatory condition can lead to increased protein binding due to increased levels of α_1 -acid glycoprotein and other acute-phase reactants⁴². Therefore, differences in medical condition among patients and within patients over time can lead to variability in the volume of distribution. However, in spite of the potential impact of protein binding on volume of distribution, there is a general consensus that changes in plasma protein binding does not result in clinically important pharmacokinetic changes for most drugs.

Drug metabolism

Metabolism is the most crucial and complex step of drug disposition and can be a major source of pharmacokinetic variability. Hepatic uptake of drugs is mediated by transporter proteins. Once in the liver, anticancer drugs undergo phase I and phase II reactions. Phase I reactions are oxidative or reductive reactions and result in the loss of pharmacological activity or the activation of inactive PRODRUGS. Phase II reactions conjugate phase I products to form usually inactive polar derivatives for renal and biliary elimination. Many of the genes that encode drug transporters and phase I and II enzymes are polymorphic, and as such are candidate sources of interindividual pharmacokinetic variability. Few identified polymorphisms to date have been shown to alter the pharmacokinetics of anticancer drugs, but we describe some examples below.

Hepatic drug uptake. The members of the organic anion-transporting polypeptide (OATP) transporter families transport drugs and their metabolites from the blood into the hepatocytes. A recent review has

compiled the currently known OATP genetic polymorphisms⁴³. Although none of these have yet been found to have clinical or pharmacokinetic consequences in humans with regard to anticancer agents, there is a pertinent example from outside oncology: an *in vivo* study of 120 healthy Japanese individuals given pravastatin, a lipid-lowering agent, demonstrated that individuals with the variant allele *SLCO1B1*15* of the transporter gene *SLCO1B1* had lower clearance values than those who were homozygous for *SLCO1B1*1b* (REF. 44). We are currently analysing the results of a PHARMACOGENETICS trial in which 65 patients receiving irinotecan underwent genotyping of relevant OATPs to determine if observed interindividual differences in irinotecan clearance can, at least in part, be explained by OATP polymorphisms.

Phase I metabolism. Phase I metabolism is dominated by the cytochrome P450 system, and more than 55 cytochrome P450 isoenzymes have been identified in humans. The important isoforms for anticancer drugs are CYP1A, CYP2B, CYP2C and CYP3A (REF. 45). CYP3A proteins are involved in the metabolism of 45–60% of all used drugs^{46,47}, and CYP3A4 accounts for most CYP3A in the liver^{48,49}. As is the case in the small intestine, CYP3A5 is not uniformly present in human livers and might be expressed in only 25–30% of people^{37,48,50}. The pharmacokinetic and clinical consequences of this observation are unknown, though one can expect that if a particular drug is extensively metabolized by this enzyme, then the clearance will manifest a high CV.

Cancer patients can have reduced cytochrome P450 activity compared with healthy individuals. CYP2C19, which is involved in the metabolism of the chemotherapeutic agent cyclophosphamide used in lymphoma and breast cancer, has reduced activity in patients with advanced cancer compared with a healthy reference population⁵¹. This difference cannot be explained by genetic differences between the two groups. In study of CYP3A activity in patients with advanced cancer, researchers noted a 14-fold variation in enzyme activity within this population, again not

PRODRUGS

Pharmacologically inactive derivatives of active drugs that must undergo metabolic conversion to the active agent.

PHARMACOGENETICS

The study of genetically determined variations in drug response.

Box 3 | Sources of ADME pharmacokinetic variability in cancer

Below are common sources of pharmacokinetic variability arranged according to the steps of absorption, distribution, metabolism and excretion (ADME) that they most affect. Prescribers should consider these variables when evaluating the potential for unexpected or unwanted outcomes when treating with anticancer agents.

Absorption

- Previous surgery, radiation or chemotherapy
- Nausea and/or vomiting
- Patient compliance
- Diet
- Genetic differences in intestinal drug-metabolizing and drug-transport systems
- Concomitant medications

Distribution

- Amount of body fat
- Presence of extravascular fluid collections (for example, PLEURAL EFFUSION)
- Hypoalbuminaemia
- Concomitant medications

Metabolism

- Hepatic dysfunction
- Altered hepatic blood flow (age-related changes)
- Genetic differences in hepatic drug-metabolizing and drug-transport systems
- Concomitant medications

Excretion

- Hepatic dysfunction
- Renal insufficiency
- Urinary pH
- Genetic differences in drug-elimination pathways
- Concomitant medications

explained by genetic polymorphisms⁵². The reason for these differences are not obvious, but hypotheses include increased levels of cytokines, impaired liver function and increased inflammatory response^{42,53–55}. These cancer-related effects can contribute to the interpatient pharmacokinetic variation of agents that are substrates of these enzymes.

Other phase I enzymes include ketoreductase, aldehyde dehydrogenase, carboxylesterases, dihydropyrimidine dehydrogenase (DPD) and cytosine deaminase. Many of these are polymorphic with described consequences for non-cancer agents, but in anticancer therapy the best-known example of a phase I functional variant is DPD deficiency. This enzyme is rate-limiting in the catabolism of 5-fluorouracil (5-FU), a standard colorectal chemotherapy, and is responsible for the degradation of 80–90% of the drug to an inactive metabolite⁵⁶. Out of 19 DPD variant alleles associated with decreased enzyme activity, a G to A point mutation in the splice donor site flanking exon 14 appears to be the most common, with an estimated frequency of 0.0091 in Caucasians^{57,58}. This mutation results in a truncated protein product and reduced activity, severely so in homozygotes⁵⁹. The pharmacokinetic consequences of DPD deficiency are decreased clearance and

increased half-life of 5-FU. Clinically, low levels of DPD have been associated with severe 5-FU-induced toxicity, including diarrhoea, neutropaenia and death^{59–62}. The low frequency of this mutation, however, makes pre-treatment screening impractical in clinical practice.

Phase II metabolism. For anticancer agents, one well-studied phase II conjugation reaction is glucuronidation, which is catalysed by uridine diphosphate glucuronosyltransferases (UGTs)⁶³. Many of these enzymes are polymorphic and these variants can have pharmacokinetic consequences. For example, gene transcriptional efficiency is inversely correlated with the number of TA repeats in the TATA box of *UGT1A1* (REF. 64), and we have reported on the pharmacokinetic impact of this *UGT1A1* polymorphism in a phase I study of irinotecan⁶⁵. In that study, we found that the AUC for SN-38, the active metabolite of irinotecan, is directly correlated with the number of TA₇ (7 TA repeats) alleles ($P=0.03$) so that TA₇ homozygotes had the highest AUC values and a mean AUC that was 1.6 times greater than that of TA₆ homozygotes. Clinically, these patients also had a significantly higher risk of severe neutropaenia. As the TA₇ allele exists at a frequency of 0.29, genetic screening in this instance might indeed be practical.

Drug excretion

The main routes of drug excretion are through the biliary tract and kidneys. Excretion of anticancer agents through the lungs, skin, sweat and tears is quantitatively negligible.

Biliary excretion. A range of transport systems are involved in the biliary excretion of drugs, including the ATP-binding cassette (ABC) transporters ABCB1, ABCC2 and ABCG2. ABCB1 is involved in the transport of AMPHIPATHIC and lipid-soluble drugs, whereas ABCC2 is mainly involved in the secretion of conjugated metabolites. The role of ABCG2 has not been fully characterized. Catalogues of ABC-transporter polymorphisms have been published^{66–70}, and these are all potential sources of pharmacokinetic variability. ABCB1, ABCC2 and ABCG2 seem to be involved in the transport of SN-38 from the liver into the biliary tree^{71,72}, and we are actively involved in the discovery of polymorphisms that affect irinotecan pharmacokinetics.

Concomitant medications and disease processes affecting the liver can negatively affect these transport mechanisms and reduce biliary excretion of anticancer drugs. For example, mechanical obstruction of the biliary tree by hepatic metastasis can interfere with biliary excretion, and the fall in serum albumin associated with malnutrition has been associated with decreased biliary excretion of anticancer drugs^{73–76}. Cancer patients occupy the entire spectrum of hepatic function, from unaffected to frank liver failure, and this invariably results in pharmacokinetic variability.

PLEURAL EFFUSION

An abnormal collection of fluid between the thin layers of tissue (pleura) lining the lung and wall of the chest cavity.

AMPHIPATHIC

Containing both hydrophilic and hydrophobic domains.

Renal excretion. Some anticancer drugs, such as platinum compounds, are eliminated primarily through the kidneys. Diseases that cause renal insufficiency, as gauged by the GLOMERULAR FILTRATION RATE (GFR), reduce the clearance of these drugs. The GFR decreases with age and can also be altered by nephrotoxic drugs. For example, the coadministration of non-steroidal anti-inflammatory pain medications, such as aspirin and ibuprofen, with cisplatin, a platinum agent used in bladder and testicular cancer, has had lethal effects⁷⁷, presumably by reducing cisplatin clearance. Urinary pH can also influence drug excretion. For example, the administration of sodium bicarbonate makes urine more alkaline and this increases the excretion of methotrexate⁷⁸, an antifolate analogue used in leukaemia, lymphoma and breast cancer. Concomitant medications, vitamins or foods that alter urinary pH can also affect renal drug excretion.

Other sources of pharmacokinetic variability

Age. Age-related changes in drug disposition (TABLE 1) can make age a significant pharmacokinetic variable. This is important because there is an 11-fold greater incidence of cancer in persons 65 years of age or older, and more than 60% of all cancers diagnosed are in individuals in this age bracket⁷⁹. These changes can be subtle and are not reflected in routine blood tests. For example, the metabolic changes described in TABLE 1 will not alter standard liver-function tests (such as serum aspartate aminotransferase and alanine aminotransferase) so that age-related hepatic dysfunction might go unrecognized, putting the patient at risk of overdose. There are currently no guidelines as to when anticancer dosing should be adjusted for age, and clinical trials directed at the elderly are required.

Prescription drug interactions. As we have already alluded to, drug–drug interactions can affect every step of drug disposition. An oncologist must not only consider the impact of the patient's prescription medication list as they decide on anticancer-drug dosing, but must also consider the possible pharmacokinetic and therapeutic consequences every time he/she prescribes a new drug. A recently described example of a drug–drug interaction with potential therapeutic implications is that of tamoxifen, a selective oestrogen-receptor modulator used in breast cancer therapy, and selective serotonin reuptake inhibitor (SSRI) antidepressants (examples include paroxetine and fluoxetine). Tamoxifen and SSRI antidepressants are both metabolized by CYP2D6.

Tamoxifen is used in breast cancer therapy in both the metastatic setting and adjuvant setting (when cure is the goal) and for the prevention of breast cancer in high-risk women. A frequent side effect of therapy is hot flashes, for which SSRI antidepressants are commonly prescribed. Investigators reported the results of a prospective clinical trial of 80 breast cancer patients beginning tamoxifen therapy⁸⁰. After 4 months of treatment, 29% of patients were taking SSRI antidepressants. Mean plasma concentrations

of endoxifen, an active metabolite, decreased by 56% with paroxetine coadministration ($P=0.02$). Moreover, reductions in endoxifen concentrations were statistically more pronounced in patients with variant as compared with wild-type *CYP2D6* genotype. Although it is not known at present whether lower endoxifen concentrations have a clinical consequence, these data raise the question of whether concomitant administration of SSRI antidepressants to reduce the side effects of tamoxifen might actually jeopardize a patient's therapy.

Herbal and vitamin supplements. There is increasing concern over the risks associated with herbal medicines and nutritional supplements when used in combination with chemotherapy. Because they are not regulated by the United States Food and Drug Administration, little is known about their pharmacology. The increased use of these products by cancer patients over recent years⁸¹ and the perceived absence of risk can have unexpected pharmacokinetic and toxic effects. For example, St John's wort (*Hypericum perforatum*) is a known ligand for the pregnane X receptor (PXR) and can therefore induce the transcription of genes regulated by PXR, including CYP3A and UGTs^{82–85}. The use of St John's wort decreases plasma concentrations of the active metabolite SN-38 in irinotecan-treated patients, prompting concerns that the efficacy of irinotecan might be reduced⁸⁶. Patients who take herbal remedies that might cause unwanted interactions are now routinely excluded from cancer clinical trials. The unknown affects of these products on anticancer therapy should prompt government regulation to, at the very least, standardize the impact of herbal remedies on patients undergoing cancer treatment.

Food. Foodstuffs can also interfere with drug pharmacokinetics. The best-described example of this is grapefruit juice, which decreases the intestinal activity of CYP3A4 (REFS 87,88). As a result, the oral bioavailability of drugs that are subject to enteric metabolism by this enzyme might be augmented by concomitant (or even previous) use of grapefruit juice. This interaction can be viewed as positive for oral anticancer drugs that otherwise have low bioavailability. However, the use of grapefruit juice can also cause unexpected and toxic drug exposure. Pharmacokinetic trials of oral anticancer agents routinely prohibit the use of grapefruit juice.

Ethnicity. Differences in drug pharmacokinetics across ethnic groups have been observed for non-anticancer agents; one well-described example is the increased oral clearance of drugs that are CYP3A and/or P-gp substrates in African Americans compared with Caucasians^{89–92}. However, similar ethnic differences have not yet been demonstrated for anticancer drugs. A clinical trial of docetaxel, which is a substrate for CYP3A4, CYP3A5 and P-gp, in Caucasian and African-American patients failed to show any difference in docetaxel pharmacokinetics

GLOMERULAR FILTRATION RATE
A measure of renal function that equals the quantity of glomerular filtrate formed per unit of time in all nephrons of both kidneys.

Table 1 | **Age-related changes that affect absorption, distribution, metabolism and excretion**

Change	Impact on drug pharmacokinetics	References
Absorption		
Reduced gastric-acid secretion; reduced splanchnic blood flow; reduced gastrointestinal motility; concurrent use of many drugs (polypharmacy)	All can potentially reduce drug bioavailability. The multiple concomitant drugs taken by elderly patients can compete for binding sites on transporter proteins or change pH. Effects of age-related changes on absorption are unclear.	137–140
Distribution		
Increased proportion of body fat; reduced intracellular water; reduced plasma albumin; anaemia; polypharmacy	Between ages of 25 and 75 years, fat content increases from 15% to 30% of body weight and intracellular water is reduced from 42% to 33%, causing a reduction in Vd of water-soluble drugs and an increase in Vd of lipid-soluble drugs. Anaemia is a risk factor for increased toxicity of red-cell-bound drugs. A decrease of up to 15–20% in plasma albumin can increase the free fraction of drug.	141–145
Metabolism		
Reduced liver mass; reduced cytochrome P450 activity; polypharmacy	Autopsy studies indicate that the mass of the liver is reduced by 20–50% by 80 years of age, thereby decreasing the amount of metabolic enzymes. Phase I metabolism is reduced, with 30% less activity of several members of the P450 system in healthy older people compared with healthy younger people. Phase II metabolism is preserved.	145–147
Excretion		
Reduced hepatic blood flow; reduced renal blood flow; reduced GFR/CrCl; polypharmacy	Hepatic excretion of drugs can be negatively impacted by a reduction in blood flow to the liver. Loss of nephron mass with age is predictable, with a reduction in GFR by 1 ml/min for every year over the age of 40 years. A reduction in GFR is not reflected by an increase in serum creatinine, and calculated estimates of CrCl in the elderly might not be accurate.	148–150

CrCl, creatinine clearance; GFR, glomerular filtration rate; Vd, volume of distribution.

or drug-induced myelosuppression between the two groups⁹³. Nonetheless, the observation of ethnic differences in outcomes after anticancer drug therapy could prompt the discovery of functional polymorphisms when there are ethnic differences in the allelic frequencies of important drug-disposition genes.

Strategies for dose individualization

Dose individualization is the best method of reducing interindividual variability. The traditional practice of normalizing dose to BSA takes into account only two of a multitude of variables — height and weight. Although BSA has been found to correlate statistically with the pharmacokinetics of a few anticancer agents (such as docetaxel⁹⁴ and paclitaxel⁹⁵), for most agents it has not. Dose normalization to BSA only makes sense when there is a statistically significant relationship between pharmacokinetics and BSA and when that relationship explains a substantial portion of the interpatient pharmacokinetic variability.

Pharmacokinetic-based dosing. Dosing schemes that are driven by the pharmacokinetic properties of a drug can be useful for individualizing dose. The classic example is carboplatin, an analogue of cisplatin that is used in lung and ovarian cancer. When it was first introduced, its dosing was based on BSA. However, clinicians quickly realized that some

patients were being underdosed, whereas others experienced unexpected toxicity⁹⁶. A strong correlation was found between carboplatin clearance and GFR (correlation coefficient, $r=0.85$), which led to the formula that is currently used: $\text{dose} = \text{AUC} \times (\text{GFR} + 25)$, where AUC is chosen (based on clinically established disease-specific AUC targets) and the patient's GFR is calculated^{97,98}. Dosing of carboplatin based on this formula is now routine.

Alternatively, initial treatment doses can be used to establish the individual's pharmacokinetics for that drug, on which subsequent doses are based. Such a scheme has been used for oral busulfan, an alkylating agent that is used in leukaemia therapies, which has linear kinetics (BOX 2) but high interindividual variability. Pharmacokinetic-based dosing of this sort is appropriate for busulfan, for which there is not only a correlation between AUC and hepatic VENO-OCCLUSIVE DISEASE (VOD), but also between AUC and recurrence rates after allogeneic bone-marrow transplant^{99–103}. However, this strategy still suffers from the risk of subtherapeutic and supratherapeutic dosing during the initial doses. A paediatric study of busulfan circumvented this problem by administering a test dose before definitive dosing¹⁰⁴. Twenty-nine patients who were to undergo busulfan-based chemotherapy first received a small test dose of 0.5 mg per kg of body weight. Test dose AUCs were

VENO-OCCLUSIVE DISEASE

A complication of bone-marrow transplantation in which there is obstruction of the terminal venules and/or sinusoids in the liver. Clinical features include hyperbilirubinaemia, painful hepatomegaly and fluid retention.

determined, and definitive doses were calculated by multiplying 0.5 mg/kg by the ratio of the target AUC to the test-dose AUC. The investigators demonstrated that the actual AUC of the definitive dose was within 80–120% of target AUC in 83% of patients and within 90–110% in 52%. The incidence of VOD was 3.4% in the test group versus 24.1% in a control group (that had been treated with standard doses). This strategy has been accepted as standard of care in some academic institutions.

Genotype-directed dosing. The goal of pharmacogenetics is to identify patients who are at risk for poor outcome to drug treatment. Pharmacogenetics can also identify those patients who will have favourable pharmacokinetics that allow them to tolerate higher-than-standard doses with possible increased antitumour effect. For example, variation in the *UGT1A1* gene correlates with irinotecan toxicity (see section on phase II metabolism)⁶⁵. Homozygosity for the TA_7 allele has been identified as a high-risk genotype for high SN-38 AUC and toxicity, whereas TA_6 homozygotes are low-risk. It is reasonable to expect that this second group will tolerate higher, and perhaps more efficacious, doses. We are currently planning a clinical trial in colorectal cancer patients to determine whether this is the case. As more drug-disposition polymorphisms are discovered, pathway-based models can be created, as it is more likely that a combination of polymorphisms in several disposition proteins is more important than a single variant. A patient could then undergo relevant genotyping before treatment and be dosed according to the results.

Phenotype-based dosing. As we have discussed, a clear relationship between genetic polymorphisms and enzyme activity has not yet been established in most cases. For this reason, researchers are exploring phenotype-based dosing as a surrogate. For example, investigators have developed a novel method of estimating the interpatient variability of CYP3A4 by measuring the urinary metabolite of exogenous cortisol¹⁰⁵. Urinary 6- β -hydroxycortisol (6- β -OHF) is significantly correlated with the clearance of docetaxel, which is metabolized by CYP3A4. In a clinical trial of docetaxel in 59 patients with non-small-cell lung cancer, patients were randomized to either a conventional BSA-based dosing group or an individualized dosing group¹⁰⁶. In the second group, estimated clearance was calculated based on the individual's measured 24-hour urinary 6- β -OHF after an administered dose of cortisol, and docetaxel dose was calculated as the product of the estimated clearance and a previously determined target AUC. The standard deviation of the AUC was significantly smaller in the individualized group compared with the BSA-based group ($P < 0.01$). Although this particular method of dosing is cumbersome, it does demonstrate the potential of this approach for reducing interpatient pharmacokinetic variability.

Population pharmacokinetic modelling. Population pharmacokinetics is the study of the variability in plasma drug concentrations between individuals who receive standard dosage regimens and who represent the target patient population. Population pharmacokinetic models aim to account for observed interindividual variation in terms of patient variables called covariates. These covariates can include any sources of variability. Population modelling allows the quantification of the relative importance of the covariates; Bayesian estimation, which evaluates the individual's data relative to the population pharmacokinetic model, can then be used to estimate patient-specific pharmacokinetic parameters to calculate an optimal dose for the individual. A detailed description of modelling methods is beyond the scope of this review, but several comprehensive discussions are available in the literature^{107–110}.

Epirubicin, an anthracycline used in breast cancer therapy, exemplifies how population modelling can lead to dose individualization. Because epirubicin is predominantly cleared by the liver, its pharmacokinetics are altered (specifically, clearance is reduced) in patients who have hepatic dysfunction, and this can result in severe toxicity with standard doses. The current product label recommends dose reduction based on serum BILIRUBIN levels (as a surrogate measure of hepatic function)¹¹¹. These recommendations are not based on data, as patients with hepatic dysfunction were excluded from the original dosing studies. For this reason, Ralph and colleagues used a population modelling approach to develop new dosage guidelines that are better tailored to the patient¹¹². Based on a data set of 109 breast cancer patients treated with epirubicin, of whom 72 were known to have liver metastases, the authors developed a population pharmacokinetic model, with clearance as the predicted parameter and serum aspartate aminotransferase (AST; a standard blood test for liver function) as the most relevant covariate: clearance (in litres (l) per hour (h)) = $72.9 - (72.9 \times 0.135 \times \ln(\text{AST}))$. Other covariates, including bilirubin, did not improve the model. With this formula and a measured AST, a patient's epirubicin clearance can be predicted. Then, using the relationship $\text{AUC} = \text{dose}/\text{clearance}$ and a target AUC of 4000 nanograms•h/ml, based on published toxicity data¹¹³, the oncologist can calculate a safe but effective dose that is individual to the patient. Despite impressive data indicating that models such as this one can improve dosing, these models have, in general, not been adapted in clinical practice, and prospective studies will be required to demonstrate the efficacy of such a strategy.

Pharmacokinetic modulation

Pharmacological inhibitors of key metabolic and transporter enzymes can be used to enhance the activity of drugs and reduce interindividual variability. This strategy has been most thoroughly studied with paclitaxel. Oral administration of paclitaxel allows for chronic continuous dosing, and both non-clinical and clinical studies have indicated that prolonged drug

BILIRUBIN

A breakdown product of haeme that circulates in the plasma, is taken up by the liver and conjugated so that it is water soluble, and is then excreted in the bile. It is routinely measured as a blood test to assess liver function.

exposure improves drug activity^{114–116}. However, as we discussed earlier, low bioavailability owing to the efficient transport by P-gp^{14–20,117,118} limits paclitaxel's clinical usefulness. In a Phase I study, coadministration of the P-gp inhibitor cyclosporine increased the apparent bioavailability of oral paclitaxel 8-fold, from 4% to 47%¹¹⁷. The investigators speculated that in addition to P-gp inhibition, drug exposure was further improved by the concomitant inhibition of hepatic and intestinal CYP3A4 by cyclosporine. Phase II studies of the combination of oral paclitaxel and cyclosporine in non-small-cell lung cancer¹¹⁹ and gastric cancer¹²⁰ showed acceptable antitumour efficacy with overall response rates comparable to other single-agent studies in these diseases^{121–126}.

Cyclosporine also inhibits the biliary excretion of irinotecan metabolites¹²⁷, and as part of a dose-escalation study, 41 colorectal cancer patients were treated with irinotecan every 2 weeks both with and without oral cyclosporine¹²⁸. Twenty patients underwent pharmacokinetic sampling during both treatments, and investigators demonstrated significant increases in irinotecan, SN-38 (active metabolite) and SN-38G (inactive metabolite) AUCs and marked reduction in irinotecan clearance (5.8 l/h/m² versus 13.4 l/h/m²). Indeed, the effect of adding cyclosporine to 100 mg/m² irinotecan was to bring the AUC in line with previously published values of AUC for 250 mg/m² standard-dose irinotecan alone, demonstrating that similar drug exposure can be obtained with a 60% lower dose. At current average wholesale prices in the United States, the approximate cost for the recommended doses of cyclosporine and irinotecan for a 1.8 m² patient per 2-week cycle is US\$1,134 versus \$1,553 for irinotecan 250 mg/m². In light of the high cost of chemotherapy, this example demonstrates a practical method of cost savings without compromising treatment.

Clinical trial design

Traditionally, Phase I pharmacokinetic studies of new anticancer agents aim to establish the Phase II recommended dose using the smallest sample size possible (usually 1–6 patients per dose level). If the true interindividual pharmacokinetic variability of a drug is high, the chances of observing that variation are low with such small patient samples. However, as the number of patients treated with the drug increases through Phase II and III studies, patients with extreme pharmacokinetics are eventually captured, but without correlative pharmacokinetic data to explain their unexpected clinical outcome (such as severe toxicity due to low drug clearance). This can be avoided by enrolling extra patients in the Phase I pharmacokinetic study at the dose that will be carried forward into Phase II and III trials to better understand the relationship of pharmacokinetic variability to toxicity and potential biomarkers. Although some investigators have adopted this practice, in general pharmaceutical companies are reluctant to invest the additional money and clinical-trial time, as doing so is not a regulatory requirement.

The recognition of significant interindividual variability should also prompt the consideration of expanding pharmacokinetic analysis into later-phase studies. Because the typical Phase I population consists of patients with advanced cancer whose disease is refractory to standard therapy, toxicity, and not efficacy, is the only expected clinical outcome in Phase I trials. Pharmacokinetic variability can best be correlated with efficacy by performing pharmacokinetic analyses in Phase II and III trials, in which efficacy is a defined end point.

The randomized concentration-controlled trial (RCCT) recognizes the relationship between variability in pharmacokinetics and variability in drug effect¹²⁹. In contrast to traditional randomized dose-controlled trials, in which drug effects to different drug dosages are measured, RCCTs assign individuals to concentration ranges. The relationship of concentration to effect is then analysed. Instead of retrospectively observing concentrations at pre-specified doses, the investigator controls concentration by adjusting dose. A recent trial of topiramate, an antiepileptic agent, demonstrates its potential value for defining the relationship between plasma concentration and response¹³⁰. The general concept of the RCCT could be incorporated into early dose-finding trials of anticancer drugs in which patients are not assigned to dose levels but to concentration levels.

Future directions

Recent advances in our understanding of cancer biology have led to the development of many new drugs. However, we must recognize the difficulties in translating an exciting compound into an efficacious drug that can be administered to a diverse population of patients. There are many steps between ingestion (or injection) and action on the target, with many sources of pharmacokinetic variability that can obscure the activity and efficacy of an agent. These sources of variability require careful consideration of the dose-response curve, both in populations of patients and in individual patients.

There needs to be greater attention to the development of pharmacokinetic information in the context of larger cancer clinical trials by collecting DNA samples (from peripheral mononuclear cells) for the genotyping of candidate polymorphisms (or even whole-genome typing) and plasma for population pharmacokinetics. Although there have been extensive studies of the relationship of pharmacokinetic data to clinical outcomes, the greater challenge will be relating genotypic data (particularly if whole-genome typing is used) to variability in both pharmacokinetics and clinical effects. Hopefully this will lead to advances comparable to those achieved with whole-genome microarray profiling to predict response and/or survival in breast cancer, leukaemia and lymphoma. Eventually, we will be able to tailor dosing based on whole-genome typing and, because this typing will be conducted before any foreseeable need for anticancer therapy, the benefits will apply to any type of pharmaceutical intervention¹³¹.

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Appendix VALSECCHI02

Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review

Matías E. Valsecchi · Enrique Díaz-Cantón · Máximo de la Vega · Susan J. Littman

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Abstract

Purpose Over the last couple of years, we have witnessed the availability of a wide variety of different therapeutic agents and the identification of effective combinations of existing ones that have transformed the way we approach and treat pancreatic cancer. Proof of this are the recent validations that combinations of conventional chemotherapy drugs, the FOLFIRINOX regimen and gemcitabine plus nab-paclitaxel, significantly improves clinical outcomes in patients with metastatic disease. However, deeper and more sophisticated understanding of the biology of this cancer as well as the ability to develop better and perhaps more precise drugs predict that the landscape may be changing even more.

Methodology and Results In this review, we will summarize the most recent treatment advances including FOLFIRINOX, gemcitabine plus nab-paclitaxel and discuss novel approaches such as immune-mediated therapies, drugs that disrupt the tumor-stromal compartment, PARP inhibitors for BRCA pathway-deficient pancreatic cancer and new generations of conventional chemotherapeutics, which are in early phases of clinical development and have shown promising early results. We will also discuss some examples of drugs that failed, despite very good preliminary data, in order to appraise the lessons learned from these negative clinical trials. Lastly, we will comment on ongoing adjuvant and neoadjuvant trials.

Conclusion We hope that at least some of these will result in positive trials and add to our armamentarium for treating this challenging malignancy.

Keywords Pancreatic cancer · FOLFIRINOX · Nab-paclitaxel · Gemcitabine · Erlotinib · Gastrointestinal cancer

Introduction

Pancreatic ductal adenocarcinoma (PDA) is undoubtedly one of the most lethal cancers. Survival rates are still poor despite the significant efforts over the years have been devoted to studying this disease. Since the mid 1990s, gemcitabine emerged as the main therapeutic armament to fight this devastating disease; however, its real clinical benefit is a modest 1-month extension in the overall survival (OS; 5.6 vs. 4.4 months) when compared to 5-FU [1, 2]. Nevertheless, these findings were encouraging and the next decade of research involved numerous studies aimed at improving gemcitabine efficacy and testing gemcitabine doublets, resulting in minor improvements in OS.

Although pessimism has reigned for some time regarding the likelihood of achieving substantial clinical improvement in outcomes in PDA, the last few years have witnessed the emergence of a variety of therapeutic strategies that have already changed our daily practice. The first was the verification that a combination of chemotherapy agents (FOLFIRINOX) could improve all the relevant clinical outcomes in patients with metastatic disease [3]. The confluence of a deeper and more sophisticated understanding of pancreatic tumor biology plus the development of better multi-agent combinations we suspect will foretell the availability of additional effective therapies in the near future.

The main objective of this review is to summarize recent therapeutic advances that represent a substantial change in the way we approach PDA in 2013. Pursuing this objective, we will describe the new multi-agent combinations recently FDA-approved, as well as drugs that are in the earlier phases of development and that have shown promising results. Lastly,

M. E. Valsecchi · S. J. Littman (✉)
Department of Medical Oncology, Thomas Jefferson University,
Philadelphia, PA 19107, USA
e-mail: susanlittman@me.com

E. Díaz-Cantón · M. de la Vega
Centro de Educación Médica e Investigaciones Clínicas (CEMIC),
Buenos Aires, Argentina

we will also discuss some examples of approaches that failed, despite good preliminary data, to evaluate the lessons learned from these negative clinical trials.

Recent Treatment Advances Already Available in Clinical Practice

From a clinical perspective, PDA is divided into three main categories: surgically resectable, locally advanced (LA), and metastatic. We often say that surgery offers the only chance of cure in PDA. While this statement is true, the actual cure rate is low—about 3–5 % at 5 years [4]. Thus, advances in the medical treatment are essential to obtain improvements in OS even with early disease.

Three multi-agent chemotherapy regimens have resulted in positive findings: FOLFIRINOX, gemcitabine + nab-paclitaxel, and gemcitabine + erlotinib (Table 1).

FOLFIRINOX

FOLFIRINOX, a regimen composed of four drugs (Folinic acid 400 mg/m², 5-FU bolus 400 mg/m² followed by 48 h infusional 5-FU 2,400 mg/m², Irinotecan 180 mg/m², and oxaliplatin 85 mg/m²) is currently considered a first-line treatment option for metastatic PDA. Prior to the testing of this multi-agent regimen, several trials explored the addition of a second agent to gemcitabine in metastatic disease. Gemcitabine was combined with platinum drugs (pooled analysis, HR=0.85, *P*=0.01), with fluoropyrimidine (pooled analysis, HR=0.90, *P*=0.03) as well as topoisomerase inhibitors (pooled analysis, HR=0.99, *P*=0.80) [2]. The median OS ranged from 6 to 9 months, and the overall effect of adding a second drug was a modest but detectable 10 % (CI: 3–15 %) improvement in OS. This slight improvement in efficacy of gemcitabine doublets was the rationale used by French investigators to study a multi-drug regimen that did not include gemcitabine. They initially conducted a robust Phase II trial demonstrating an impressive 26 % response rate and a median OS of 10.2 months [5]. Based on this and the fact that toxicity although significant was manageable, investigators of the PRODIGE Intergroup designed a randomized Phases II–III clinical trial comparing FOLFIRINOX to single-agent gemcitabine as first-line treatment for metastatic PDA [3]. A number of 342 patients with histologically confirmed metastatic disease and no significant comorbidities were enrolled. The primary endpoint was OS; secondary endpoints were PFS, tumor response (RECIST), safety, and quality of life. The study was closed early when an interim analysis showed a striking 4.3 months prolongation in median OS favoring FOLFIRINOX (11.1 vs. 6.8 months; HR=0.57, *P*<0.001). Median PFS was 6.4 vs. 3.3 months (*P*<0.001) and ORR was 31 % vs. 9.5 % (*P*<0.001). There was also a significant

Table 1 Summary of positive clinical trials that lead to practice changes in metastatic PDA

Intervention	Study description	No. of patients	Comparison	Median OS	Median DFS or TTP	ORR	1-year survival	References
<i>Gemcitabine</i>								
Phase 3	Randomized, multicenter international	160	Gemcitabine vs. 5-Flourouracil	5.65 vs. 4.41 months	9 vs. 4 weeks	5.4 % vs. 0 %	18 % vs. 2 %	Burris H, et al. [1]
<i>FOLFIRINOX</i>								
Phase 2	Single arm; multicenter	47	None	10.2 (8.1–14.4 months)	8.2 (5.3–11.6 months)	26 % (13–39 %)	43 %	Conroy et al. [5]
Phase 3	Phases 2–3, randomized, placebo-controlled, multicenter, international.	342	FOLFIRINOX vs. Gemcitabine	11.1 vs. 6.8 months	6.4 vs. 3.3 months	31.6 % vs. 9.4 %	48 % vs. 20 %	Conroy et al. [3]
<i>Nab-Paclitaxel</i>								
Phase 2	Single arm, open-label, multicenter, phase I/II	67	None	12.2 (8.9–18 months)	7.9 (5.8–11 months)	46 % (N/A)	48 %	Von Hoff et al. [21]
Phase 3	Randomized phase III, multicenter	861	Gemcitabine ± Nab-Paclitaxel or Placebo	8.5 vs. 6.7 months	5.5 vs. 3.7 months	23 % vs. 7 %	35 % vs. 22 %	Von Hoff et al. [22]
<i>Erlotinib</i>								
Phase 3	Randomized, double-blinded, placebo-controlled, international	569	Gemcitabine ± erlotinib or Placebo	6.24 vs. 5.91 months	3.75 vs. 3.55 months	8.6 % vs. 8.0 %	23 % vs. 17 %	Moore M, et al. [25]

increase in grades 3–4 toxicities mainly related to cytopenias, neutropenic fever, diarrhea, vomiting, and peripheral neuropathy (all with $P < 0.01$).

Since the publication of this pivotal clinical trial, many single and multi-institutional studies have been reported confirming the efficacy of this regimen. Two main issues have arisen regarding the general application of these findings. The first pertains to the ability to utilize the entry criteria of the Accord II trial for non-study metastatic PDA patients. To address this, investigators from British Columbia performed a retrospective review of 100 consecutive cases in their database to determine the proportion of “real-world” patients that would have met eligibility. They found that only 26 patients would have been eligible, with the main reasons for exclusion being older age (22 %), poor performance status (64 %), and organ dysfunction (28 %) [6]. The second issue relates to the tolerability of this regimen outside of the highly controlled environment of a clinical trial. “Tolerability” of FOLFIRINOX remains controversial with some reports showing easily manageable side effects [7, 8], while others demonstrate significant toxicity with 32 % hospitalization [9] and treatment discontinuation in one third of the patients [10]. Conscious of these limitations, Mahaseh and colleagues proposed a modified FOLFIRINOX in which the 5-FU bolus was removed and growth factor prophylaxis was used routinely. Authors reported significantly less grade 3–4 toxicity but similar activity [11]. Additionally, in a small retrospective analysis of 35 patients treated at the Yale Cancer Center, 29 (85 %) who received dose-attenuated FOLFIRINOX showed no significant reduction in response rate [12]. These results are reassuring and have enhanced the acceptability of this regimen among general oncologists who frequently adjust drug doses based on the individual patient's performance status. Of concern, however, is the possibility that personal physician modifications effect survival outcomes. This illustrates what is common knowledge today that a minority of metastatic patients are really candidates for FOLFIRINOX. We certainly need better biomarkers to assist us in determining which patients really benefit from this regimen [13].

FOLFIRINOX has also been investigated in earlier stages of disease. Kharofa and colleagues retrospectively evaluated 12 patients with unresectable PDA and who received neoadjuvant FOLFIRINOX followed by concurrent chemoradiation therapy with either gemcitabine or 5-FU. Seven patients (58 %) had R0 resection and the median survival was not reached after 13 months of follow-up [14]. In a similar retrospective analysis of 18 patients with unresectable and borderline-resectable PDA, seven (39 %) were taken to the OR after neoadjuvant FOLFIRINOX, five having R0, one R1 resections and one was not resectable [15]. Toxicity in this population was significant with grades 3–4 toxicities including neutropenia (22 %), neutropenic fever (17 %), thrombocytopenia

(11 %), fatigue (11 %), and diarrhea (11 %). In a second retrospective single-institution experience with FOLFIRINOX followed by chemo-radiation in LA PDA ORR was 27.3 % and median PFS was 11.7 %. While 22 % (5 of 22) were able to undergo R0 resections, the durability of these responses were short with three developing distant metastases after 5 months [9]. Lastly, investigators from the University of Pittsburgh reported that 7 out of 25 patients with unresectable or borderline resectable PDA underwent surgical resection after receiving FOLFIRINOX [16].

Nab-Paclitaxel

Nab-paclitaxel (Abraxane®) is an albumin-bound, 130-nM particle, formulation of paclitaxel administered as a colloidal suspension [17]. This drug was originally developed to overcome the well-known anaphylactic reactions associated with the conventional Cremophor EL formulation of paclitaxel. However, this change in formulation presumably related to the intra-tumoral drug delivery resulted in efficacy improvement in PDA [18]. The molecular mechanism of this therapy enhancement is not fully understood. It was originally thought to be related to high expression of the protein SPARC, which is known to bind albumin, by the tumoral stromal cells. However, recent investigations suggested that an albumin receptor (gp60) on endothelial cells could be involved in transporting paclitaxel into the tumoral interstitial space [19]. Preclinical studies showed that the addition of nab-paclitaxel to gemcitabine increases intratumoral gemcitabine levels due to a marked decrease in the primary gemcitabine metabolizing enzyme, cytidine deaminase, suggesting synergy between these two drugs may contribute to clinical benefit in pancreatic cancer [20].

The first proof of principle that nab-paclitaxel was effective in metastatic PDA came from a Phase I/II trial in which nab-paclitaxel plus gemcitabine was tested in 67 metastatic patients. After reaching a MTD of 125 mg/m², 44 patients completed the Phase II portion of the study showing a median PFS of 7.9 months (95 % CI: 6–11 months), a median OS of 12.2 months (95 % CI: 9–18 months), and a 1-year survival of 48 % [21].

The open label, international, randomized Phase III trial (MPACT study) was initially presented in 2013 at ASCO GI and supports the use of the nab-paclitaxel/gemcitabine combination in metastatic PDA. Investigators randomized 861 patients to either gemcitabine 1,000 mg/m² alone for 7 weeks followed by a rest week vs. nab-paclitaxel 125 mg/m² plus gemcitabine 1,000 mg/m² for 3 weeks followed by a rest week and treated until progression. The primary endpoint was OS and secondary endpoints included PFS, ORR, safety, and tolerability of this combination. The median OS was 8.5 months for the combination vs. 6.7 months for gemcitabine alone (HR=0.72; $P < 0.001$). Moreover, the time

to treatment failure was significantly prolonged with the combination from 3.5 to 5.1 months (HR=0.70; $P<0.001$). 1-year survival was also improved (35 % vs. 22 %, $P<0.001$) [22]. Sub-analysis, presented at ASCO 2013, showed liver metastases and poor PS (KPS<80) predicted the greatest advantage of the combination. Based on this data, the FDA has approved nab-paclitaxel plus gemcitabine as a first-line treatment option for patients with metastatic PDA citing a high unmet need and few effective treatments (announced in September 6, 2013). As in the case of FOLFIRINOX, nab-paclitaxel is being tested in earlier stages of disease [23, 24].

Erlotinib

Erlotinib plus gemcitabine is the only other drug combination that has proven to be of some benefit in a randomized Phase III clinical trial for patients with LA and metastatic PDA. In 2007, Canadian investigators presented the results of the NCI PA.3 study in which 569 patients were randomly assigned to gemcitabine 1,000 mg/m² weekly for 7 weeks followed by a week rest followed by 4-week cycles plus erlotinib 100–150 mg or placebo [25]. Patients were treated until disease progression or toxicity. The results showed a minimal improvement in median OS (6.2 vs. 5.9 months; HR=0.82, $P=0.038$) and an absolute 6 % benefit in 1-year OS (23 % vs. 17 %, $P=0.023$). The study also showed a statistically significant improvement in DFS but no difference in ORR. Patients receiving erlotinib experienced higher frequencies of rash, diarrhea, infection, and stomatitis. There were six protocol-related deaths, all in the arm containing erlotinib attributed to interstitial pneumonitis (2), sepsis (2), neutropenic sepsis (1), and CVA (1). A total of eight patients, seven in the erlotinib group, developed an interstitial lung disease-like syndrome. Since the publication of this clinical trial, there has been significant controversy as to whether the short duration of benefit is balanced by the risks. However, given the lack of effective treatments, the combination did achieve FDA approval in November 2005.

Due to their greater potential for benefit, FOLFIRINOX and gemcitabine plus nab-paclitaxel combination chemotherapy are the preferable options for patients with better performance status and organ function. Notwithstanding, and for reasons not entirely clear, some patients respond unusually well to erlotinib plus gemcitabine. A remarkable observation reported in NCI PA.3 is the association between the development of cutaneous rash and clinical outcome in erlotinib-treated patients. Patients with grade $\geq$ 2 skin rash had a 43 % 1-year survival and 10.5 months median OS in comparison 16 % and 5.3 months for those without rash, respectively ($P<0.001$). Although technically a negative trial, with overall outcomes nearly identical to NCI PA.3, a similar correlation regarding the predictive value of the skin rash was made in an open label Phase II study of erlotinib 100 mg daily and

fixed-dose rate gemcitabine 1,000 mg/m² [26]. Patients with grade $\geq$ 2 rash had a significantly higher chance of treatment benefit (OS 42 vs. 15 weeks, $P=0.03$). The striking similarity in survival between this trial and the NCI PA.3 also suggests that the pharmacokinetic modulation of gemcitabine appears to be of little clinical advantage [27]. In the Phase II RACHEL trial, erlotinib was dose escalated from 150 to 250 mg/day until at least grade 2 skin rash was obtained. Disappointingly, dose escalation did not result in clinical benefit [28].

Novel Therapies in Early Phases of Clinical Development

There are now numerous follow-on trials testing FOLFIRINOX and gemcitabine-nab-paclitaxel in earlier disease stages. Most notably, it is clear that both are effective in LA PDA and the value of radiation in addition to multi-agent chemotherapy is still to be determined. While we wait for these trials to mature it is interesting to also speculate about a number of novel therapies in the pipeline. Caution must prevail when considering these therapies, as encouraging results in early phases of development do not necessarily translate into clinically relevant outcomes, when tested in larger populations or when compared with the standard of care.

Immunotherapy

We have recently witnessed a strong resurgence for immune therapies in cancer treatments. The approval of sipuleucel-T immunotherapy and ipilimumab to treat prostate and melanoma cancers are just two examples [29, 30]. PDA does not seem to be the exception, although due to the aggressive biology of this malignancy immune-based therapies have generally been combined with chemotherapy.

A comprehensive review of the potential tumor-specific antigens as well as the strategies used against PDA can be found on other reviews and is beyond the scope of this overview [31]. Briefly, potential methods of immune activation against pancreatic tumors include: (a) whole-cell vaccines (e.g., genetically modified to over-express a particular epitope); (b) peptide vaccines designed to boost CD 8⁺ cytotoxic T-lymphocyte response; and (c) DNA vaccines in which modified DNA coding for a target antigen is inserted into a vector which is directly taken up into tumoral cells.

Algenpantucel-L immunotherapy, a whole-cell allogenic pancreatic cancer vaccine developed by NewLink Genetics (Ames, IA, USA) is based on the concept of hyperacute rejection that occurs with xenotransplantation. The vaccine is composed of two irradiated human pancreatic cell lines that have been genetically modified to over-express murine $\alpha(1,3)$ -galactosyltransferase resulting in expression of α -galactosyl (α -gal) epitopes on membrane glycoproteins and glycolipids. Since these epitopes are not expressed by human cells an

immediate hyperacute rejection response occurs similar to that observed with transplant rejection. Vaccine exposure results in antibody-dependent cell-mediated cytotoxicity with lysis of cells containing the α -gal epitopes and the consequent development of a strong T-cell mediated anti-tumor immunity. A multi-institutional, open-label, Phase 2 trial was published [32]. A number of 73 patients with resected PDA (R0 or R1) received algenpantucel-L in addition to conventional gemcitabine followed by 5-FU based chemo-radiation, as adjuvant treatment. Primary endpoint was 12-month DFS; secondary endpoints included OS and toxicity. 80 % patients had positive lymph nodes. No significant side effects were reported other than fatigue and local skin reactions. The median DFS was 14 months and the 1-year DFS was 62 %. Median OS was not reached but the 1-year OS was 86 %. Higher vaccine doses resulted in improved DFS (80 % vs. 51 %; $P=0.02$) and OS (96 % vs. 79 %; $P=0.053$) at 12 months. A Phase III clinical trial with similar design and a target of 722 subjects has just completed enrollment.

Other Phase II clinical trials were reported with less encouraging results. Lutz et al. [33] designed a single-institution adjuvant study of 60 patients with resected PDA who received an initial injection of an irradiated GM-CSF transfected whole cell vaccine followed by 5-FU-based chemo-radiation therapy and up to four additional immunizations. Median DFS and OS were 17.3 and 24.8 months, respectively. Overall, the vaccine was well tolerated. A randomized, multicenter, placebo-controlled study with G17DT (Gastrimmune), an anti-gastrin17 immunogen, showed a non-significant improvement in OS compared to placebo in advanced disease [34]. Yanagimoto and colleagues [35] reported a median survival of 9 months with a 1-year survival rate of 38 % in 21 patients with metastatic disease who received a personalized peptide vaccine to HLA in combination with standard weekly gemcitabine.

Stromal Disruption

Tumor stroma was once considered an inert bystander but is now regarded as a key component of tumor biology. The stroma of PDA is composed of an abundant extra-cellular matrix that does not act simply as a mechanical support but actively facilitates tumor development [36, 37]. The complex interplay between cancer cells and the various components of the tumor microenvironment has led to the testing of novel therapies to interrupt these biological processes.

The first mechanism explored was the use of inhibitors of the matrix metalloproteinases. Unfortunately, multiple studies showed that this approach is quite ineffective [38]. A second strategy involves the inhibition of cell-stroma interactions fueled by soluble factors secreted from stromal cells and used by tumors to enable the development of tumor vasculature or tumor growth. Bevacizumab (Genentech/Roche) showed no

activity in multiple Phase I/II trials [39]. Sorafenib was also ineffective in a Phase II study [40]. Dovitinib (an inhibitor of FGFR-3) is being tested in combination with gemcitabine/capecitabine in a Phase I trial. A randomized Phase II study of tivantinib (small molecule inhibitor of c-Met) vs. gemcitabine in treatment-naïve patients with advanced PDA was completed and results are pending. In a French Phase II trial, 22 patients with LA or metastatic PDA received oral masitinib (inhibitor of c-kit and PDGFR kinases) combined with standard gemcitabine. The reported median TTP and OS were 6.4 months and 7.1 months, respectively [41]. A Phase III study recently updated in unresectable PDA using gemcitabine plus masitinib vs. placebo showed no benefit in OS (7.7 vs. 7.0 months); however, patients with a deleterious genomic biomarker had a significant improvement in OS (11 vs. 5 months, $P<0.001$) [42]. Rigosertib, a phosphatidylinositol-3-kinase inhibitor, showed activity in a Phase I trial [43] and is currently being tested in a Phase II/III randomized clinical trial. Trabectedin, an antisense molecule which is specifically designed to target TGF- β 2 mRNA, showed encouraging results in Phase I/II and a Phase II is planned [44].

Three developmental pathways (WNT, notch, and the hedgehog) have been implicated in induction of epithelial-to-mesenchymal transformation as well as pancreatic cancer progression and maintenance of cancer stem cells [45]. Many new compounds targeting these pathways are being tested. A recent Phase II clinical trial with hedgehog pathway inhibitor saridegib (Infinity Pharmaceuticals) showed no benefit when added to gemcitabine; but some activity was seen in a Phase Ib trial with FOLFIRINOX [46]. Several Phase II trials of hedgehog pathway inhibitor vismodegib (Genentech/Curtis) and Phase I trials of LDE225 (Novartis) in combination with gemcitabine are ongoing. Notch inhibitors, RO4929097 and MK0752, concluded Phase I studies and will move forward into Phase II [47, 48]. We will have to wait until all these studies are completed before any formal conclusion can be made about this group of drugs.

PARP Inhibitors

Studies have demonstrated an increased risk of PDA among relatives of patients with PDA 7.8 % compared to 0.6 % in controls—even after adjusting for other factors [49]. In Ashkenazi Jews, a family history of PDA is a strong predictor for BRCA2 mutation (OR=6.1) [50]. Familial pancreatic cancer represents approximately 5 % of all newly diagnosed PDA. Genetic predisposition to PDA is polygenic; seen individuals with mutations in Fanconi anemia pathway genes (BRCA2, BRCA1, and PALB2), DNA mismatch repair genes (MSH2, MSH6, MLH1, and PMS2), CDK2A/p16 (FAMMM syndrome), PRSS1 (hereditary pancreatitis), and LKB1/STK11 (Puetz-Jeghers) [51].

BRCA1/2 harbors particular therapeutic interest because homozygous mutant pancreatic cells are exquisitely sensitive to DNA cross-linking agents such as mitomycin C and cisplatin as well as PARP (Poly[ADP-ribose] polymerase) inhibitors [52]. There are several PARP-1 inhibitors in clinical trials. At ASCO GI 2103, Pishvaian and colleagues presented preliminary results of the Phase I portion of their trial combining veliparib (ABT-888, Abbott Laboratories) with FOLFOX in metastatic PDA. Of 22 patients treated on the Phase I portion of the study, the two best responders were patients with BRCA2 mutations; one had a PR with stable disease after 17 months and the second had a CR with normalization of CA 19–9 after 10 months [53]. The Phase II portion of the study was modified to include patients with known or suspected BRCA genetic mutations. Another Phase II clinical trial of patients with confirmed BRCA1/2 mutation treated with olaparib (AZD2281, AstraZeneca) monotherapy was presented at ASCO 2013. A number of 23 patients were included resulting in 1 CR, 4 PRs, and 8 SD for an ORR of 21.7, and 40.9 % 1-year survival [54]. Although final results are not yet available, these results are encouraging.

Modified Conventional Chemotherapeutics

PEP02 (MM-398, Merrimack Pharmaceuticals) is a novel nanoparticle liposomal formulation of irinotecan that has improved pharmacokinetics and tumor biodistribution. In a recent Phase II clinical trial of 40 patients with metastatic gemcitabine-refractory PDA, PEP02 120 mg/m² every 3 weeks showed a median PFS and OS of 9 and 21.6 weeks, respectively. Grade 3/4 adverse events included cytopenias, diarrhea and fatigue [55]. An international Phase III clinical trial (NAPOLI 1; NCT01494506) of this product in combination with 5-FU is underway.

S-1 (Teyssuno®) is a fourth generation oral fluoropyrimidine that contains tegafur, gimeracil, and oteracil potassium. In a Japanese phase II, randomized trial (PC-01 Study), 116 patients with stages III–IV PDA were randomized to gemcitabine plus S-1 or placebo. Median (13.7 vs. 8.0 months) and 1-year (29 % vs. 55.9 %) OS was better in the S-1 group ($P=0.035$). However, treatment discontinuation due to toxicity was seen in 27 % of the S-1 group [56]. S-1 is currently approved for treatment of gastrointestinal malignancies in Asia and Europe. A Phase III trial (JASPAC-01) of 385 patients comparing S-1 to gemcitabine for adjuvant therapy of resected PDA. In this study powered for non-inferiority, S-1 was not only non-inferior ($P<0.001$) but also superior ($P<0.001$) to gemcitabine. The authors concluded that S-1 was better than gemcitabine and should be considered the new standard for resected PDA [57].

High-dose intravenous (IV) vitamin C (ascorbate) has been shown to synergize with gemcitabine leading to enhanced killing of tumor cells by a pro-oxidative mechanism. Two

Phase I studies have shown that combination of pharmacological doses of ascorbate with gemcitabine are safe in advanced pancreatic cancer [58, 59]. In the first, 8 of 14 patients treated with gemcitabine and erlotinib in combination with high-dose IV vitamin C had a reduction in the size of the pancreatic primary. In the second, among nine patients PFS was 26 weeks and OS was 12 months. Two Phase II trials are currently ongoing testing the efficacy of high-dose IV ascorbate to enhance efficacy of gemcitabine-based chemotherapy.

Key Negative Trials

We will briefly discuss key Phases II–III clinical trials that were negative, in spite of a strong biological rationale and/or promising Phase II results. Table 2 serves as a summary.

Anti-VEGF

In 2010, the CALGB reported the results of a randomized Phase III clinical trial in which 602 patients with stages III–IV PDA were randomized to receive either gemcitabine alone or in combination with bevacizumab [39]. The results were disappointing with no difference in median OS (5.8 vs. 5.9 months). In the preceding single-arm Phase II study, a median 8.8 month OS and 21 % ORR was seen in 52 patients with metastatic disease [60]. In reflection, the results of this small, single-arm study were not significantly better than what was previously published for gemcitabine alone. Fixed dose rate gemcitabine plus bevacizumab followed by chemo-radiation in LA potentially resectable disease fared no better [61].

Axitinib, an oral and selective inhibitor of VEGFs, currently approved in the USA for advanced renal cell cancer, was also tested in PDA. In a randomized placebo-controlled Phase II study, 103 patients with unresectable or metastatic PDA were treated with gemcitabine, with or without axitinib. The ORR for gemcitabine plus axitinib was 7 % vs. 3 % for gemcitabine alone, and the median OS was 6.9 vs. 5.6 months, respectively [62]. Investigators interpreted this non-statistically significant prolongation of 1.3 months as a signal of activity and proceeded with a Phase III clinical trial enrolling 632 patients [63]. In a pre-planned interim analysis done in January 2009, an independent committee concluded the study was futile and it was terminated. The reported median OS was 8.5 vs. 8.3 months (HR=1.014; 95 % CI: 0.786–1.309).

Cetuximab

At the same time that CALGB reported its negative study with bevacizumab, the SWOG group released the results of a randomized Phase III clinical trial of similar design using cetuximab instead of bevacizumab. The median OS was 6.3 vs. 5.9 months for the experimental [64]. Again, the preceding

Table 2 Summary of key negative clinical trials in metastatic PDA

Intervention	Study description	No. of patients	Comparison	Median OS	Median DFS or TTP	ORR	1-year survival	References
<i>Bevacizumab</i>								
Phase 2	Single arm; multicenter, single institution	52	None	8.8 (7.4–9.7 months)	5.4 (3.7–6.2 months)	21 %	29 %	Kindler et al. [39]
Phase 3	Randomized, double-blind, placebo-controlled, international	602	Gemcitabine ± bevacizumab or Placebo	5.9 vs. 5.8 months	3.8 vs. 2.9 months	10 % vs. 13 %	Not reported (~15 % both)	Kindler et al. [60]
<i>Cetuximab</i>								
Phase 2	Single arm; multicenter	41	None	7.1 months	3.8 months	12 %	31.7 %	Xiong et al. [65]
Phase 3	Randomized, double-blind, placebo-controlled	745	Gemcitabine ± Cetuximab or Placebo	6.3 vs. 5.9 months	3.4 vs. 3.0 months	12 % vs. 14 %	Not reported (~20 % both)	Philip et al. (2010) [62]
<i>Ganitumab</i>								
Phase 2	Randomized, Placebo-controlled	125	Gemcitabine ± Ganitumab, Conatumumab or Placebo	8.7 vs. 7.5 vs. 5.9 months	5.1 vs. 4.0 vs. 2.1 months	10 % vs. 3 % vs. 3 %	39 % vs. 20 % vs. 23 %	Kindler H, et al. (2012)[69]
<i>Axitinib</i>								
Phase 2	Randomized, multi-center, open label	103	Gemcitabine ± Axitinib or Placebo	6.9 vs. 5.6 months	4.2 vs. 3.7 months	7 %	37 % vs. 23.5 %	Spano et al. [62]
Phase 3	Randomized, double-blinded	632	Gemcitabine ± Axitinib or Placebo	8.5 vs. 8.3 months	4.4 months (both)	5 % vs. 2 %	Not reported	Kindler et al. (2011) [61]

study was a single-arm Phase II study of the combination of cetuximab and gemcitabine that included only 41 patients. Median OS of 7.1 months and a 12 % RR was felt to be encouraging, but not significantly higher than gemcitabine alone [65]. Negative results for this combination were also observed in the adjuvant setting [66].

Insulin-Like Growth Factor Receptor (IGF-R) Blockade

Blockade of IGF-R1 is underpinned by strong pre-clinical data [67, 68]. Ganitumab, Amgen's human monoclonal antibody that targets IGF-1R, was studied in combination with gemcitabine in a Phase II trial of 42 patients with metastatic disease. Median OS of 8.7 months and 1-year survival rates were 39 % [69], slightly better than placebo. In August 2012, following a preplanned interim analysis of the Phase III GAMMA trial, Amgen stopped the study because the addition of ganitumab to gemcitabine was unlikely to demonstrate improvements in OS. Similarly, anti-IGF-1R monoclonal antibody cixutumumab (ImClone) in combination with gemcitabine/erlotinib did not improve PFS or OS in metastatic PDA [70]. A Phase II three-arm study of dalotuzumab (MK-0646, Merck) in combination with gemcitabine with or without erlotinib (NCT00769483) was recently completed.

Gemcitabine Elaidate (CO-1.01, CP-4126)

Gemcitabine elaidate is a lipophilic, unsaturated fatty acid ester derivative of gemcitabine (Clovis) designed to allow the drug to enter tumoral cells by passive diffusion and therefore independently of the human equilibrative nucleoside transporter-1 (hENT1). The pivotal LEAP study, a randomized Phase II international clinical trial, required the measurement of hENT in metastatic biopsies prior to randomization, hoping to correlate hENT expression with gemcitabine benefit. A number of 361 patients were enrolled rapidly, but unfortunately, no difference in OS was found in either the hENT1-low or in the overall intent-to-treat population. The study also demonstrated that hENT1 status has no clinical utility for determining gemcitabine sensitivity [71].

Future Directions in the Adjuvant and Neoadjuvant Settings

At the current time, we do not know the benefit of multi-agent chemotherapy in the adjuvant setting and therefore we still rely on results of CONKO-1 and ESPAC-3 that demonstrated a role for single-agent gemcitabine and 5-FU. The testing of combination chemotherapy regimens in resectable and LA disease is ongoing and hopefully will also lead to clinical advances. Table 3 summarizes some of the most relevant ongoing clinical trials.

The majority of the larger active trials are testing conventional chemotherapy agent combinations. In the adjuvant setting, the first trial that results are expected to be available is the recently completed NewLink Genetics Phase III study that compares standard of care gemcitabine with and without HyperAcute-Pancreas immunotherapy (Algenpantucel-L) followed by chemo-radiation. FOLFIRINOX is being formally tested in surgically resected disease by French investigators (UNICANCER Group) in a Phase III clinical trial in which subjects with R0 or R1 resections are randomized to a modified version of FOLFIRINOX or standard gemcitabine. The target number is 490 and the estimated completion date is in 2018. The Phase III NCI-sponsored trial RTOG-0848 compares erlotinib in combination with gemcitabine vs. gemcitabine alone in the first randomization and the additional benefit of chemoradiation in the second randomization. Estimated enrollment is 950, with estimated completion of the primary outcome measure (OS from 1st randomization) targeted for 2020. Enrollment has been slow to this trial, necessitating the addition of additional cooperative groups and sites worldwide. An interesting Phase II ACOS trial centered at MD Anderson also assesses the benefit of gemcitabine and erlotinib in surgically-resectable disease. In this study, two cycles of the 3 weeks on 1-week off combination is given prior to resection and reinitiated post-pancreatoduodenectomy. Blood and tissue analysis is planned for correlative studies. An alternative adjuvant approach is the two-arm Phase III trial from Germany comparing gemcitabine alone to gemcitabine plus cisplatin with regional hyperthermia (HEAT, NCT01077427). The preceding Phase II trial demonstrated a low toxicity rate and an OS of 16.9 months.

FOLFIRINOX has already been shown to be an effective treatment option in LA PDA as demonstrated by several single institution studies, with response rates as high as 50 % [14–16]. German investigators will assess the effectiveness of chemotherapy and chemoradiation vs. chemotherapy alone in LA unresectable pancreatic cancer in the four-arm CONKO-7 trial. A total of 830 patients will first receive either induction FOLFIRINOX or gemcitabine. Following completion of induction chemotherapy subjects will then receive 50.4 Gy radiation plus radiosensitizing gemcitabine OR continue with the same chemotherapy. The expected completion date of this trial is 2018. A Phase II trial of similar design is being conducted at MD Anderson (NCT01560949). Investigators at Stanford University also plan to test FOLFIRINOX in combination with chemoradiation; however, in this trial, subjects will undergo treatment with modified FOLFIRINOX plus or minus SBRT radiation with 5-FU as the radiosensitizing agent. Secondary objectives include evaluation of the utility of FDG- PET and biomarker identification.

The University of Florida has launched the Phase II GAIN-1 trial in resectable and borderline-resectable pancreatic cancers testing gemcitabine + nab-paclitaxel as neoadjuvant

Table 3 Selected active phase II and III ongoing adjuvant and neo-adjuvant clinical trials

Mechanism of action/ sponsor	Clinical setting/Identifier	Phase	Control arm	Population	Number targeted	Primary outcome	Comments
<i>Conventional chemotherapy</i>							
mFOLFIRINOX (UNICANCER)	Adjuvant (NCT01526135)	III	Gem	Resected (R0-R1)	490	DFS	Arm A: Gem Arm B: mFOLFIRINOX (No 5-FU bolus)
mFOLFIRINOX (Stanford University)	Neo-adjuvant (NCT01926197)	III	mFOLFIRINOX	Locally advanced, UR	172	PFS	Arm A: mFOLFIRINOX Arm B: mFOLFIRINOX → 5-FU CR (SBRT)
FOLFIRINOX (Univer. Erlangen-Nürnberg)	Neo-adjuvant (NCT01827553)	III	Gem	Locally advanced UR	830	OS	Arm A: induction FOLFIRINOX → Gem CR or FOLFIRINOX Arm B: induction Gem → Gem CR or Gem
Gemcitabine + Oxaliplatin (University Zurich)	Neo-adjuvant (NCT01314027)	III	Gem	Resectable	310	PFS	Arm A: Neoadj GemOx → Surgery → Adj Gem Arm B: Surgery → Adj Gem
Gemcitabine + NabPaclitaxel (University Florida)	Neo-adjuvant (NCT01470417)	II	None	Resectable & BR	60	RR	High-risk resectable/BR disease receive GemNab- pac → GEM CR
Algenpantucel-L (NewLink Genetics)	Adjuvant (NCT01072981)	III (completed)	Gem ± CR	Resected (R0-R1)	722	OS	Arm A: Surgery → Gem ± 5FU CR Arm B: Surgery → Algenpantucel-L + Gem ± CR
Algenpantucel-L (NewLink Genetics)	Neo-adjuvant (NCT01836432)	III	FOLFIRINOX	BR and locally advanced UR	280	OS	Arm A: FOLFIRINOX → 5FU CR Arm B: Algenpantucel-L + FOLFIRINOX → 5FU CR
<i>Targeted agents</i>							
Erlotinib (RTOG)	Adjuvant (NCT01013649)	III	Gem	Resected, R0-R1	950	OS	Double randomization: Gem vs. Gem + erlotinib → 5FU CR vs. no 5FU CR
Erlotinib (ACOS)	Neo-adjuvant (NCT00733746)	II	None	Potentially resectable	123	2-year OS	Gem + erlotinib pre- and post-surgery

Gem gemcitabine, m modified, Adj adjuvant, CR chemoradiation (unless otherwise specified = 50.4 cGy), BR borderline resectable, UR unresectable

therapy. Serological (CA 19.9), radiological, and pathological response rate are the main outcomes. Lastly, European researchers are currently testing another commonly used regimen (gemcitabine + oxaliplatin) in a Phase III clinical trial. Patients assigned to the control arm will receive standard surgical resection followed by adjuvant gemcitabine. Patients on the investigational arm will receive 8 weeks of neoadjuvant gemcitabine/oxaliplatin chemotherapy followed by surgery in addition to gemcitabine adjuvantly. Preliminary results of this trial will be available by the end of 2014.

Conclusions

We have summarized here the most recent treatment advances in PDA, including the results of the FOLFIRINOX and nab-paclitaxel plus gemcitabine Phase III trials. We discussed novel approaches such as immune-mediated therapies, drugs designed to disrupt the tumor-stromal compartment and to take advantage of genetic defects in DNA repair as well as new generations of conventional chemotherapeutics, all in early stages of clinical development with promising results. We hope that at least some of these agents will result in positive trials and add to our armamentarium for treating this challenging malignancy.

We are encouraged by recent leaps forward in the treatment of PDA. Future research will focus on identifying molecularly based clinical subtypes of pancreatic cancer and the further development of criteria to assist in our clinical decision-making. The long sought after goal of personalizing drug choices based on pancreatic tumor and patient biology will hopefully be possible. Can we define better biomarkers particularly for guidance in the neoadjuvant treatment of potentially resectable disease? How will these recent advances, primarily in the treatment of metastatic disease, help to improve outcomes for surgically-amenable pancreatic cancer? This of course is the treatment goal we are most asked by our patients cure? With the availability of effective treatments for metastatic PDA, we are now able to work toward this goal.

Conflict of interest The authors declare that they have no conflict of interest.

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Appendix VASILE01

(group-3; median OS 10 months) as compared to 15 pts with -634GG genotype (group-4; median OS 8 months; $p = 0.15$). However, median OS was 13 months in 13 group-3 arm B pts, 6 months in 6 group-4 arm B pts ($p = 0.016$); 9 months in 15 group 3 arm A pts and 11 months in 9 group 4 arm A pts ($p = 0.67$). These results suggest that polymorphisms of genes involved in expression of the main ligand for VEGFR2 (VEGFA 634G > C) and of efflux transporters (ABCB1 3435C > T) are promising candidates as predictive marker for selecting pts with MPA who may benefit of MS. Given the small sample size of these analyses, a larger confirmatory trial is necessary and appears worthwhile.

Disclosure: All authors have declared no conflicts of interest.

725P PATHOLOGICAL PROOF AND SURVIVAL FOR PATIENTS WITH BILIARY-TRACT OR PANCREATIC TUMOR

C. Desauw¹, F. El Hajbi², K. Ligier³, A. Duhamel⁴, F. Richard⁴, C. Rose²

¹Medical Oncology, C.H.U. Claude Huriez, Lille, FRANCE, ²Hôpital St Vincent De Paul, Service D'onco-Hématologie, Université Catholique de Lille, Lille, FRANCE, ³Registre Général Des Cancers De Lille Et De Sa Région, Centre de Référence Régional en Cancérologie, Lille, FRANCE, ⁴Unité de Biostatistiques, EA2694, Univ Lille Nord de France, Lille, FRANCE

As recommended by ESMO, a final pathological diagnosis (PD) has to be obtained before any chemotherapy, radiotherapy or other non-surgical oncological therapy for pancreatic or biliary tract cancer. PD is also required for inclusion in a clinical trial. In practice, it is sometimes difficult to obtain this pathological proof because of difficult access or poor performance status. Treatment decision is then collegial, based on a clinical, radiological and biological suspicion. We studied patient survival based on availability of PD from the cancer registry of Lille and its region (800 000 inh. - North France). We reviewed patients records over 15 years old diagnosed in 2005 or 2008 for a pancreatic or biliary tract cancer (neuroendocrine excluded). The point was made on 01/12/2011. Patients were divided into 5 groups: PD and surgery (PD-Surg), PD and radiotherapy or chemotherapy (PD-RC), PD and untreat (PD-Un), no PD and radiotherapy or chemotherapy (noPD-RC), no PD and untreat (noPD-Un). Observed survival analysis was obtained from Kaplan-Meier method and statistical significance from log-rank test. Males accounted for 45.8% of 260 patients. The average age was 71.8 years (+/- 12.1). 59.6% were diagnosed as pancreas cancer. PD was not obtained in 54.2% (60% in pancreas and 45.7% in biliary tract respectively). Seven patients were lost of follow-up.

n (%)	PD-Surg	PD-RC	noPD-RC	PD-Un	noPD-Un
Median survival (days)	709 (17.3)	44 (16.9%)	37 (14.2%)	30 (11.5%)	104 (40%)
2 years survival	46.7%	p > 0.2 6.8%	2.9%	p > 0.9 0%	2.1%

27 patients were alive beyond 24 month: 21 in PD-Surg group, 3 in PD-RC, 1 in noPD-RC and 2 in noPD-Un. In conclusion, the absence of PD is common in clinical practice, without apparent impact on survival. 14.2% of patient were treated without PD. These patients are not take account in current recommendations. Centralized monitoring of this condition would be required. In the absence of treatment plan, PD is not essential.

Disclosure: All authors have declared no conflicts of interest.

726P NEOADJUVANT MODIFIED FOLFOXIRI IN LOCALLY ADVANCED PANCREATIC CANCER

E. Vasile¹, N. De Lio², C. Cappelli³, L. Ginocchi¹, S. Caponi¹, A. Sainato⁴, C. Greco⁴, F. Mosca⁴, A. Falcone¹, U. Boggi²

¹Oncologia, Trapianti e Nuove Tecnologie in Medicina, Polo Oncologico - Azienda Ospedaliero-Universitaria Pisana - Istituto Toscano Tumori, Pisa, ITALY, ²Dipartimento di Oncologia, dei Trapianti e delle Nuove Tecnologie In Medicina, U.O. Chirurgia Generale e Trapianti - Azienda Ospedaliero-Universitaria Pisana, Pisa, ITALY, ³Dipartimento Di Radiodiagnostica e Radiologia Interventistica, Azienda Ospedaliero-Universitaria Pisana, Pisa, ITALY, ⁴Dipartimento di Oncologia, dei Trapianti e delle Nuove Tecnologie In Medicina, U.O. Chirurgia Generale 1 Universitaria - Azienda Ospedaliero-Universitaria Pisana, Pisa, ITALY

Background: FOLFIRINOX has shown high activity in metastatic pancreatic cancer patients. Considering its activity, the regimen could be of interest also for patients with inoperable locally advanced disease. Our group had developed a very similar schedule in colorectal cancer named FOLFOXIRI which contains no bolus 5-fluorouracil and a slight lower dose of irinotecan with good tolerance and activity.

Methods: We have performed a phase II trial in order to prospectively evaluate the activity of a modified (m)FOLFOXIRI regimen in locally advanced pancreatic cancer.

mFOLFOXIRI consisted of: oxaliplatin 85 mg/sqm, irinotecan 150 mg/sqm and folinic acid 200 mg/sqm on day 1, plus infusional 5-fluorouracil 2800 mg/sqm administered in 48 hours on days 1 to 3, with cycle repeated every 14 days. The study enrolled patients with cytological or histological diagnosis of pancreatic adenocarcinoma, stage III locally advanced disease without evidence of metastatic disease, ECOG performance status (PS) 0 or 1, age 18-75. The primary end-point of the study was the percent of patients who can achieve radical surgical resection after chemotherapy; the trial was designed with a percentage of low activity of 30% and a percentage of interest of 50% with an α and β error of 0.05 and 0.20.

Results: Twenty-two patients have been so far enrolled; 8 men and 14 women; PS was 0 in 10 patients. Median age was 60 years (range 44-75). Celiac axis was involved in 7 patients, superior mesenteric artery in 10 cases, both arteries in 5 patients. Among the 15 patients so far evaluated, 6 partial responses (40%) and 9 stable disease (60%) have been observed. A local treatment after chemotherapy was received by 9 patients until now: 5 (55.5%) underwent to radical surgery; 1 underwent an explorative laparotomy with evidence of liver metastases; 3 received concomitant chemo-radiotherapy with gemcitabine. Median progression-free survival was 24.5 months and median overall survival was 30.1 months.

Conclusions: Chemotherapy with mFOLFOXIRI seems active in locally advanced pancreatic cancer patients and may allow to obtain a downstaging of disease leading some patient to achieve a curative surgical resection. Longer follow up is needed to better evaluate long-term outcome of this strategy.

Disclosure: All authors have declared no conflicts of interest.

727P COMPARISON IN 1323 PATIENTS OF PREOPERATIVE IMAGING STAGING AND PATHOLOGICAL EXAMINATION OF RESECTED PANCREATIC HEAD ADENOCARCINOMA: SERIES OF THE ASSOCIATION FRANÇAISE DE CHIRURGIE

M. Gilibert¹, J.M. Boher², J.L. Raoul³, O. Turrini³, F. Paye⁴, P. Bachelier⁵, J. Delpero⁶, G. Afc⁷

¹Medical Oncology, Institut Paoli Calmettes, Marseille Cedex, FRANCE, ²Bioinformatics, Institut Paoli-Calmettes, Marseille, FRANCE, ³Oncology, Institut Paoli-Calmettes, Marseille, FRANCE, ⁴Surgery, Hopital Saint Antoine, Paris, FRANCE, ⁵Surgery, Hopital de Hautepierre, Strasbourg, FRANCE, ⁶Surgical Oncology, Institut Paoli-Calmettes, Marseille, FRANCE, ⁷France, Association Francaise de Chirurgie, France, FRANCE

Resection is possible in less than 15% of pancreatic ductal adenocarcinoma (PDAC) patients. Prognosis is dismal and particularly related to arterial, venous or lymph node invasion. In this retrospective analysis were compared imaging preoperative data and pathological reports on arterial, venous and lymph node invasion in a large series of PDAC benefiting from pancreaticoduodenectomy. Retrospective series of 1323 patients resected for a PDAC of the head of pancreas in 35 French and 2 Swiss centers, data analyzed by the Association Française de Chirurgie; 142 with (95 chemoradiotherapy, 47 chemotherapy; given to a borderline tumor in 65% and systematically in 35%) and 1181 without preoperative treatment. Preoperative imaging consisted in: ceTscan (97%), ceMRI (45%), US (65%) and endoscopic US (59%). Were calculated concordance, Sensibility, Specificity, PPV and NPV of preoperative data compared to pathological conclusions. Artery-Artery + Vein-Vein+ LN- LN+ Imaging negative 1047 16 788 137 246 613 positive 17 9 40 130 38 157 Concordance 97% 84% 38% Se 36% 49% 20% Spe 98% 95% 87% PPV 35% 76% 80% NPV 98% 85% 29%. In conclusion, in this biased series of patients who were operated on from a PDAC, the value of preoperative imaging "in the real life" is not optimal, particularly regarding arterial and lymph node involvement

Disclosure: All authors have declared no conflicts of interest.

728P RANDOMIZED PHASE II TRIAL OF S-1 VERSUS S-1 PLUS OXALIPLATIN (SOX) IN PATIENTS WITH GEMCITABINE REFRACTORY PANCREATIC CANCER

T. Okusaka¹, S. Ohkawa², H. Isayama³, A. Fukutomi⁴, K. Yamaguchi⁵, M. Ikeda⁶, A. Funakoshi⁷, M. Nagase⁸, S. Nakamori⁹, Y. Hamamoto¹⁰

¹Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, JAPAN, ²Department of Gastroenterology, Kanagawa Cancer Center Hospital, Kanagawa, JAPAN, ³Department of Gastroenterology, Graduate School of Medicine The University of Tokyo, Tokyo, JAPAN, ⁴Division of Gastrointestinal, Shizuoka Cancer Center, Shizuoka, JAPAN, ⁵Division of Gastroenterology, Saitama Cancer Center, Saitama, JAPAN, ⁶Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Chiba, JAPAN, ⁷Department of Gastroenterology, National Kyushu Cancer Center, Fukuoka, JAPAN, ⁸Department of Medical Oncology, Jichi Medical University Hospital, Tochigi, JAPAN, ⁹Department of Surgery, Osaka National Hospital, Osaka, JAPAN, ¹⁰Tochigi, Department of Clinical Oncology, Tochigi Cancer Center, Tochigi, JAPAN

Background: Gemcitabine (Gem) monotherapy or Gem-based combination therapy is used as standard first-line therapy for advanced pancreatic cancer (PC). There is no consensus on second-line therapy in patients (pts) with disease progression (PD)

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Article

Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study

Caterina Vivaldi ^{1,2,*}, Lorenzo Fornaro ^{2,†}, Carla Cappelli ³, Irene Pecora ², Silvia Catanese ², Francesca Salani ², Andrea Cacciato Insilla ⁴ , Emanuele Kauffmann ⁵, Francescamaria Donati ³, Giulia Pasquini ², Valentina Massa ², Niccolò Napoli ⁵, Monica Lencioni ², Piero Boraschi ³, Daniela Campani ⁴, Ugo Boggi ⁵, Davide Caramella ⁶, Alfredo Falcone ^{1,2} and Enrico Vasile ²

¹ Department of Translational Research and New Surgical and Medical Technologies, University of Pisa, Via Savi 6, 56126 Pisa, Italy

² Division of Medical Oncology, Pisa University Hospital, Via Roma 67, 56126 Pisa, Italy

³ Department of Diagnostic Imaging, Pisa University Hospital, Via Paradisa 2, 56124 Pisa, Italy

⁴ Department of Surgical, Medical, Molecular Pathology and Critical Area, Division of Surgical Pathology, Pisa University Hospital, Via Paradisa 2, 56124 Pisa, Italy

⁵ Department of Transplant and General Surgery, Pisa University Hospital, Via Paradisa 2, 56124 Pisa, Italy

⁶ Diagnostic and Interventional Radiology, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy

* Correspondence: caterinavivaldi@gmail.com; Tel.: +39-050-992466; Fax: +39-050-992467

† These authors contributed equally to this work.

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Abstract: Early tumor shrinkage (ETS) and depth of response (DoR) predict favorable outcomes in metastatic colorectal cancer. We aim to evaluate their prognostic role in metastatic pancreatic cancer (PC) patients treated with first-line modified-FOLFIRINOX (FOLFOXIRI) or Gemcitabine + Nab-paclitaxel (GemNab). Hence, 138 patients were tested for ETS, defined as a $\geq 20\%$ reduction in the sum of target lesions' longest diameters (SLD) after 6–8 weeks from baseline, and DoR, i.e., the maximum percentage shrinkage in the SLD from baseline. Association of ETS and DoR with progression-free survival (PFS) and overall survival (OS) was assessed. ETS was reached in 49 patients (39.5% in the FOLFOXIRI, 29.8% in the GemNab group; $p = 0.280$). In the overall population, ETS was significantly associated with better PFS (8.0 vs. 4.8 months, $p < 0.001$) and OS (13.2 vs. 9.7 months, $p = 0.001$). Median DoR was -27.5% (-29.4% with FOLFOXIRI and -21.4% with GemNab, $p = 0.016$): DoR was significantly associated with better PFS (9.0 vs. 6.7 months, $p < 0.001$) and OS (14.3 vs. 11.1 months, $p = 0.031$). Multivariate analysis confirmed both ETS and DoR are independently associated with PFS and OS. In conclusion, our study added evidence on the role of ETS and DoR in the prediction of outcome of PC patients treated with first-line combination chemotherapy.

Keywords: early tumor shrinkage; depth of response; pancreatic cancer; FOLFOXIRI; gemcitabine plus nab-paclitaxel

1. Introduction

Pancreatic cancer (PC) is the seventh leading cause of cancer-related death worldwide and is one of the most aggressive tumor types, with almost as many deaths ($n = 432,000$) as incident cases ($n = 459,000$) [1].

Considering all stages, from 2014 to 2018, the overall five-year survival rate increased from 6% to 9%, but it still stands very poor [2]. The majority of patients have metastatic disease at the time of diagnosis and a five-year survival rate of 3% [3].

Although in recent years research has been focusing on molecular alterations in order to develop targeted treatments [4], to date chemotherapy remains the standard of care in advanced disease. In the metastatic setting, two important clinical trials recently changed the standard of care from single-agent gemcitabine to combination chemotherapy [5,6]. Indeed, in the phase III PRODIGE4/ACCORD11 study, Conroy et al. demonstrated that FOLFIRINOX (5-fluorouracil, irinotecan, and oxaliplatin) was associated with a significant improvement in median overall survival (OS), global health status, and quality of life, as compared to Gemcitabine alone [5]. Our group, with a modified schedule of the Gruppo Oncologico Nord Ovest FOLFOXIRI regimen [7], obtained similar results. Likewise, in the MPACT trial, Von Hoff et al. demonstrated that the Gemcitabine plus Nab-paclitaxel (GemNab) regimen was associated with a longer OS in comparison to Gemcitabine monotherapy [5]. Since then, these two regimens (triplet or doublet combination) have been used as gold standard first-line treatments for patients with advanced PC in good clinical conditions [8].

In the last years, the availability of these different treatment options for advanced PC has highlighted the need to identify factors that may predict outcomes and define the quality of response (in terms of precocity and depth) in patients undergoing combination chemotherapies. In addition, no specific data suggest the use of one regimen over the other one, even though they largely differ with regard to route of administration, side effects and costs [9].

While early tumor shrinkage (ETS) and depth of response (DoR) have been convincingly correlated with survival in metastatic colorectal cancer [10–12], few data are available for other gastrointestinal malignancies [13] and, in particular, for metastatic PC. The first evidence in this field comes from a limited study including 59 advanced PC patients treated with FOLFIRINOX, suggesting that early response to chemotherapy may predict a favorable outcome [14]. Moreover, an exploratory analysis from MPACT investigators seems to demonstrate a significant tumor shrinkage with GemNab in both primary pancreatic and metastatic lesions [15], leading the way to ongoing evaluation of GemNab in locally advanced disease [16].

Since the available data are still scarce, our aim is to evaluate the prognostic role of ETS and DoR in a larger cohort of metastatic PC patients treated with modern combination regimens such as FOLFOXIRI and GemNab.

2. Results

2.1. Patients Characteristics and Treatment Efficacy

One hundred thirty-eight patients treated at our institution from August 2010 to November 2017 were enrolled. Eighty-one received FOLFOXIRI, while 57 were treated with GemNab. The most relevant characteristics of the study population are summarized in Table 1.

With a median follow-up of 34.3 months, a median of six cycles of chemotherapy were administered to each patient (range: 1–16). Considering the entire population, median progression-free survival (PFS), post-progression survival (PPS) and OS were 6.2, 5.0 and 10.9 months, respectively. The response rate (RR) was 34% (47 patients, all partial responses), while the disease control rate (DCR) was 71% (98 patients). At the time of analyses, 134 patients (97%) had progressed and 102 (74%) had died. Of 134 patients experiencing disease progression, 98 (73%) received a second-line chemotherapy treatment: of these, 65% were given combination regimens (GemNab, Folfox, Folfiri or Gemcitabine–Capecitabine doublets), while 35% were treated with monotherapies (mainly Gemcitabine). In detail, the more frequently chosen regimens were as follows: GemNab in 26% of cases, Gemcitabine monotherapy in 23%, Folfiri in 23% and Folfox in 9%.

Table 1. Patients' characteristics at baseline.

Characteristics	All Patients		FOLFOXIRI Cohort		GemNab Cohort	
	<i>n</i> = 138	%	<i>n</i> = 81	%	<i>n</i> = 57	%
Age years, median (range)	64 (41–76)	-	62 (41–75)	-	68 (47–76)	
Age (years)						
<65	80	58	60	74	20	35
≥65	58	42	21	26	37	65
Gender						
Male	71	51.4	40	49.4	31	54.4
Female	67	48.6	41	50.6	26	45.6
ECOG Performance Status						
0	84	68.4	62	76.5	22	38.6
1	54	39.2	19	23.5	35	61.4
Histology: Adenocarcinoma						
Ductal	123	89.1	74	91.4	49	86
On IPMN	12	8.7	6	7.4	6	10.6
Acinar	2	1.4	1	1.2	1	1.7
Squamous	1	0.7	-	-	1	1.7
Site of primitive tumor						
Head/uncinate process	65	47.1	39	48.1	26	45.6
Body/tail	73	52.9	42	51.9	31	54.4
Number of metastatic sites						
Median (range)	2 (1–5)	-	2 (1–5)		2 (1–4)	
Synchronous disease						
Yes	101	73.2	58	71.6	43	75.4
No	37	26.8	23	28.4	14	24.6
Metastatic sites						
Liver	108	78.3	65	80.2	43	75.4
Peritoneum	41	29.7	27	33.3	14	24.6
Lung	32	23.2	14	17.3	18	31.6
Bones	4	2.9	2	2.5	2	3.5
Local recurrence	7	5.1	3	3.7	4	7
Lymph nodes	20	14.4	4	4.8	16	28
Previous treatments						
Curative-intent surgery	37	26.9	24	29.6	13	22.8
Adjuvant chemotherapy	25	18.1	18	22.2	7	12.3
Ca 19.9 [KU/L]						
Normal value	27	19.5	15	18.5	13	22.8
<59 ULN	60	43.4	39	48.1	22	38.6
≥59 ULN	42	30.4	20	24.7	20	35.1
Not evaluable	9	6.5	7	8.6	2	3.5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Gemcitabine Nab-Paclitaxel (GemNab); IPMN, Intraductal papillary mucinous neoplasm; ULN, Upper Limit of Normal.

Looking separately at the two cohorts of therapy, the FOLFOXIRI group reached a RR and DCR of 36% and 70%, respectively, while in the GemNab group a RR of 35% and a DCR of 72% were observed. As expected, median PFS (6.4 vs. 6.2 months, $p = 0.55$) and OS (11.5 vs. 10.6 months, $p = 0.32$) did not differ significantly between FOLFOXIRI and GemNab. With respect to subsequent treatments, 67/81 (83%) patients who progressed after first-line FOLFOXIRI received a second-line one. Of these, the vast majority (76%) was administered a Gemcitabine-based regimen, as expected (GemNab, Gemcitabine alone, Gemcitabine-Capecitabine in 36%, 30% and 10% of cases, respectively). Moving to the GemNab population, 31/53 (58%) non-responding patients of the GemNab cohort received a second line chemotherapy. Most of them were fit for combination regimens: indeed, 39% of patients were administered Folfiri and 29% Folfex.

2.2. ETS and DoR

In the entire population, at the first radiological evaluation at 6–8 weeks after treatment initiation the median reduction of the sum of target lesions' diameters (SLD) from baseline was −8.39% and ETS was reached in 49 patients (35.5%) (39.5% in the FOLFOXIRI and 29.8% in the GemNab group, respectively; $p = 0.280$).

Among 102 evaluable patients, the median value of DoR was −27.52% (−29.4% with FOLFOXIRI and −21.4% with GemNab, $p = 0.016$); median time to DoR was 3.15 months (interquartile range 2.5–5.7 months). Similar to ETS, 55.2% of the patients in the FOLFOXIRI group and 43.2% in the GemNab one achieved a DoR equal to or superior than the median value ($p = 0.230$) (Table 2). On the other hand, considering DoR as a continuous variable, patients in the FOLFOXIRI cohort achieved a significantly higher DoR ($p = 0.037$). Moreover, looking at DoR quartile distribution, 20 out of 58 patients in the FOLFOXIRI group and five out of 44 patients in the GemNab group laid in the quartile with the highest DoR ($p = 0.007$). Median time to DoR was 3.9 months (interquartile range 2.5–5.8 months) in FOLFOXIRI cohort and 2.9 months (interquartile range 2.4–5.6 months) in GemNab cohort, respectively ($p = 0.293$).

Table 2. ETS and DoR distribution according to treatment.

ETS and DoR Cut-Offs	All Patients <i>n</i> (%)	FOLFOXIRI <i>n</i> (%)	GemNab <i>n</i> (%)	<i>p</i> -Value
ETS				
≥20%	49 (35.5)	32 (39.5)	17 (29.8)	0.28
<20%	89 (64.5)	49 (60.5)	40 (70.2)	
DoR				
I quartile (−81.81%–−44.87%)	25	20 (34.5)	5 (11.3)	0.039
II quartile (−44.87%–−27.52%)	26	12 (20.7)	14 (31.8)	
III quartile (−27.52%–−7.34%)	26	15 (25.8)	11 (25)	
IV quartile (−7.33%–+48%)	25	11 (18.9)	14 (31.8)	
≥median	51	32 (55.2)	19 (43.2)	0.23
<median	51	26 (44.8)	25 (56.8)	

Abbreviations: GemNab, Gemcitabine Nab-Paclitaxel; ETS, early tumour shrinkage; DoR, depth of response.

2.3. Survival Analyses

In the whole population, at univariate analyses greater values of both ETS and DoR were significantly associated with better PFS (both $p < 0.05$) and OS (both $p < 0.05$) (Table 3).

Table 3. Impact of clinical and pathologic features on PFS and OS (univariate analysis) in the whole population.

Clinical and Pathological Features	PFS		OS	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
ECOG performance status 0 vs. 1	1.655 (1.160–2.361)	0.005	2.216 (1.479–3.320)	<0.001
Gender male vs. female	1.020 (0.725–1.435)	0.907	1.124 (0.769–1.643)	0.547
Sites of metastases, yes vs. no				
Liver	0.774 (0.513–1.166)	0.22	0.606 (0.375–0.980)	0.041
Lung	1.221 (0.899–1.994)	0.165	1.416 (0.868–2.311)	0.164
Peritoneum	0.974 (0.670–1.417)	0.891	0.942 (0.622–1.425)	0.776
Number of metastatic sites 1–2 vs. 3–5	0.905 (0.622–1.316)	0.6	1.324 (0.811–1.882)	0.324
Primary site head-uncinate process vs. body-tail	0.718 (0.509–1.013)	0.059	0.844 (0.577–1.235)	0.382

Table 3. Cont.

Clinical and Pathological Features	PFS		OS	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Previous surgery on primary tumour				
yes vs. no	1.026 (0.694–1.516)	0.897	1.422 (0.912–2.218)	0.12
Ca19.9 level <ULN vs. ≥ULN	0.803 (0.523–1.235)	0.318	1.332 (0.798–2.224)	0.273
ETS				
≥20% vs. <20%	0.444 (0.308–0.640)	<0.001	0.493 (0.324–0.750)	0.001
As a continuous variable	1.029 (1.023–1.035)	<0.001	1.012 (1.008–1.016)	<0.001
DoR				
<median value vs. ≥median value	0.461 (0.304–0.669)	<0.001	0.601 (0.376–0.960)	0.033
As a continuous variable	1.025 (1.016–1.034)	<0.001	1.019 (1.008–1.029)	<0.001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio (95% CI, 95% confidence interval); OS, overall survival; p, p-value; PFS, progression-free survival; ULN, upper limit of normal; ETS, early tumor shrinkage; DoR, depth of response.

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At univariate analysis, the other significant factor with respect to PFS was ECOG performance status (PS) 0 (median PFS 7.3 vs. 5.5 months, $p = 0.005$), while ECOG PS 0 (median OS 13.9 vs. 9.5 months, $p < 0.001$) and the absence of liver metastasis (median OS 15.8 vs. 10.1 months, $p = 0.039$) were significantly correlated to OS (Table 3).

2.3.1. ETS: Correlation with Survival

In the overall population, ETS as a continuous variable was significantly associated with PFS ($p < 0.001$) and OS ($p < 0.001$). Patients achieving ETS ≥ 20% showed a longer PFS than those achieving a tumour shrinkage < 20% (median 8.0 vs. 4.8 months, $p < 0.005$) as well as a longer OS (median 13.2 vs. 9.7 months, $p = 0.001$) (Figure 1).

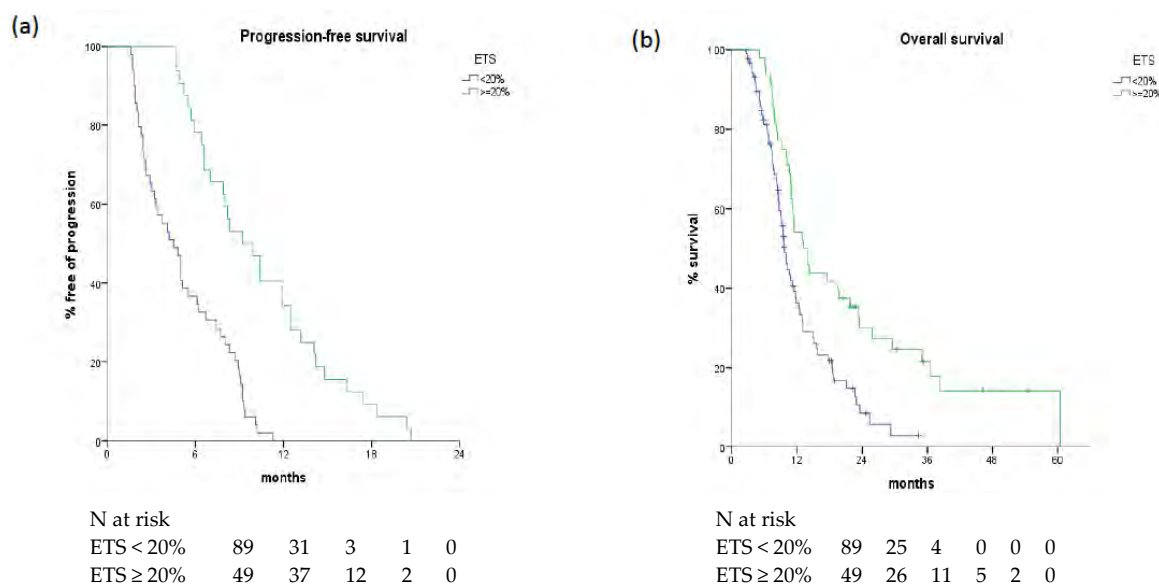


Figure 1. Progression-free survival (a) and overall survival (b) according to ETS values in overall population.

Similar results were observed in the FOLFOXIRI cohort: those who had a SLD reduction ≥ 20% demonstrated a longer OS (median 17.5 vs. 10.1 months, $p = 0.001$) and the PFS (median 9.2 vs. 4.5 months, $p < 0.001$) (Table 4). On the other hand, in the GemNab cohort the presence of ETS ≥ 20% was not associated with OS (median 10.0 vs. 10.6 months, $p = 0.853$) or PFS (median 7.3 vs. 4.9 months, $p = 0.209$) (Table 4, Figure 2).

Table 4. Median OS and PFS with respect to ETS and DoR in the two treatment groups.

was not associated with OS (median 10.0 vs. 10.6 months, $p = 0.853$) or PFS (median 7.3 vs. 4.9 months, $p = 0.209$) (Table 4, Figure 2).

Table 4. Median OS and PFS with respect to ETS and DoR in the two treatment groups.

PFS and OS in Treatment Groups	ETS			DoR		
	$\geq 20\%$	$< 20\%$	p -Value	$\geq$ Median	$<$ Median	p -Value
median PFS (months)						
FOLFOXIRI	9.2	4.5	< 0.001	9.2	6.7	< 0.001
GemNab	7.3	4.9	0.209	7.5	6.4	0.093
median OS (months)						
FOLFOXIRI	17.5	9.6	< 0.001	19.5	11.5	0.005
GemNab	10.6	10	0.853	10.9	10.6	0.818

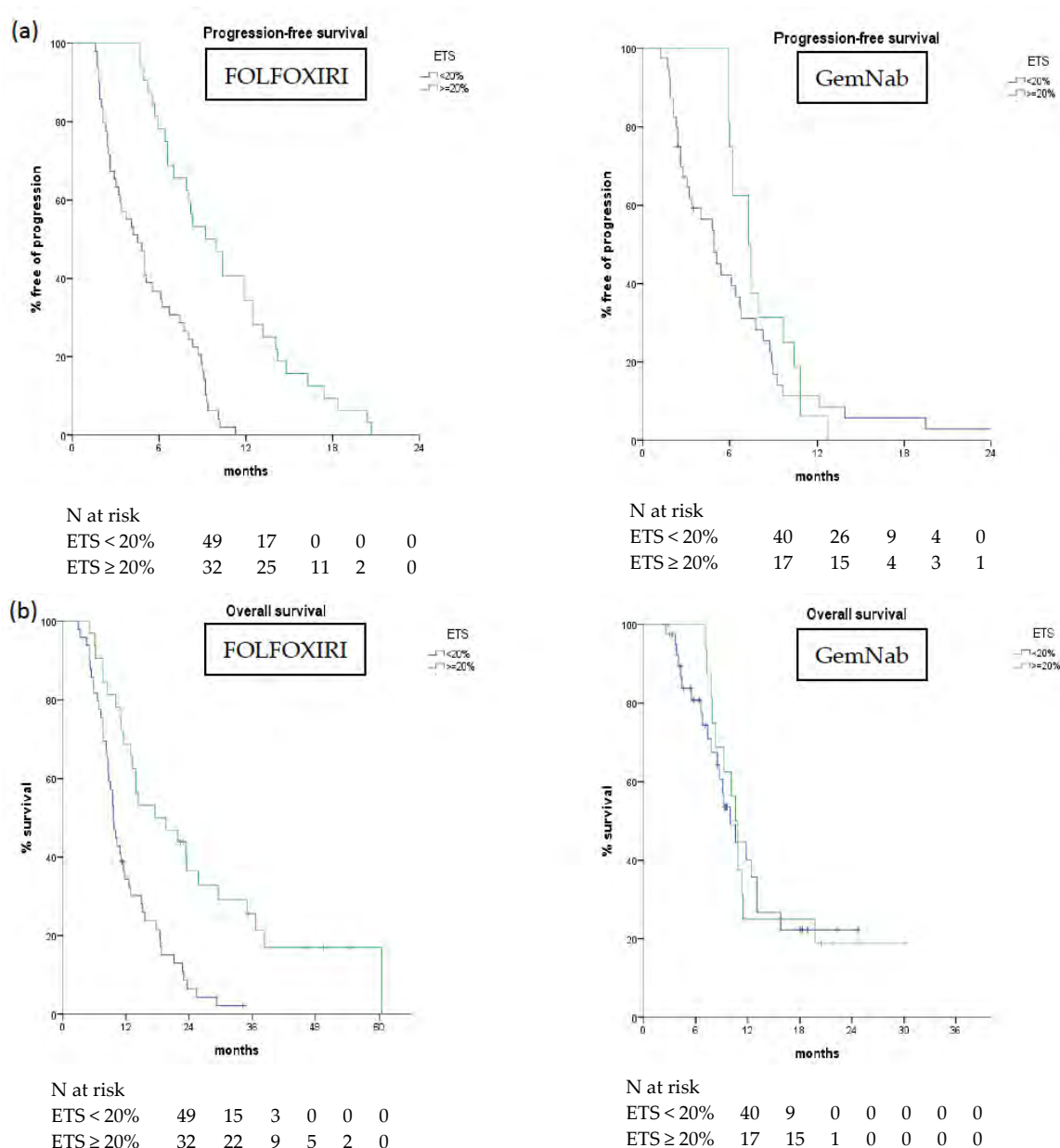


Figure 2. Progression-free survival (a) and overall survival (b) according to ETS in FOLFOXIRI and GemNab group.

2.3.2. DoR: Correlation with Survival

In the overall assessable population, a highly significant association of DoR, both as a continuous and a discrete variable, with PFS and OS was found (Figure 3, Table 3).

2.3.2. DoR: Correlation with Survival

In the overall assessable population, a highly significant association of DoR, both as a continuous and a discrete variable, with PFS and OS was found (Figure 3, Table 3).

DoR was also correlated with improved PPS (HR 1.003, 95% CI 1.003–1.022, $p = 0.007$) and patients achieving deeper responses had better outcome in terms of PPS compared to the others (median 12.9 vs. 3.8 months, $p = 0.002$).

Considering the two treatment cohorts separately DoR was associated with better PFS and OS when evaluated as a continuous (PFS $p < 0.001$, OS $p = 0.001$) and a discrete variable (PFS $p < 0.001$, OS $p = 0.005$) in patients treated with FOLFIRI. In the GemNab group, when evaluated as a continuous variable DoR was associated with better PFS ($p = 0.001$) but not OS ($p = 0.175$), while when considered as a discrete variable it did not reach statistical significance (PFS $p = 0.093$; OS $p = 0.818$). In the FOLFIRI group, patients with deeper responses had longer PFS and OS. In particular, median PFS and median OS were 9.9 months and 22.9 months in patients belonging to the first quartile vs. 7.7 months ($p = 0.004$) and 11.7 months ($p = 0.005$), respectively, of the other groups (Figure 4). Among patients treated with GemNab, a deeper response was significantly associated with PFS (median 10.8 vs. 6.7 months, $p = 0.031$) but the correlation with OS did not formally reach statistical significance (median 19.8 vs. 10.6 months, $p = 0.097$) (Figure 4). All survival data comparisons between the two treatment groups are summarized in Table 4.

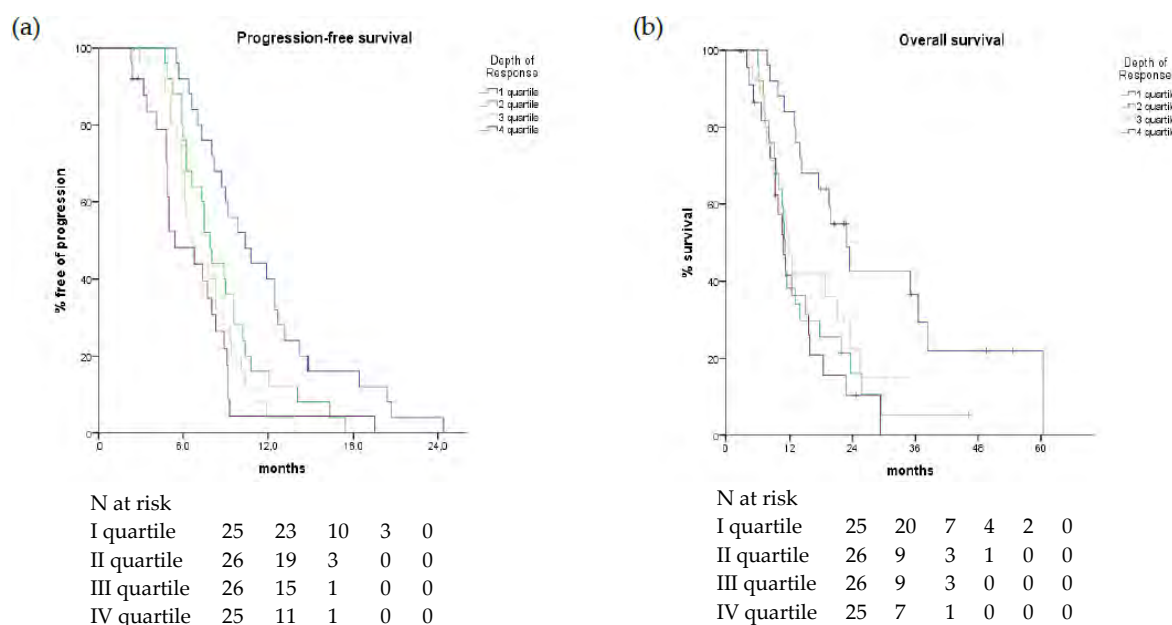
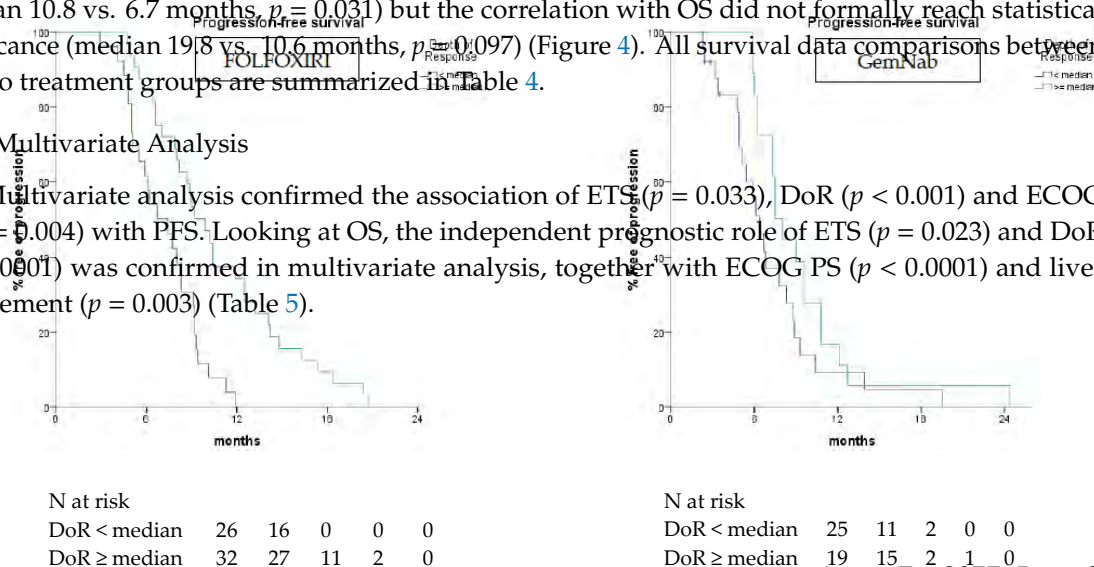


Figure 3. Progression-free Survival (a) and Overall Survival (b) curves according to DoR quartiles in overall population.

Among patients treated with GemNab, a deeper response was significantly associated with PFS (median 10.8 vs. 6.7 months, $p = 0.031$) but the correlation with OS did not formally reach statistical significance (median 19.8 vs. 10.6 months, $p = 0.097$) (Figure 4). All survival data comparisons between the two treatment groups are summarized in Table 4.

2.3.3. Multivariate Analysis

Multivariate analysis confirmed the association of ETS ($p = 0.033$), DoR ($p < 0.001$) and ECOG PS ($p = 0.004$) with PFS. Looking at OS, the independent prognostic role of ETS ($p = 0.023$) and DoR ($p < 0.0001$) was confirmed in multivariate analysis, together with ECOG PS ($p < 0.0001$) and liver involvement ($p = 0.003$) (Table 5).



II quartile	26	19	3	0	0
III quartile	26	15	1	0	0
IV quartile	25	11	1	0	0

II quartile	26	9	3	1	0	0
III quartile	26	9	3	0	0	0
IV quartile	25	7	1	0	0	0

Figure 3. Progression-free survival (a) and Overall Survival (b) curves according to DoR quartiles in overall 8 of 12 population.

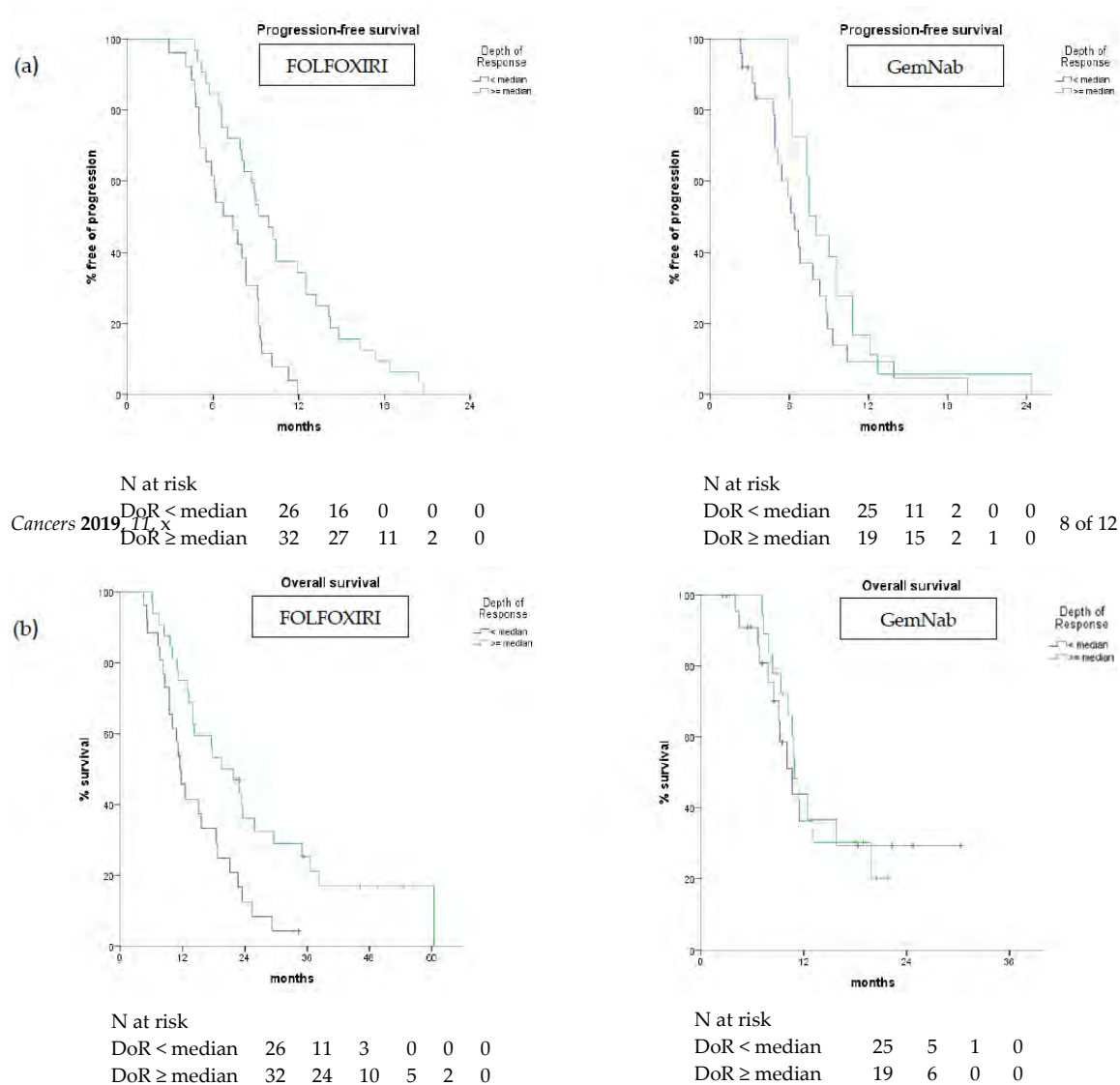


Figure 4. Progression-free survival (a) and overall survival (b) curves according to DoR ≥ vs. < median value in FOLFOXIRI and GemNab groups.

Table 5. Multivariate analysis.

2.3.3. Multivariate Analysis

Multivariate analysis confirmed the association of ETS ($p = 0.033$) and DoR ($p = 0.001$) and ECOG PS ($p = 0.004$) with PFS. Looking at OS, the independent prognostic role of ETS ($p = 0.023$) and DoR ($p < 0.0001$) was confirmed in multivariate analysis together with ECOG PS ($p < 0.0001$) and liver involvement ($p = 0.003$) (Table 5).

Variables	PFS		OS	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
ETS				
<20% vs. ≥20%	1.890 (1.054–3.389)	0.033	2.349 (1.126–4.897)	0.023
DoR				
continuous variable	1.035 (1.022–1.049)	<0.0001	1.038 (1.022–1.055)	<0.0001
ECOG performance status				
I vs. 0	1.902 (1.235–2.929)	0.004	3.074 (1.843–5.125)	<0.0001
Presence of liver metastases				
no vs. yes	-	-	0.428 (0.244–0.750)	0.003

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio (95% CI, 95% confidence interval); OS, overall survival; PFS, progression-free survival; ETS, early tumor shrinkage; DoR, depth of response.

3. Discussion

The present analysis is one of the first aiming to investigate the role of ETS and DoR in patients with metastatic PC. Patients achieving tumor response to chemotherapy are known to have a better prognosis but data regarding the quality of the response in terms of precocity and depth in advanced PC are lacking as well as head-to-head comparison between the two most common first-line chemotherapy regimens used, such as FOLFIRINOX and GemNab.

According to our results, ETS and DoR significantly correlate with survival outcome in patients with advanced PC treated with combination chemotherapy. The association with both PFS and OS is maintained in the multivariate model together with other well-known clinical prognostic variables, underlining how an early and deep tumor shrinkage may represent an independent prognostic factor not only in terms of progression delay, but also in extending survival. To the best of our knowledge, our report is the first that demonstrates the prognostic value of DoR in PC; moreover, we confirmed previously published data for ETS in a larger patient cohort [14]. The prognostic role of PS and liver involvement that emerged from our analysis had already been identified in ACCORD11/PRODIGE4 and MPACT trial analyses [5,17], thus strengthening the value of our results in an independent population treated at a single Institution.

As our aim was to preliminarily evaluate the prognostic role of ETS and DoR in two different parallel cohorts and not to make a comparison between the two regimens in terms of efficacy, no significant difference was noticed in terms of ETS between FOLFOXIRI and GemNab, while results in terms of DoR seem to favor the triplet regimen. The difference between the two regimes in terms of DoR emerges both considering the depth measurements as a continuous variable, as well as looking at patient distribution among the DoR quartiles. Due to the retrospective nature of our work, patients enrolled in the two cohorts may be imbalanced as regarding baseline characteristics and this aspect may have influenced compliance to treatment and activity results. While randomized comparisons are lacking, these data could support the choice of a more intensive regimen such as FOLFIRINOX as a preferable upfront option in those cases where a greater shrinkage is required, such as patients with high tumor burden, symptomatic disease or in the locally advanced setting.

Moving towards the separate evaluation of the two treatment cohorts, we noticed that the prognostic value of ETS was maintained in the FOLFOXIRI cohort while only a trend towards statistical significance was reached in the GemNab cohort. One could argue that this discrepancy could be related to the difference in terms of activity between the two regimens, which could be greater than the difference observed on long-term survival outcomes. Furthermore, the imbalance between the two cohorts in terms of number of patients (the subjects treated with FOLFOXIRI represent 2/3 of the entire population) may have also affected the results. Similar considerations apply to DoR that maintains its prognostic role with FOLFOXIRI for both PFS and OS, while it was significantly correlated only to OS with GemNab.

Some limitations of our study should be acknowledged. It is a retrospective experience conducted in a single center and patients in the two treatment cohorts are not matched by number or by baseline characteristics. However, we observed similar results with FOLFOXIRI and GemNab in our series when compared to those reported in the highly selected populations enrolled in phase III trials and we confirmed the relevance of first-line treatment in determining the survival outcomes in this challenging scenario.

Therefore, validation of our findings in larger, prospective studies is essential in order to definitively validate ETS and DoR as surrogate endpoints in PC. In particular, an ETS $\geq 20\%$ has proved to be a simple, reproducible parameter able to predict outcome in terms of PFS and OS, also showing the advantage of earlier assessment compared to RECIST response in routine practice. Moving from this consideration, it could be interesting to use ETS as a selection or stratification criterion in order to enhance modern strategies in PC treatment, such as sequential treatments with different regimens: nowadays, results achieved with such an approach in unselected populations have been indeed modest or inconclusive [18,19]. On the other hand, the correlation of DoR with PFS makes it a suitable

parameter to anticipate the possibility of administering subsequent lines of treatment in metastatic PC patients.

4. Materials and Methods

We retrospectively evaluated patients diagnosed with metastatic PC who received first-line combination chemotherapy at our institution between August 2010 and November 2017. All the included patients had a histologically-confirmed diagnosis of pancreatic carcinoma, evidence of distant organ/lymph-nodes involvement or local recurrence not susceptible to loco-regional treatments, good clinical conditions at enrollment (ECOG PS ≤ 1) and underwent a radiological assessment at baseline (performed <28 days from first treatment cycle), after 6–8 weeks since the first drug administration and every eight weeks thereafter until disease progression. Objective responses were evaluated according to RECIST criteria v.1.1.

Each patient received intravenous (i.v.) infusion of oxaliplatin (85 mg/sqm), irinotecan (165 mg/smq), 5-fluorouracil (3200 mg/sqm 48 h continuous infusion) and folinic acid (200 mg/sqm), all administered on day 1 every 14 days in the FOLFOXIRI regimen, or i.v. infusion of gemcitabine (1000 mg/sqm) plus nab-paclitaxel (125 mg/sqm) administered on days 1, 8 and 15 of a 28-day cycle in the GemNab regimen. Treatments were administered until disease progression, unacceptable toxicity or patient's consent withdrawal. Dose adjustment of single drugs were made as per routine clinical practice and drugs labels.

Two independent investigators evaluated RECIST response, and any controversy was solved by a third independent radiologist with expertise in PC assessment. The independent radiologist was not aware of the regimen received by the patient. ETS and DoR were assessed for each patient as follows: ETS was defined as a reduction $\geq 20\%$ of the SLD at radiological assessment after 6–8 weeks from treatment start. DoR was defined as the maximum percentage reduction of the SLD, with respect to baseline evaluation, i.e., $\text{DoR} = [(\text{SLD at best response}) - (\text{SLD at baseline}) \times 100] / (\text{SLD at baseline})\%$. Patients who presented the onset of new lesions at first radiological assessment were excluded from DoR analyses. ETS was considered both as continuous and binary variable ($\geq 20\%$ vs. $< 20\%$), whereas DoR was considered either as continuous, as binary ($\geq \text{median}$ vs. $< \text{median value}$) and ordinal (with four levels based on quartile distribution) variable. DoR quartiles were defined as follows: I quartile: -81.8% to -44.87% ; II quartile: -44.86% to -27.52% ; III quartile: -27.51% to -7.34% ; IV quartile: -7.33% to $+48\%$.

Clinical, pathological and laboratory data were collected at baseline and throughout treatment duration (see Table 1).

Estimations of time-to-event curves were generated by the Kaplan–Meier method. OS was defined as the time from the first day of treatment until the day of death from any cause. PFS was defined as the time from the first day of treatment until the day of disease progression or death from any cause. PPS was defined as the time between the first documented disease progression and death. Patients alive at the time of analyses were censored at the date of their last follow-up visit, whereas those without disease progression were censored at the time of the last radiologic assessment.

Correlation of ETS and DoR with PFS and OS were co-primary endpoints. We used the log-rank test to compare OS and PFS, setting significance at $p < 0.05$ for a two-sided test. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated by a stratified Cox proportional hazards model. For PFS and OS we initially performed a univariate assessment of the prognostic effect of each explored determinant, then a multivariate analysis was carried out using a stepwise Cox proportional hazards regression modelling and setting statistical significance at $p < 0.05$. The correlation of ETS and DoR with treatment were performed by chi-square test and Mann–Whitney test. Statistical analyses were carried out using statistical software packages SPSS 20.0 (IBM, Chicago, IL, USA) and Graphpad v8.0 (GraphPad Software, San Diego, CA, USA).

5. Conclusions

The improvement of therapeutic options for metastatic PC prompted the need for the identification of markers predicting the efficacy of first-line therapy and reliably anticipating patient prognosis, in order to guide clinician's choice toward the most appropriate treatment for the individual subject.

Our results obtained in a large retrospective cohort of metastatic PC patients treated with standard regimens such as modified FOLFIRINOX and GemNab suggest that an earlier and deeper tumor shrinkage is able to predict long-term outcome of PC patients. Further validation of our findings in independent prospective cohorts is warranted before implementing the use of ETS and DoR in clinical trials and in routine patients' management.

Author Contributions: Conceptualization: C.V. and E.V.; methodology: C.V., L.F. and E.V.; software: C.V. and E.V.; validation: C.V., L.F. and E.V.; formal analysis: C.V.; investigation: all authors; resources: all authors; data curation: C.V., S.C., F.S., I.P., G.P. and V.M.; writing—original draft preparation: C.V., F.S. and I.P.; writing—review and editing: all authors; visualization: all authors; supervision: L.F., E.V. and A.F.; project administration, C.V., I.P., S.C., F.S., G.P., V.M.

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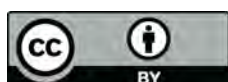
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Appendix VIVALDI03



Comprehensive pharmacogenetic analysis of *DPYD*, *UGT*, *CDA*, and *ABCB1* polymorphisms in pancreatic cancer patients receiving mFOLFIRINOX or gemcitabine plus nab-paclitaxel

Caterina Vivaldi¹ · Stefania Crucitta² · Silvia Catanese¹ · Federico Cucchiara² · Elena Arrigoni² · Irene Pecora¹ · Eleonora Roffi² · Lorenzo Fornaro¹ · Francesca Salani¹ · Valentina Massa¹ · Enrico Vasile¹ · Riccardo Morganti³ · Romano Danesi^{1,2} · Marzia Del Re²

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Abstract

Modified FOLFIRINOX (mFOLFIRINOX) and gemcitabine + nab-paclitaxel (GemNab) regimens represent a standard treatment in advanced pancreatic cancer (aPC). *DPYD* and *UGT1A1* variants are relevant predictors of fluoropyrimidine and irinotecan-associated adverse events (AEs). Furthermore, data about the associations between polymorphisms in *ABCB1* and *CDA* genes and GemNab-related toxicities are still controversial. The present study analyzes the association between *DPYD*, *UGT*, *ABCB1*, *CDA* variants, and AEs in aPC patients (pts) treated with mFOLFIRINOX or GemNab. Blood samples collected from 104 aPC pts treated with mFOLFIRINOX and 63 with GemNab were tested for *DPYD* c.1679T>G, IVS14+1G>A, c.2194G>A, c.2846A>T, *UGT1A1**28, *CDA* c.79A>C, and *ABCB1* c.1236C>T, c.2677G>T/A, c.3435C>T by real-time PCR and automatic sequencing. In mFOLFIRINOX cohort, *DPYD* IVS14+1GA genotype was associated with G4 hematological AEs, while the *UGT1A1**28 significantly correlated with the risk of thrombocytopenia ($p = 0.006$). In the GemNab cohort, a significant association between *CDA* c.79CC and high-grade nausea was observed ($p = 0.002$). Moreover, the presence of at least a mutant allele in *ABCB1* increased the risk of overall hematological AEs ($p = 0.01$), both further strengthened by the presence of *CDA* c.79CC ($p = 0.0002$). *DPYD* IVS14+1A allele is confirmed to be associated with fluoropyrimidine life-threatening toxicities, and *UGT1A1**28 is related with a higher risk of hematologic AEs following irinotecan treatment. *CDA* c.79C and *ABCB1* c.1236T, c.2677T/A, and c.3435T mutant alleles are predictive biomarkers of GemNab-related AEs. All these variants should be considered in aPC pts candidate to mFOLFIRINOX or GemNab treatments.

These authors contributed equally: Caterina Vivaldi, Stefania Crucitta

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✉ Romano Danesi
romano.danesi@unipi.it

¹ Medical Oncology Unit 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

² Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

³ Departmental Section of Statistical Support for Clinical Trials, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Introduction

Pancreatic cancer is the 4th leading cause of cancer-related deaths in US [1] and trends for pancreatic cancer mortality are rising both in US and in Europe [2].

Systemic chemotherapy represents the standard of care in advanced disease and, based on the efficacy results obtained from randomized trials, two regimens are currently recommended as first-line treatment: the combination of 5-fluorouracil (5FU), oxaliplatin and irinotecan (FOLFIRINOX) and the combination of gemcitabine and nab-paclitaxel (GemNab), both able to improve patients' outcome compared to gemcitabine monotherapy [3, 4]. Recently, adjuvant treatment with modified FOLFIRINOX (mFOLFIRINOX) resulted in better overall survival (OS) and disease-free survival (DFS) compared to gemcitabine

monotherapy; for this reason, mFOLFIRINOX represents the new standard of care also for resected patients [5].

Both FOLFIRINOX and GemNab are associated with relevant toxicities, especially neutropenia, thrombocytopenia, and diarrhea [3, 4], although different clinical factors such as age, sex and comorbidities could influence treatment compliance [6, 7]. Importantly, a decreased function in enzymes involved in drug metabolism could play a major role in developing treatment-related AEs.

The metabolism of irinotecan and 5-FU involves two liver enzymes, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and dihydropyrimidine dehydrogenase (DPD), respectively [8, 9]. The UGT1A1*28 polymorphism is characterized by an increased number of the [TA] repeated sequence in the TATA region of the UGT1A1 promoter (6 [TA] repetitions represent the wild-type condition (*1/*1) and 7 repetitions are the mutant condition *28/*28). The [TA] increase is related to a reduced UGT1A1 expression, therefore, the amount of metabolized irinotecan decreases allowing an increased risk of toxicity. It has been demonstrated that homozygous and heterozygous patients for UGT1A1*28 presented higher grades of diarrhea and neutropenia as a result of poor-metabolizer phenotype [10, 11]. Similarly, DPD activity is strongly reduced in presence of one of the following four mutations: IVS14+1G>A (rs3918290, DPYD*2A), c.1679T>G (rs55886062, DPYD*13), c.2846A>T (rs67376798), and c.1129-5923C>A (rs75017182, c.1236G>A/HapB3), proving to be relevant clinical predictors of fluoropyrimidine-associated toxicity [12, 13]. Interestingly, the association between DPD polymorphism c.2194G>A and clinically significant AEs in cancer patients treated with fluoropyrimidines has been also demonstrated [14–17].

Regarding the GemNab regimen, several studies evaluated the presence of single nucleotide polymorphisms (SNPs) in the ATP Binding Cassette Subfamily B Member (ABCB transporters), and in the cytidine deaminase (CDA) genes in patients treated with gemcitabine or taxanes-based chemotherapy and developing severe AEs [18–21] with controversial results. Polymorphisms in ABCB gene have been reviewed and correlated with diverse expression of efflux pumps in several tissue compartments and, as a result, modified drug levels [22]. Chang et al. demonstrated an association between ABCB1 polymorphisms (c.2677G/T>A and c.3435C>T) and toxicity (mucositis and diarrhea) in advanced gastric cancer patients treated with paclitaxel-based chemotherapy [23]. Furthermore, ABCB1 polymorphisms have been related to hematological AEs in cancer patients receiving taxanes [21, 24–28]. CDA is involved in the metabolic inactivation of gemcitabine [29], and the c.79A>C polymorphism has been reported to cause a reduction in CDA enzyme activity, allowing a reduced metabolism of gemcitabine and consequently increased risk of AEs [30]. In the phase III Radiation Therapy Oncology Group (RTOG)

9704 study evaluating the addition of gemcitabine to pre- and post- chemoradiation with 5FU in resected pancreatic cancer patients, the presence of CDA c.79A>C polymorphism was associated with gemcitabine hematological toxicity [19]. Similarly, in a retrospective analysis, CDA c.79A>C was correlated with grade 3–4 neutropenia in 149 advanced pancreatic cancer patients who underwent gemcitabine-based chemoradiotherapy [18]. In contrast, the analysis lead by Okazaky et al. did not show any association between CDA c.79A>C and the AEs of gemcitabine-based chemoradiotherapy in pancreatic cancer patients [31].

The present study is aimed to evaluate the role of known polymorphisms in DPYD, UGT, ABCB, and CDA genes and their possible association with toxicity in pancreatic cancer patients treated with modified FOLFIRINOX (mFOLFIRINOX) [32] or GemNab.

Patients and methods

Patients' characteristics

Patients affected by advanced pancreatic adenocarcinoma and treated at the University Hospital of Pisa with first-line mFOLFIRINOX or gemcitabine + nab-paclitaxel between 2010 and 2017 were enrolled. All patients were treated with standard schedule and dose reductions were performed in case of toxicity as per clinical practice. Administered schedule for mFOLFIRINOX was as follows: oxaliplatin 85 mg/sqm intravenously on day 1, irinotecan 165 mg/sqm intravenously on day 1, leucovorin 200 mg/sqm intravenously on day 1, fluorouracil 3200 mg/sqm 48 h continuous infusion starting on day 1, cycles repeated every 14 days. Administered schedule for gemcitabine + nab-paclitaxel was as follows: gemcitabine 1000 mg/sqm intravenously on days 1, 8, and 15 + nab-paclitaxel 12 mg/sqm on days 1, 8, and 15, cycles repeated every 28 days.

Main inclusion criteria were: availability of data regarding toxicity and efficacy of first-line treatment, a minimum of 1 administered completed chemotherapy cycle, and availability of blood sample.

The study was approved by the Ethics Committee of Pisa University Hospital and conducted in accordance with the principles of the Declaration of Helsinki; all patients gave their signed informed consent before blood collection and DNA analysis.

Laboratory investigators were blinded to the clinical information on patients' outcome.

Methods

Three ml of whole blood were taken from all patients, stored in EDTA, and genomic DNA was extracted from

200 µl by the Biorobot EZ1 (Qiagen®, Valencia, CA). The analysis of *DPYD*, *CDA* and *ABCB1* variants were conducted on a Real-Time PCR instrument (HT 7900 Life Technologies, Carlsbad, CA), by using the TaqMan® SNP Genotyping Assay. *UGT1A1**28 variant was evaluated on a Sanger Sequencing 3100 instrument (Life Technologies, Carlsbad, CA). Analyzed variants included: *DPYD* c.1679T>G, IVS14+1G>A, c.2194G>A, c.2846A>T; *UGT1A1**28; *CDA* c.79A>C; *ABCB1* c.1236C>T, c.2677G>T/A, c.3435C>T. Negative, positive controls, and blanks were used to assess the genotype of each variant analyzed.

Statistical analysis

Toxicity during treatment was graded by the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03. Categorical data were described by absolute and relative frequencies, whereas quantitative data were reported as mean and standard deviation. The frequencies of *DPYD*, *UGT1A1*, *CDA*, and *ABCB1* polymorphisms were compared to the worldwide population, and Hardy–Weinberg equilibrium was assessed.

The association between each gene polymorphism and AEs was evaluated by chi-square test, adjusting the *p* value by the appropriate *z*-test for proportions. Odds ratio was also calculated. A significant threshold of 0.025 was considered for *DPYD* c.2194G>A and *UGT1A1**28 analysis, after Bonferroni correction. Likewise, Bonferroni post hoc test for multiple testing of 2 genes (*CDA*, *ABCB1*) was applied, giving a significant threshold of 0.025 (=0.05/2). Applying this across the common variants tested (*n* = 4) would give a Bonferroni-corrected *p* value of 0.0125.

Mann–Whitney analysis was used to evaluate the different grades of AEs and SNPs. Progression-free survival (PFS) and OS were defined as the time from treatment start to progression disease or death, respectively. The Kaplan–Meier method was used to create PFS curves and log-rank test was used to evaluate the differences between curves.

Statistical significance was defined by a *p* value < 0.05. Analysis was performed by MedCalc version 14.8.1 and IBM SPSS statistics for Windows, version 26.0 (Armonk, NYI).

Results

A total 167 patients were consecutively enrolled in this study and divided in 2 cohorts, depending on the treatment received; 104 patients were treated with mFOLFIRINOX and 63 with GemNab. Main clinical characteristics of the whole population are reported in Table 1. The calculation of Hardy–Weinberg equilibrium was performed; nevertheless,

Table 1 Patient characteristics.

Characteristics	All patients		Cohort 1 (mFOLFIRINOX)		Cohort 2 (GemNab)	
	<i>N</i> = 167	%	<i>N</i> = 104	%	<i>N</i> = 63	%
Age years, median (range)	64 (44–77)		63 (44–75)		65 (45–77)	
Gender						
Male	82	49	51	49	31	49
Female	85	51	53	51	32	51
ECOG performance status						
0	115	69	83	80	32	51
1	49	29	20	19	29	46
2	3	2	1	1	2	3
Previous surgery on primary tumor						
Yes	31	19	16	15	15	24
No	136	81	88	85	48	76
Tumor stage						
III	44	26	41	39	3	5
IV	123	74	63	61	60	95
Number of metastatic sites median (range)	1 (1–4)		2 (1–5)		2 (1–4)	
Metastatic sites						
Liver	88	53	47	45	41	63
Lung	18	11	7	7	11	17
Lymph nodes	37	22	23	22	14	22
Peritoneum	34	20	17	16	17	27
Local recurrence	5	3	2	2	3	5
Other	7	4	4	4	3	5
Number of administered cycles median (range)	–		8 (1–27)		4 (1–19)	

not all the polymorphisms were found to be in equilibrium (Table 2).

Cohort 1

In the mFOLFIRINOX cohort, 53 (51%) patients experienced grade ≥3 AEs, with 44 (42%) patients reporting hematologic and 20 (19%) patients reporting gastrointestinal toxicities, respectively. Main grade >2 AEs were neutropenia (40.4%), diarrhea (7.7%), and stomatitis (6.7%). In fifty-one patients (49%) at least one cycle of chemotherapy was postponed and 39 (37%) patients needed a dose reduction.

The *DPYD* analysis found one patient carrier of the IVS14+1GA genotype, 8 patients had the c.2194GA genotype, while no carriers of c.1679T>G or c.2846A>T were found. At the *UGT* analysis, 38 patients were *UGT1A1**1/*28, while 18 patients were *UGT1A1**28/*28. Additionally, three patients showed the concomitant presence of *DPYD* c.2194GA, and *UGT1A1**1/*28 genotype.

Table 2 Frequency of DPYD, UGT1A1, CDA, and ABCB1 SNPs.

SNPs	Genotypes	N	(%)	HWE (P_{HWE})
DPYD c.2194G>A	GG	96	92	0.17 (0.68)
	GA	8	8	
	AA	—	—	
UGT1A1*28	*1/*1	48	46.2	4.28 (0.04) ^a
	*1/*28	38	36.5	
	*28/*28	18	17.3	
CDA c.79A>C	AA	18	28.6	0.39 (0.53)
	AC	29	46	
	CC	16	25.4	
ABCB1 c.1236C>T	CC	16	25.4	0.15 (0.69)
	CT	33	52.4	
	TT	14	22.2	
ABCB1 c.2677G>T/A	GG	18	28.6	9.43 (0.002) ^a
	GT	19	30.1	
	TT + TA	26	41.3	
ABCB1 c.3435C>T	CC	17	27	0.40 (0.53)
	CT	29	46	
	TT	17	27	

SNPs single nucleotide polymorphisms, N number of patients.

^aDisequilibrium of HWE.

The statistical analysis for the IVS14+1GA was not performed since only one patient was carrier of the mutant allele; however, the patient experienced G4 hematological (febrile neutropenia and thrombocytopenia) and G3 non-hematological (mucositis) AEs after the first cycle at a standard dose and treatment was interrupted.

Three out of five patients harboring c.2194GA genotype and wild-type UGT experienced at least one grade >2 AEs during treatment and the most frequent grade >2 AEs were neutropenia (60%) and stomatitis (20%). Twenty-seven out of 53 patients (51%) bearing UGT1A1*28 (hetero or homozygous condition) with a wild-type DPYD genotype experienced at least one grade >2 AE during treatment and most frequent grade >2 AEs were neutropenia (43%) and stomatitis (8%). Two out of the three patients showing the concomitant presence of DPYD c.2194GA and UGT1A1*1/*28 genotype experienced grade >2 AE (neutropenia).

No significant association between c.2194GA and any grade of hematologic ($p = 0.08$ for thrombocytopenia risk) and gastrointestinal 5-FU related toxicity or hand-foot syndrome (HFS; $p = 0.096$) was found.

Regarding irinotecan, the association between UGT1A1*28 and any grade (or grade ≥ 3) of hematologic or gastrointestinal toxicities was evaluated. The UGT1A1*28 allele was significantly correlated with the risk of developing thrombocytopenia (OR 3.17, 95% CI 1.27–7.93, $p = 0.006$). Moreover, stratifying patients based on the presence of mutant alleles and their risk of developing

thrombocytopenia, the *28/*28 or *1/*28 genotypes were at increased risk with respect to the *1/*1 (i.e., the risk of thrombocytopenia decreased with this order: *28/*28 > *1/*28 > *1/*1, $p = 0.003$). Grouping patients based on their haplotypes, including DPYD and UGT, a significant association in the subgroup of patients carrying a wild-type DPYD and UGT1A1*1/*28 was found with gastrointestinal toxicities ($p = 0.004$; Table 3).

In terms of efficacy, no difference in PFS (Hazard Ratio 0.81, 95% confidence interval 0.47–1.40, $p = 0.45$) and OS (HR 1.22, 95% CI 0.67–2.27, $p = 0.51$) were reported in patients harboring *28 alleles who underwent dose reduction ($N = 26$) compared to wild-type patients treated with standard dose who did not need dose adjustments ($N = 33$) (Fig. 1).

Sixteen out of 104 patients in the FOLFIRINOX cohort undergone resection of primary tumor prior to chemotherapy starting. None of them was carrier of a DPYD polymorphism, while ten patients harbored the UGT variant (four were UGT1A1*1/*28 and six were UGT1A1*28/*28). Incidence of diarrhea and high-grade diarrhea did not significantly differ between resected and not-resected patients ($p = 0.74$ and $p = 0.33$, respectively). In resected patients no significant association between UGT polymorphisms and any grade (or grade ≥ 3) diarrhea was found ($p = 0.95$ and $p = 0.69$, respectively).

Cohort 2

In the GemNab cohort, 36 (57%) patients experienced at least a grade ≥ 3 AEs, with 35 (56%) patients reporting hematologic toxicities and 2 (3%) patients reporting gastrointestinal toxicities, respectively. Main grade >2 AEs were neutropenia (48%), anemia (17%) and thrombocytopenia (13%). In forty-two patients (67%) at least one cycle of chemotherapy has been postponed and in 18 (29%) dose of chemotherapy was reduced due to AEs.

The analysis of the CDA c.79A>C polymorphism discovered 29 heterozygous and 16 homozygous patients. The analysis of ABCB1 identified a total of 47 mutant patients; in detail, 33 heterozygous and 14 homozygous patients for the c.1236C>T SNP; 19 heterozygous and 26 homozygous patients for the c.2677G>TA polymorphism and 29 heterozygous and 17 homozygous patients for the c.3435C>T SNP. Thirty-six patients showed concomitant presence of CDA and ABCB1 variants. In detail, CDA c.79AC and c.79CC variants were concomitantly found with ABCB1 c.1236CT/TT, c.2677GT/AT/TT, and c.3435CT/TT in 23 and 13 patients, respectively.

Grouping patients based on their haplotypes, including CDA and ABCB1 together, a significant association

Table 3 Associations of mFOLFIRINOX toxicity and candidate SNPs by grouping for concomitant polymorphisms.

Genotype	Non-hematologic toxicities	Nausea (yes vs. no) p value	Nausea ≥ G3 (no vs. yes) p value	Vomiting (no vs. yes) p value	Vomiting ≥ G3 (no vs. yes) p value	Diarrhea (yes vs. no) p value	Diarrhea ≥ G3 (no vs. yes) p value	Stomatitis (yes vs. no) p value	Stomatitis ≥ G3 (no vs. yes) p value	Hand-foot syndrome (no vs. yes) p value	Overall all (yes vs. no) p value	Overall ≥ G3 (no vs. yes) p value
c.2194GG UGT1A1*1/*1		0.94	0.19	0.42	0.77	0.99	0.19	0.77	0.45	0.94	0.09	0.16
c.2194GG UGT1A1*1/*28		0.94	0.37	0.55	0.32	0.63	0.79	0.73	0.13	0.84	0.004	0.64
c.2194GG UGT1A1*28/*28		0.74	0.92	0.06	0.26	0.59	0.16	0.76	0.18	0.18	0.33	0.05
c.2194GA UGT1A1*1/*1		0.25	0.62	0.13	0.73	0.89	0.54	0.54	0.17	0.17	0.67	0.92
c.2194GA UGT1A1*1/*28		0.31	0.62	0.27	0.79	0.84	0.60	0.19	0.62	0.08	0.71	0.34
Genotype	Hematologic toxicities	Neutropenia (yes vs. no) p value	Neutropenia ≥ G3 (no vs. yes) p value	Thrombocytopenia (no vs. yes) p value	Thrombocytopenia ≥ G3 (no vs. yes) p value	Anemia (yes vs. no) p value	Anemia ≥ G3 (no vs. yes) p value	Overall (yes vs. no) p value	Overall ≥ G3 (yes vs. no) p value			
c.2194GG UGT1A1*1/*1		0.31	0.27	0.003	0.80	0.67	0.98	0.41	0.82			
c.2194GG UGT1A1*1/*28		0.96	0.67	0.20	0.21	0.32	0.75	0.16	0.83			
c.2194GG UGT1A1*28/*28		0.62	0.94	0.42	0.39	0.35	0.94	0.63	0.56			
c.2194GA UGT1A1*1/*1		0.74	0.22	0.10	0.71	0.52	0.63	0.83	0.44			
c.2194GA UGT1A1*1/*28		0.22	0.45	0.26	0.75	0.20	0.68	0.86	0.71			

SNPs single nucleotide polymorphisms, G grade.

Values in bold are significant.

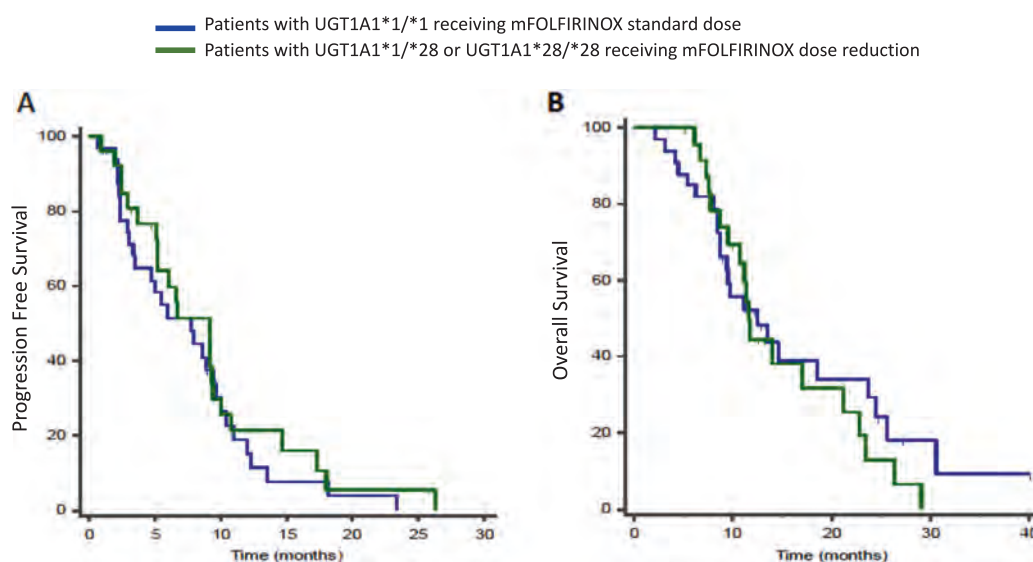


Fig. 1 Involvement of UGT1A1*28 in clinical outcome of patients. Progression-free survival (A) and overall survival (B) in patients harboring UGT1A1*28 alleles who needed dose reduction vs. wild-type patients treated with standard dose mFOLFIRINOX.

between CDA c.79CC and high-grade nausea was observed in the subgroup of patients carrying the CDA mutant genotype and wild-type ABCB1 ($p = 0.002$; Table 4). Moreover, patients with a heterozygous or homozygous variant for one of the ABCB1 SNPs had an increased risk of hematological toxicities, including anemia ($p = 0.01$; Table 4), and the presence of CDA c.79CC strengthened these significant associations ($p = 0.0002$; Table 4). Comprehensive statistical analysis is reported in Supplementary Table 1.

Discussion

The role of DPYD and UGT polymorphisms in fluoropyrimidine and irinotecan-correlated toxicity was initially investigated in colorectal cancer [14, 33]. In pancreatic cancer, an exploratory analysis of the observational JASPAC 06 trial investigated the correlation between the incidence of AEs in Japanese patients treated with FOLFIRINOX and UGT1A1*6 and *28 variant alleles. In this study, patients with UGT1A1 heterozygous genotype experienced severe toxicity (i.e., diarrhea) compared with patients without UGT1A1*6 or *28 alleles [34].

Recently, a case report described a 59-year-old metastatic pancreatic cancer patient receiving FOLFIRINOX therapy showing a severe 5-FU toxicity after a single cycle. Interestingly, the sequencing on entire DPYD gene revealed heterozygous genotypes for three different polymorphisms: DPYD*2A (IVS14+1G>A), c.1601G>A and c.2194G>A. The patient was also carrier of the UGT1A1*28/*28 genotype [35]. Similarly, Velez-Velez et al. presented a case of

a patient with pancreatic adenocarcinoma who was found homozygous for the UGT1A1*28 allele, and heterozygous for a DPYD variant through pharmacogenomic testing. In this case, severe toxicity was prevented by a reduction of starting dose, and these results suggested the clinical value of integrating pharmacogenomic testing into clinical practice to allow a preemptive dose reduction in patients at high risk of toxicity [36].

Our study confirms the association between DPYD IVS14+1A allele with life-threatening toxicities. While other published studies demonstrated an association between c.2194G>A and fluoropyrimidine-related toxicity [37, 38], we were unable to find significant correlations, probably due to the small number of c.2194GA allele carriers.

The clinical impact of the c.2194G>A SNP still need to be confirmed prospectively; however, published retrospective studies showed a correlation with fluoropyrimidine-related toxicity [15, 16, 39, 40]. The TOSCA trial confirmed the association between c.2194G>A and fluoropyrimidine-related toxicity in 508 colorectal cancer patients treated with FOLFOX or XELOX adjuvant chemotherapy for 3 or 6 months [16]. In a subgroup analysis carried out from the CAIRO trial, the c.2194G>A was significantly associated with grade 3–4 diarrhea, even if with a low predictive value (41%) [40]. An association between the c.2194G>A and neutropenia was also found in the PETACC-8 trial, which enrolled 1545 patients affected by colorectal cancer, receiving standard adjuvant FOLFOX4 or FOLFOX4 in combination with cetuximab [15]. A recent published study on 366 fluoropyrimidines-treated patients confirmed the association between the c.2194G>A and severe neutropenia [17].

Table 4 Significant associations of GemNab AEs and candidate SNPs by grouping for co-occurring polymorphisms. Bonferroni post-hoc test was applied across the common CDA and *ABCB1* variants ($n = 4$) giving a significant threshold of 0.0125 ($=0.05/4$).

Genotype	Non-hematologic toxicities					Hematologic toxicities									
	Nausea (yes vs. no) <i>p</i> value	Nausea ≥ G3 (yes vs. no) <i>p</i> value	Vomiting (yes vs. no) <i>p</i> value	Diarrhea (no vs. yes) <i>p</i> value	Diarrhea ≥ G3 (yes vs. no) <i>p</i> value	Stomatitis (no vs. yes) <i>p</i> value	Overall (yes vs. no) <i>p</i> value	Neutropenia (yes vs. no) <i>p</i> value	Neutropenia ≥ G3 (no vs. yes) <i>p</i> value	Thrombocytopenia (yes vs. no) <i>p</i> value	Thrombocytopenia ≥ G3 (no vs. yes) <i>p</i> value	Anemia (yes vs. no) <i>p</i> value	Anemia ≥ G3 (no vs. yes) <i>p</i> value	Overall (yes vs. no) <i>p</i> value	Overall ≥ G3 (yes vs. no) <i>p</i> value
CDA c.79AA ABCB1 c.1236 _{CT} ABCB1 c.2677 _{GG} ABCB1 c.3435 _{CT}	0.27	0.86	0.56	0.37	0.86	0.51	0.05								
CDA c.79AC ABCB1 c.1236 _{CC} ABCB1 c.2677 _{GG} ABCB1 c.3435 _{CC}	0.80	0.64	0.59	0.23	0.05	0.26	0.19								
CDA c.79AC ABCB1 c.1236 _{TT} ABCB1 c.2677 _{TT/TA/AA} ABCB1 c.3435 _{TT}	0.02	0.05	0.02	0.23	0.64	0.26	0.19								
CDA c.79CC ABCB1 c.1236 _{CC} ABCB1 c.2677 _{GG} ABCB1 c.3435 _{CC}	0.67	0.002	0.10	0.71	0.75	0.35	0.37								
CDA c.79CC ABCB1 c.1236 _{CT} ABCB1 c.2677 _{GT/GA} ABCB1 c.3435 _{CT}	0.54	0.64	0.13	0.73	0.05	0.45	0.42								
CDA c.79CC ABCB1 c.1236 _{CT} ABCB1 c.2677 _{TT/TA/AA} ABCB1 c.3435 _{CT}	0.11	0.79	0.40	0.21	0.79	0.35	0.01								
CDA c.79AA ABCB1 c.1236 _{CC} ABCB1 c.2677 _{GG} ABCB1 c.3435 _{CT}	0.16	0.34	0.35	0.70	0.85	0.04	0.38								
CDA c.79AA ABCB1 c.1236 _{CT} ABCB1 c.2677 _{GT/GA} ABCB1 c.3435 _{CT}	0.50	0.05	0.23	0.42	0.01	0.30	0.01								
CDA c.79AA ABCB1 c.1236 _{CT} ABCB1 c.2677 _{TT/TA/AA} ABCB1 c.3435 _{CC}	0.47	0.29	0.35	0.70	0.85	0.04	0.38								
CDA c.79AC ABCB1 c.1236 _{CC} ABCB1 c.2677 _{GG} ABCB1 c.3435 _{CT}	0.16	0.34	0.35	0.70	0.84	0.04	0.38								
CDA c.79CC ABCB1 c.1236 _{CT} ABCB1 c.2677 _{TT/TA/AA} ABCB1 c.3435 _{CT}	0.05	0.17	0.90	0.58	0.0002	0.47	0.0002								

Values in bold are significant.

Concerning UGT, the presence of 1A1*28 allele was significantly associated with AEs, including thrombocytopenia and neutropenia, as also reported in literature [10, 11, 41].

With regards to GemNab treatment, the present study evaluated the role of polymorphisms in CDA and ABCB1 genes and their relationship with toxicity development. Previous analyses independently investigated this association in patients affected by solid tumor—including pancreatic cancer—with controversial results [18–21, 23, 42–45].

A multicenter prospective clinical trial in gemcitabine-treated pancreatic patients failed to identify CDA status as predictive marker of toxicities [45]. Similarly, a study conducted by Chang et al. did not show a correlation between ABCB1 genotypes and paclitaxel AEs [44]. In the present study, the combined presence of heterozygous or homozygous variants for CDA c.79A>C and ABCB1 significantly correlated with gastrointestinal and hematological AEs. A meta-analysis [46] suggested that CDA c.79A>C may be a potential genotype marker of gemcitabine-related severe anemia, in agreement with our findings. Similarly, Ding et al. suggested that CDA c.79C allele is associated with high-grade hematological AEs and reduced CDA activity [20].

The present study considered the most frequent CDA/ABCB1 variants for Caucasian populations [47, 48]. Nonetheless, other variants have been considered in other studies, according to the ethnicity. As an example, the screening for CDA c.208G>A polymorphism may have a clinical meaning in Asian and Japanese population treated with gemcitabine, being reported as a major cause of life-threatening toxicities [49–51]. No other evidence emerged in literature for ABCB1 gene. Despite the present study has some limitations, including its retrospective nature, it provides one of the first extensive pharmacogenetic characterization of pancreatic cancer patients treated with FOLFIRINOX or GemNab regimens and it would be certainly interesting to evaluate the possible correlation between SNPs and AEs in a larger validation prospective cohort, to develop a genotype-guided approach for treatment personalisation.

Given the difficult management and the poor outcome of pancreatic cancer, the improvement in tolerability represents an essential issue both in advanced and in early stages. To date, several recommendations suggest the preemptive screening of the DPYD and UGT1A1*28 variants, suggesting dose adjustment in poor metabolizers [52, 53].

Recently, EMA's safety committee has recommended that patients should be tested for DPD deficiency before starting treatment with fluorouracil, capecitabine, and tegafur [54].

The Italian Association of Medical Oncology and the Italian Society of Pharmacology (AIOM-SIF working

group) released a national recommendation for DPYD and UGT screening, including also the c.2194G>A variant [55]. The suggested dose reduction in patients harboring the IVS14+1GA, c.1679TG, 2846AT genotypes is 50%, and for homozygous patients a fluoropyrimidines-based treatment is not suggested. A dose reduction of 15% or 30% in the presence of heterozygous or homozygous c.2194G>A genotypes, respectively, is suggested. A recent meta-analysis demonstrated the significant relationship between UGT1A1*28 polymorphism with toxicity and response to irinotecan-based chemotherapy [56]. However, our data demonstrate that in the presence of a deficient genotype, the response to treatment is not reduced in case of dose adjustment.

In order to prevent the occurrence of treatment-related AEs in pancreatic cancer patients carrying DPYD or UGT1A1*28 variants, a screening test prior to start FOLFIRINOX regimen is therefore required.

For patients with at least one mutated allele of UGT1A1, careful management of hematological and gastrointestinal toxicity is recommended, and a modified FOLFIRINOX with a dose reduction of 30% of irinotecan in homozygous patients might be appropriate.

In conclusion, no upfront genotyping test seems to predict AEs in pancreatic cancer patients treated with GemNab. Further studies with larger validation cohorts are needed to confirm the possible influence of CDA and ABCB1 polymorphisms on GemNab related toxicities. Conversely, in accordance with literature data, our results support DPYD and UGT1A1 genotype-guided dosing schedules for the management of patients candidate to FOLFIRINOX regimen.

Data availability

Data and results are available at the Unit of Clinical Pharmacology and Pharmacogenetics, University Hospital of Pisa.

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Author contributions Conception and design: MDR, CV. Development of methodology: MDR, SC, ER, and EA. Clinical protocols/amendments: MDR, RD. Acquisition of data: MDR, SC, ER, EA, and CV. Analysis and interpretation of data: MDR, CV, SC, FC, RM, and RD. Writing, review, and/or revision of the paper: all authors. Administrative, technical, or material support: MDR, SC, ER, and RD. Study supervision: MDR, RD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate The study was approved by the Ethics Committee of Pisa University Hospital. Written informed consent was obtained from each patient included, and this study was performed in accordance with the Declaration of Helsinki.

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Appendix WAINBERG03



NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial



Zev A Wainberg, Davide Melisi, Teresa Macarulla, Roberto Pazo Cid, Sreenivasa R Chandana, Christelle De La Fouchardière, Andrew Dean, Igor Kiss, Woo Jin Lee, Thorsten O Goetze, Eric Van Cutsem, A Scott Paulson, Tanios Bekaii-Saab, Shubham Pant, Richard A Hubner, Zhimin Xiao, Huanyu Chen, Fawzi Benzaghrou, Eileen M O'Reilly

Summary

Background Pancreatic ductal adenocarcinoma remains one of the most lethal malignancies, with few treatment options. NAPOLI 3 aimed to compare the efficacy and safety of NALIRIFOX versus nab-paclitaxel and gemcitabine as first-line therapy for metastatic pancreatic ductal adenocarcinoma (mPDAC).

Methods NAPOLI 3 was a randomised, open-label, phase 3 study conducted at 187 community and academic sites in 18 countries worldwide across Europe, North America, South America, Asia, and Australia. Patients with mPDAC and Eastern Cooperative Oncology Group performance status score 0 or 1 were randomly assigned (1:1) to receive NALIRIFOX (liposomal irinotecan 50 mg/m², oxaliplatin 60 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m², administered sequentially as a continuous intravenous infusion over 46 h) on days 1 and 15 of a 28-day cycle or nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m², administered intravenously, on days 1, 8, and 15 of a 28-day cycle. Balanced block randomisation was stratified by geographical region, performance status, and liver metastases, managed through an interactive web response system. The primary endpoint was overall survival in the intention-to-treat population, evaluated when at least 543 events were observed across the two treatment groups. Safety was evaluated in all patients who received at least one dose of study treatment. This completed trial is registered with ClinicalTrials.gov, NCT04083235.

Findings Between Feb 19, 2020 and Aug 17, 2021, 770 patients were randomly assigned (NALIRIFOX, 383; nab-paclitaxel–gemcitabine, 387; median follow-up 16·1 months [IQR 13·4–19·1]). Median overall survival was 11·1 months (95% CI 10·0–12·1) with NALIRIFOX versus 9·2 months (8·3–10·6) with nab-paclitaxel–gemcitabine (hazard ratio 0·83; 95% CI 0·70–0·99; p=0·036). Grade 3 or higher treatment-emergent adverse events occurred in 322 (87%) of 370 patients receiving NALIRIFOX and 326 (86%) of 379 patients receiving nab-paclitaxel–gemcitabine; treatment-related deaths occurred in six (2%) patients in the NALIRIFOX group and eight (2%) patients in the nab-paclitaxel–gemcitabine group.

Interpretation Our findings support use of the NALIRIFOX regimen as a possible reference regimen for first-line treatment of mPDAC.

Funding Ipsen.

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Introduction

Pancreatic ductal adenocarcinoma remains one of the most lethal malignancies, with an estimated 5-year survival of only 3% for patients diagnosed with metastatic disease.^{1,2} In the past decade, two combination chemotherapy regimens, a quadruplet of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and a doublet, nab-paclitaxel and gemcitabine, have emerged as first-line standard of care.^{3–5} However, these regimens have never been compared directly leaving uncertainty about the optimal treatment regimen. With the exception of microsatellite instability-high pancreatic

cancer, immune checkpoint inhibitors have demonstrated only partial benefits, and although there has been much interest in using genomic profiling to improve outcomes, relatively few patients are eligible to receive molecularly targeted agents.^{6–8} The poor prognosis and low number of treatment options available for most patients highlight the need for further research to compare efficacious and tolerable new treatment approaches, and to maximise the benefits of cytotoxic chemotherapy regimens.

Irinotecan is a topoisomerase I inhibitor acting mainly via its active metabolite, SN-38.⁹ Liposomal irinotecan

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For the plain language summary see Online for appendix 1

David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA (Z A Wainberg MD); Università degli studi di Verona and Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy (D Melisi MD); Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain (T Macarulla MD); Hospital Universitario Miguel Servet, Zaragoza, Spain (R Pazo Cid MD); Cancer and Hematology Centers of Western Michigan, Grand Rapids, MI, USA (S R Chandana MD); Centre Léon Bérard, Lyon, France (C De La Fouchardière MD); St John of God Subiaco Hospital, Subiaco, WA, Australia (A Dean MD); Masaryk Memorial Cancer Institute, Brno, Czech Republic (I Kiss MD); National Cancer Center, Goyang, South Korea (W J Lee MD); Krankenhaus Nordwest, Frankfurt am Main, Germany (T O Goetze MD); University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium (E Van Cutsem MD); Texas Oncology-Baylor Charles A Sammons Cancer Center, Dallas, TX, USA (A S Paulson MD); Mayo Clinic, Scottsdale, AZ, USA (T Bekaii-Saab MD); MD Anderson Cancer Center, Houston, TX, USA (S Pant MD); The Christie NHS Foundation Trust, and Division of Cancer Sciences, University of Manchester, Manchester, UK

Research in context

Evidence before this study

Evidence around these trials was gathered from clinical guidelines and clinical experience; therefore no systematic search was undertaken. In the past decade, two combination chemotherapy regimens, fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and nab-paclitaxel and gemcitabine, have emerged as first-line standard of care for patients with metastatic pancreatic ductal adenocarcinoma. In phase 3 trials, FOLFIRINOX and nab-paclitaxel and gemcitabine have each been compared with gemcitabine alone, but the two regimens have never been compared head to head, leaving uncertainty about the optimal first-line treatment option. Liposomal irinotecan is a liposomal formulation that encapsulates irinotecan, a topoisomerase I inhibitor, in a lipid bilayer vesicle. Encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to its active metabolite, SN-38. Thus, at equivalent doses, liposomal irinotecan demonstrates higher and sustained intratumoural levels of irinotecan and SN-38 relative to free irinotecan. In a phase 1/2 trial (NCT02551991) liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX), demonstrated promising antitumour activity in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma.

Added value of this study

To our knowledge, NAPOLI 3 is the first phase 3 trial, performed in community and academic centres worldwide, to compare two combination chemotherapy regimens head to head in patients with pancreatic ductal adenocarcinoma who have not previously received treatment for metastatic disease. Before NAPOLI 3, decisions as to the optimal combination chemotherapy regimen for most patients were based on cross-trial comparisons. As well as comparing with a standard-of-care regimen, NAPOLI 3 had fewer restrictions on eligibility than most phase 3 pancreatic cancer trials, for example no upper age restrictions and no exclusion for patients with clinical ascites. Before NAPOLI 3, the last trial to meet the primary endpoint of overall survival in patients with metastatic pancreatic ductal adenocarcinoma was the MPACT trial in 2013, which led to the approval of first-line nab-paclitaxel and gemcitabine with a median overall survival of 8.5 months. The NALIRIFOX regimen provides a new reference standard on which to base further improvements in the future.

Implications of all the available evidence

The findings of this study support the use of the NALIRIFOX regimen as a new possible standard of care and reference regimen for the first-line treatment of patients with metastatic pancreatic ductal adenocarcinoma.

(R A Hubner MD); Ipsen, Cambridge, MA, USA (Z Xiao MD, H Chen PhD, F Benzaghou MD); Memorial Sloan Kettering Cancer Center, New York, NY, USA (E M O'Reilly MD)

Correspondence to: Zev A Wainberg, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90404, USA zwainberg@mednet.ucla.edu

(ONIVYDE, ONIVYDE pegylated liposomal; historical names include nal-IRI, MM 398, or PEP02; Ipsen, Cambridge, MA, USA) is a liposomal formulation that encapsulates irinotecan in a lipid bilayer vesicle. Encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to SN-38. Thus, at equivalent doses, liposomal irinotecan demonstrates higher and sustained intratumoural levels of irinotecan and SN-38 relative to free irinotecan.^{10,11} Data from a pilot study of liposomal irinotecan in patients (n=13) with refractory advanced solid tumours reported five-fold higher levels of SN-38 in tumour biopsy samples than in plasma 72 h after dosing, suggesting local metabolic activation of irinotecan to SN-38.¹²

In the phase 3 NAPOLI 1 trial, liposomal irinotecan in combination with fluorouracil and leucovorin significantly prolonged overall survival versus fluorouracil and leucovorin in patients with metastatic pancreatic ductal adenocarcinoma whose disease had progressed following gemcitabine-based therapy.¹³ A phase 1/2 trial (NCT02551991) demonstrated promising antitumour activity with liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma. Median progression-free survival was 9.2 months (95% CI 7.69–11.96) and overall survival was 12.6 months (8.74–18.69).¹⁴

Building on these findings, the phase 3 NAPOLI 3 study (NCT04083235) aimed to compare NALIRIFOX with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma not previously treated in the metastatic setting.

Methods

Study design and participants

NAPOLI 3 was a randomised, open-label, phase 3 study conducted at 187 community and academic centres in 18 countries worldwide across Europe, North America, South America, Asia, and Australia (appendix 2 p 16). The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice and the requirements of the US Food and Drug Administration or local regulatory authorities regarding the conduct of human clinical trials. The protocol was approved by the local institutional review board and independent ethics committees of the participating centres. Protocol amendments made after the study started are described in the protocol.

Eligible participants were aged 18 years or older with histologically or cytologically (according to the eighth edition of the American Joint Committee on Cancer staging manual)¹⁵ confirmed pancreatic ductal adenocarcinoma previously untreated in the metastatic setting. Patients who received previous treatment for pancreatic

See Online for appendix 2

For the protocol see <https://s3.eu-west-2.amazonaws.com/ox-files/Protocol.pdf>

ductal adenocarcinoma with chemotherapy in the adjuvant setting were excluded; however, those who had received their last dose of adjuvant therapy more than 12 months before study entry and who had no persistent treatment-related toxicity were eligible. Patients had to have one or more metastatic tumours measurable with CT or MRI according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1¹⁶ and an Eastern Cooperative Oncology Group performance status score of 0 or 1. The initial diagnosis of metastatic disease must have occurred within the 6 weeks before screening. Full eligibility criteria are provided in appendix 2 (pp 10–12). Patients provided written informed consent at screening.

Randomisation and masking

In this open-label NAPOLI 3 study, patients were randomly assigned (1:1) to receive NALIRIFOX or nab-paclitaxel and gemcitabine, stratified by geographical region (North America vs east Asia vs the rest of the world), performance status (Eastern Cooperative Oncology Group performance status score of 0 vs 1), and liver metastases (yes vs no). The randomisation scheme was prepared using block randomisation via a third party, and randomisation was performed by a third party by means of an integrated interactive voice response or web response system.

Procedures

Patients received NALIRIFOX (liposomal irinotecan 50 mg/m², oxaliplatin 60 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m², administered sequentially as a continuous intravenous infusion over 46 h) on

days 1 and 15 of a 28-day cycle, or nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m², administered intravenously, on days 1, 8, and 15 of a 28-day cycle.

Tumour evaluations were performed by CT or MRI at screening (baseline) and every 8 weeks until progressive disease using RECIST version 1.1. In patients without disease progression at the time of treatment discontinuation, tumour evaluations were performed every 8 weeks during follow-up until progressive disease, or until the start of another anticancer treatment, whichever came first.

Treatment continued until radiologically determined disease progression (as per RECIST version 1.1)¹⁶ or unacceptable toxicity as assessed by individual investigators. Patients completed a 30-day follow-up assessment after permanent discontinuation of study treatment, then entered long-term follow-up (every 2 months) during which survival status was monitored until death, loss to follow-up, withdrawal of consent, or study closure, whichever occurred first. Details are in appendix 2 (p 13). Full details of study procedures and schedules can be found in the protocol.

Outcomes

The primary outcome was overall survival for NALIRIFOX versus nab-paclitaxel and gemcitabine, defined as the number of months from randomisation to the date of death owing to any cause. Secondary outcomes were progression-free survival (time from randomisation to first documented disease progression using RECIST version 1.1 by investigator review or death due to any cause, whichever occurred first) and overall response rate (proportion of patients with a best overall response of partial or complete response) classified using RECIST version 1.1 by investigator review. Details of the per-protocol study endpoints are in appendix 2 (pp 13–14).

Adverse events were recorded and coded using the Medical Dictionary for Regulatory Activities (version 25.0), and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).¹⁷

Statistical analysis

The primary endpoint of overall survival was evaluated when at least 543 events were observed across the two treatment groups to provide at least 90% power to detect a hazard ratio (HR) of 0.75 with an overall two-sided type one error level of 0.05. The planned sample size was 750 patients and could be increased if a review of accumulating overall survival events suggested that timing of the final analysis be extended. Assuming median overall survival was 12 months in the NALIRIFOX group and 9 months in the nab-paclitaxel and gemcitabine group,^{3,4,13} a total of 543 events were needed to detect an HR of 0.75 with 90% power at a two-sided alpha level of 5%. The Hwang-Shih-DeCani method was used to control the type I error and was utilised with respective

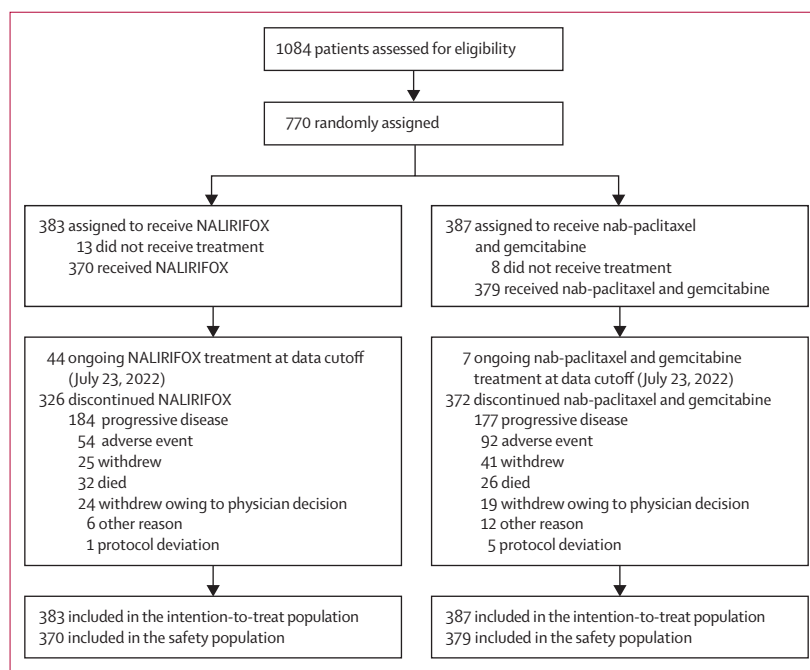


Figure 1: Trial profile

NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

	NALIRIFOX (n=383)	Nab-paclitaxel and gemcitabine (n=387)
Age, years		
Mean (SD)	62·8 (9·7)	64·0 (8·3)
Median (range; IQR)	64·0 (20–85; 57–70)	65·0 (36–82; 59–70)
Sex		
Female	179 (47%)	157 (41%)
Male	204 (53%)	230 (59%)
Race		
White	315 (82%)	324 (84%)
Asian	20 (5%)	18 (5%)
Black or African American	12 (3%)	7 (2%)
Other	7 (2%)	6 (2%)
Multiple	3 (1%)	0
American Indian or Alaska Native	0	2 (1%)
Native Hawaiian or other Pacific Islander	0	1 (<1%)
Not reported	26 (7%)	29 (7%)
ECOG performance status score		
0	160 (42%)	168 (43%)
1	222 (58%)	219 (57%)
2	1 (<1%)*	0
Metastatic sites		
1	114 (30%)	138 (36%)
2	120 (31%)	108 (28%)
≥3	149 (39%)	141 (36%)
Liver metastases	307 (80%)	311 (80%)
Geographical region		
North America	120 (31%)	122 (32%)
East Asia	11 (3%)	11 (3%)
Rest of the world	252 (66%)	254 (66%)

(Table 1 continues in next column)

	NALIRIFOX (n=383)	Nab-paclitaxel and gemcitabine (n=387)
(Continued from previous column)		
Main pancreatic tumour location		
Head	147 (38%)	156 (40%)
Other†	236 (62%)	231 (60%)
Baseline CA 19–9‡		
<37 U/mL	60 (16%)	71 (18%)
≥37 U/mL	321 (84%)	316 (82%)
Median (range; IQR)	1856·0 (0·6–8000·0; 178·0–8000·0)	1544·0 (0·6–8000·0; 93·7–8000·0)
Any previous anti-cancer therapy	22 (6%)	27 (7%)
Chemotherapy	14 (4%)	16 (4%)
Radiotherapy	10 (3%)	6 (2%)
Surgical procedure	18 (5%)	25 (7%)
Time from diagnosis of metastatic disease at study entry to randomisation, weeks		
Mean (SD)	3·6 (2%)	3·9 (2%)
Median (range; IQR)	3·0 (0·6–9·1; 2·1–4·7)	3·6 (0·4–10·9; 2·4–5·1)

Data are n (%), unless otherwise stated. Data are based on the intention-to-treat population. CA=carbohydrate antigen. ECOG=Eastern Cooperative Oncology Group. NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin. *One patient was considered to have an ECOG performance status score of 2 after randomisation and continued to receive treatment. †Body, tail, or unknown location. ‡Baseline values were missing for two patients (1%) in the NALIRIFOX arm. The upper limit of detection was 8000 U/mL.

Table 1: Baseline characteristics

two-sided alpha allocations of 0·006 (HR<0·931) and 0·048 (HR<0·844) in the interim and final analyses. No pre-assigned definitions of minimal clinically relevant difference were applied. If the primary overall survival endpoint was statistically significant, secondary endpoints were tested in a hierarchical approach in the order of progression-free survival followed by overall response rate. Further details are in appendix 2 (pp 14–15).

Efficacy was assessed in all randomly assigned patients according to the intention-to-treat principle. Safety was assessed in all patients who received at least one dose of treatment. An independent data monitoring committee was established for this study. For time-to-event endpoints including overall survival and progression-free survival, the stratified log-rank test was used to assess between-group differences. Kaplan-Meier methods were used to estimate median (95% CI) survival and HRs (95% CI) were estimated using stratified Cox proportional hazard models. Prespecified sensitivity analyses were conducted for overall survival and progression-free survival, including

subgroup analyses according to a priori stratification factors and other prognostic variables. For the overall survival analysis, patients without a recorded date of death were censored according to the last recorded date alive. For the progression-free survival analysis, patients without a recorded death or progression were censored on the date of the last evaluable tumour assessment. Overall response rate by RECIST version 1.1 according to investigator review and accompanying 95% CIs was calculated and compared between treatment groups using the Cochran–Mantel–Haenszel method, adjusted for randomisation stratification factors. Analyses were performed using SAS version 9.3 or higher. The trial was registered with ClinicalTrials.gov, NCT04083235 and EudraCT, 2018-003585-14.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and review and approval of the manuscript.

Results

Between Feb 19, 2020 and Aug 17, 2021, 770 patients were randomly allocated to receive NALIRIFOX (383 patients) or nab-paclitaxel and gemcitabine (387 patients) and comprised the intention-to-treat population (figure 1,

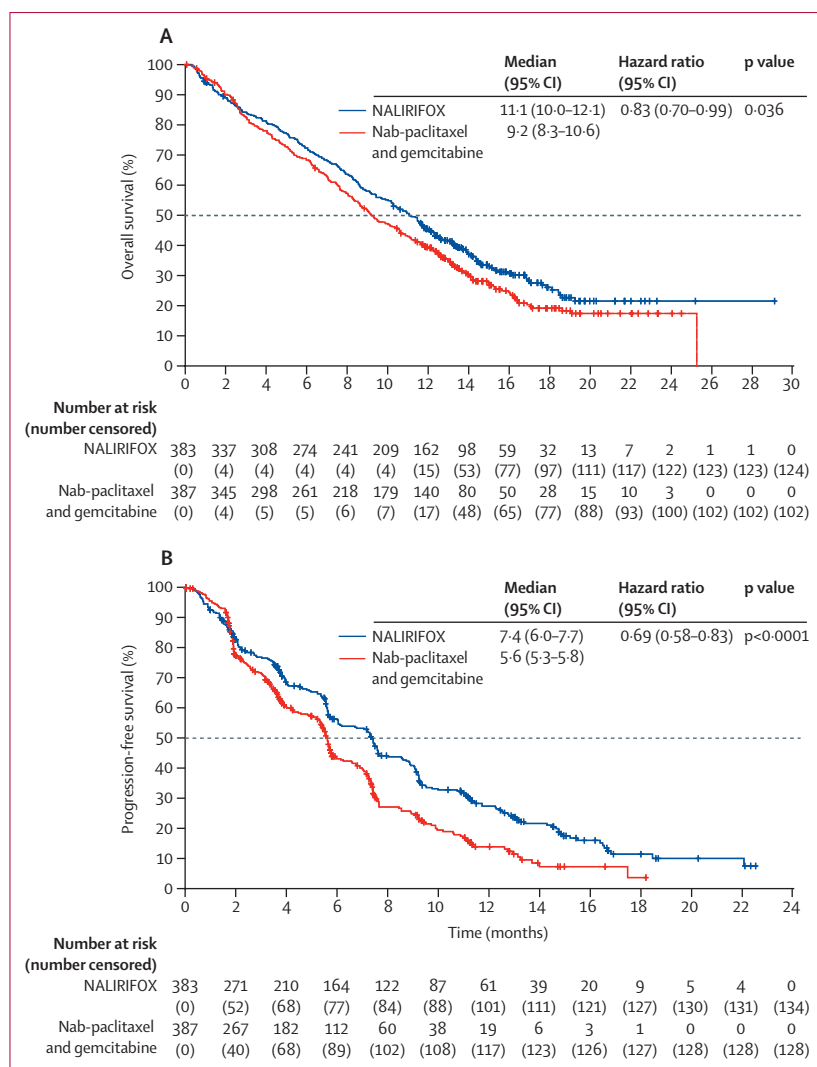


Figure 2: Kaplan-Meier estimates of overall survival (A) and progression-free survival (B)
NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

table 1). A summary of major protocol deviations in the intention-to-treat population is in appendix 2 (p 23). The safety population comprised 749 patients (NALIRIFOX, 370 patients; nab-paclitaxel and gemcitabine, 379 patients) who had received at least one dose of any study medication. At the data cutoff (July 23, 2022), 44 patients (12%) in the NALIRIFOX group and seven (2%) in the nab-paclitaxel and gemcitabine group were still receiving the trial regimen. The most common reason for discontinuation of treatment was disease progression in 184 patients (48%) in the NALIRIFOX group and 177 patients (46%) in the nab-paclitaxel and gemcitabine group.

The survival analysis was based on 544 deaths over a median follow-up of 16.1 months (IQR 13.4–19.1). Median overall survival was 11.1 months (95% CI 10.0–12.1) in the NALIRIFOX group and 9.2 months

(8.3–10.6) in the nab-paclitaxel and gemcitabine group (HR 0.83 [95% CI 0.70–0.99]; $p=0.036$; figure 2, table 2). Overall survival at 12 months was 45.6% (40.5–50.5) in the NALIRIFOX group and 39.5% (34.6–44.4) in the nab-paclitaxel and gemcitabine group. Overall survival at 18 months was 26.2% (20.9–31.7) for NALIRIFOX and 19.3% (14.8–24.2) for nab-paclitaxel and gemcitabine.

Median progression-free survival was 7.4 (95% CI 6.0–7.7) months in the NALIRIFOX group and 5.6 [5.3–5.8] months in the nab-paclitaxel and gemcitabine group (HR 0.69 [0.58–0.83]; $p<0.0001$; figure 2, table 2). Progression-free survival rates at 12 months were 27.4% (22.3–32.7) in the NALIRIFOX group and 13.9% (9.7–18.9) in the nab-paclitaxel and gemcitabine group. Progression-free survival rates at 18 months were 11.4% in the NALIRIFOX group and 3.6% in the nab-paclitaxel and gemcitabine group.

Overall survival and progression-free survival benefits with NALIRIFOX versus nab-paclitaxel and gemcitabine were generally consistent across prespecified subgroups (figure 3).

160 (42%) of 383 participants in the NALIRIFOX group had an objective response, as did 140 (36%) of 387 in the nab-paclitaxel and gemcitabine group ($p=0.11$; table 2). The median duration of response was 7.3 months (95% CI 5.8–7.6) in the NALIRIFOX group and 5.0 months (3.8–5.6) in the nab-paclitaxel and gemcitabine group (HR 0.67 [95% CI 0.48–0.93]; table 2).

Overall, 187 (51%) of 370 patients in the NALIRIFOX group and 206 (54%) of 379 patients in the nab-paclitaxel and gemcitabine group received subsequent systemic anticancer therapy (appendix 2 p 24). The most common subsequent therapies (appendix 2 p 25) were gemcitabine-based (153 [41%] patients) in the NALIRIFOX group and fluorouracil-based (134 [35%] patients) in the nab-paclitaxel and gemcitabine group. In a pre-planned sensitivity analysis for overall survival (censored at the time of subsequent therapy initiation or last known date of being alive, whichever occurred first), median overall survival was longer for the NALIRIFOX group than for the nab-paclitaxel and gemcitabine group (15.1 months for the NALIRIFOX group vs 9.2 months for the nab-paclitaxel and gemcitabine group; HR 0.71 [95% CI 0.56–0.90]; nominal $p=0.0048$). A pre-planned sensitivity analysis of overall survival in the per-protocol population (patients who had no major protocol deviations [appendix 2 p 26]; NALIRIFOX, $n=363$; nab-paclitaxel and gemcitabine, $n=372$) demonstrated a median overall survival of 11.5 months (10.2–12.3) in the NALIRIFOX group versus 9.3 months (8.5–10.7) in the nab-paclitaxel and gemcitabine group (HR 0.82 [0.69–0.97]; nominal $p=0.022$).

Among the 749 patients who received study treatment, the median duration of treatment was 24.3 weeks (IQR 8.4–42.1; median of 5.0 treatment cycles) in the NALIRIFOX group and 17.6 weeks (8.1–30.1; median of

	NALIRIFOX (n=383)	Nab-paclitaxel and gemcitabine (n=387)	Effect size (95% CI)	p value
Overall survival				
Median overall survival, months (95% CI)	11.1 (10.0–12.1)*	9.2 (8.3–10.6)*	HR 0.83 (0.70–0.99)†	0.036
Survival rate, % (95% CI)				
6 months	72.4 (67.6–76.6)	68.4 (63.5–72.8)	..	..
12 months	45.6 (40.5–50.5)	39.5 (34.6–44.4)	..	..
18 months	26.2 (20.9–31.7)	19.3 (14.8–24.2)	..	..
Progression-free survival				
Median progression-free survival, months (95% CI)	7.4 (6.0–7.7)*	5.6 (5.3–5.8)*	HR 0.69 (0.58–0.83)†	<0.0001
Progression-free survival rate, % (95% CI)				
6 months	56.4 (50.7–61.6)	43.2 (37.6–48.6)	..	..
12 months	27.4 (22.3–32.7)	13.9 (9.7–18.9)	..	..
18 months	11.4 (7.1–16.9)	3.6 (0.5–12.3)	..	..
Response according to investigator assessment				
Overall response				
Number of patients with overall response	160	140	..	..
Rate of overall response (investigator review), % (95% CI)	41.8 (36.8–46.9)‡	36.2 (31.4–41.2)‡	OR 1.26 (0.95–1.69)§	0.11
Median duration of response, months (95% CI)¶	7.3 (5.8–7.6)*	5.0 (3.8–5.6)*	HR 0.67 (0.48–0.93)†	..
Best overall response, n (%)				
Complete response	1 (<1%)	1 (<1%)	..	..
Partial response	159 (42%)	139 (36%)	..	..
Stable disease	99 (26%)	101 (26%)	..	..
Progressive disease	38 (10%)	56 (15%)	..	..
Not evaluable	86 (23%)	90 (23%)	..	..

Data are based on the intention-to-treat population. NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin. HR=hazard ratio. OR=odds ratio. *Kaplan–Meier estimate. †HRs and 95% CIs are based on a stratified Cox proportional hazards regression model, stratified by baseline Eastern Cooperative Oncology Group performance status, region, and liver metastases per interactive web response system; reference is nab-paclitaxel and gemcitabine. ‡95% CIs are calculated using the Clopper–Pearson method. §ORs, 95% CIs, and p values are obtained using the Cochran–Mantel–Haenszel method, adjusted by baseline Eastern Cooperative Oncology Group performance status, region, and liver metastases per interactive web response system; reference is nab-paclitaxel and gemcitabine. ¶Duration of response was limited to responders. ||Included are 68 patients (18%) in the NALIRIFOX group and 64 (17%) in the nab-paclitaxel and gemcitabine group who did not have an assessment after the baseline visit.

Table 2: Overall survival, progression-free survival, and response rates

4.0 treatment cycles) in the nab-paclitaxel and gemcitabine group (table 3). Dose reductions per NAPOLI 3 protocol were required in 220 (60%) of 370 patients who received NALIRIFOX and 204 (54%) of 379 patients who received nab-paclitaxel and gemcitabine (table 3).

Treatment-emergent adverse events occurred in 369 (>99%) of 370 patients who received NALIRIFOX and 376 (99%) of 379 patients who received nab-paclitaxel and gemcitabine (table 3). The most common grade 3–4 treatment-emergent adverse events were neutropenia, diarrhoea, and hypokalaemia in the NALIRIFOX group and neutropenia, anaemia, and peripheral neuropathy in the nab-paclitaxel and gemcitabine group (table 3). Treatment-related treatment-emergent adverse events leading to death occurred in six (2%) of 370 patients in the NALIRIFOX group and eight (2%) of 379 patients in the nab-paclitaxel and gemcitabine group. Additional information related to adverse events, including serious treatment-emergent adverse events, is in appendix 2 (pp 28–46).

Discussion

In the NAPOLI 3 trial, the NALIRIFOX regimen demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival compared with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma who had not previously received treatment in the metastatic setting. The observed improvements in overall survival and progression-free survival were generally consistent regardless of baseline Eastern Cooperative Oncology Group performance status score (0 or 1), region (North America or the rest of the world), or presence of liver metastasis based on prespecified subgroup analyses. The improvement in overall survival is unlikely to be attributable to differences in subsequent therapy because similar proportions of patients received subsequent therapy in each treatment group (51% in the NALIRIFOX group and 54% in the nab-paclitaxel and gemcitabine group).

No unexpected safety concerns were identified with the use of NALIRIFOX as first-line therapy in NAPOLI 3.

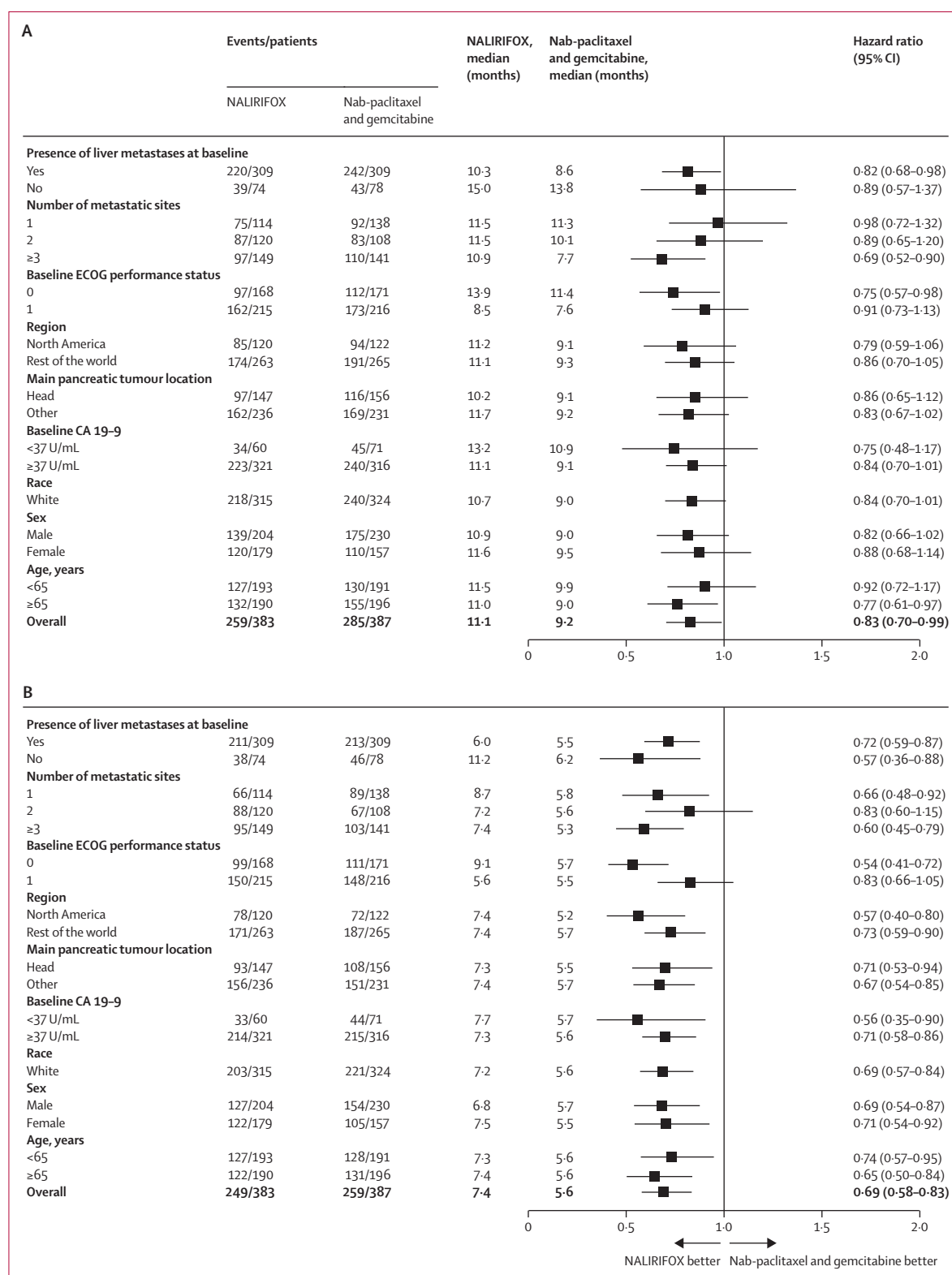


Figure 3: Forest plot of overall survival (A) and progression-free survival (B) in selected subgroups

The overall hazard ratio is based on stratified analysis and subgroup hazard ratios are based on unstratified analyses. CA=carbohydrate antigen. ECOG=Eastern Cooperative Oncology Group. NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

Patients remained on NALIRIFOX for a median of 6 weeks longer (1·5 treatment cycles) than those receiving nab-paclitaxel and gemcitabine, indicating that NALIRIFOX was relatively well tolerated. Furthermore, the rates of grade 3–4 peripheral neuropathy were lower in the NALIRIFOX group than in the nab-paclitaxel and gemcitabine group (3·2% vs 5·8%). Similar to the previous phase 1/2 study,¹⁴ the most frequent grade 3–4 treatment-emergent adverse events in the NALIRIFOX group included neutropenia and hypokalaemia, and gastrointestinal disorders such as diarrhoea and nausea. However, rates of haematological grade 3–4 treatment-emergent adverse events including neutropenia, anaemia, and thrombocytopenia were lower with NALIRIFOX (a quadruplet combination therapy) than with nab-paclitaxel and gemcitabine group (a doublet combination therapy). The safety profile of NALIRIFOX could be related to several factors. One possibility is the use of lower doses of oxaliplatin, which help to reduce toxicities such as in cumulative peripheral neuropathy. Additional factors that include the use of the liposomal formulation of irinotecan, which was designed to maximise tumour exposure while minimising systemic toxicity, might also play a role.¹⁸

Although direct comparisons are not possible, it is important to consider the NAPOLI 3 results (n=770) within the context of the phase 3 PRODIGE 4/ACCORD 11 trial (n=342),³ which compared FOLFIRINOX with gemcitabine alone and led to its use as a first-line treatment for metastatic pancreatic ductal adenocarcinoma. Enrolment in PRODIGE 4 was limited to patients aged 75 years or younger and was exclusively in France, whereas NAPOLI 3 had no age restrictions and was a global trial, with a mixture of community and academic sites. In the PRODIGE trial, FOLFIRINOX demonstrated superiority over gemcitabine alone (median overall survival 11·1 months [95% CI 9·0–13·1] vs 6·8 months [5·5–7·6]).³ Indeed, NAPOLI 3 is the only study that has demonstrated superiority of quadruplet therapy (using liposomal irinotecan) over doublet therapy with nab-paclitaxel and gemcitabine. The median progression-free survival was 7·4 months (95% CI 6·0–7·7) and the overall response rate per investigator was 41·8% for NALIRIFOX in NAPOLI 3, and 6·4 (5·5–7·2) months and 31·6%, respectively, for FOLFIRINOX in PRODIGE.³ In NAPOLI 3, rates of grade 3–4 peripheral sensory neuropathy and neutropenia with NALIRIFOX were lower than those reported for FOLFIRINOX (3·5% vs 9·0% and 23·8% vs 45·7%, respectively), probably owing to a lower cumulative dose of oxaliplatin with the NALIRIFOX regimen,³ which was selected based on review of dose-limiting toxicities in the previous phase 1/2 dose expansion and dose exploration study.¹⁴

Compared with other cancers, there have been only small improvements in survival rates in patients with pancreatic ductal adenocarcinoma over the past 30 years.

	NALIRIFOX (n=370)	Nab-paclitaxel and gemcitabine (n=379)
Median duration of treatment, weeks	24·3 (0·4–100·9; 8·4–42·1)	17·6 (0·7–81·7; 8·1–30·1)
Median number of treatment cycles	5·0 (1–24; 2–10)	4·0 (1–20; 2–7)
Any dose reductions	220 (60%)	204 (54%)
TEAEs		
Any TEAE	369 (>99%)	376 (99%)
Any treatment-related TEAE	352 (95%)	352 (93%)
Grade ≥3 TEAE	322 (87%)	326 (86%)
Grade ≥3 treatment-related TEAE	262 (71%)	258 (68%)
Any TEAE leading to discontinuation	118 (32%)	112 (30%)
Any treatment-related TEAE leading to discontinuation	94 (25%)	88 (23%)
Any TEAE leading to dose reduction	208 (56%)	190 (50%)
Any treatment-related TEAE leading to dose reduction	198 (54%)	184 (49%)
Any serious TEAEs	201 (54%)	195 (52%)
Any treatment-related serious TEAEs	98 (27%)	72 (19%)
TEAEs leading to death	22 (6%)	23 (6%)
Treatment-related TEAEs leading to death	6 (2%)	8 (2%)
TEAEs of grade 3–4 occurring in ≥5% of patients in either treatment arm		
Diarrhoea	75 (20%)	17 (5%)
Nausea	44 (12%)	10 (3%)
Vomiting	26 (7%)	8 (2%)
Decreased appetite	32 (9%)	10 (3%)
Hypokalaemia	56 (15%)	15 (4%)
Fatigue	23 (6%)	20 (5%)
Asthenia	33 (9%)	19 (5%)
Neutropenia	52 (14%)	93 (25%)
Neutrophil count decreased	36 (10%)	51 (14%)
Anaemia	39 (11%)	66 (17%)
Peripheral neuropathy	12 (3%)	22 (6%)
Increased γ-glutamyltransferase	23 (6%)	21 (6%)

Data are median (range; IQR) or n (%). NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin. TEAE=treatment-emergent adverse event.

Table 3: Duration of treatment, exposure, and overview of TEAEs in the safety population.

Early-stage disease is undetectable in patients without symptoms, and effective screening methods are not yet available. Decisions about first-line therapy for patients with metastatic pancreatic ductal adenocarcinoma are limited by differing toxicity profiles and a lack of direct comparisons, as well as factors such as performance status, genetic alterations (eg, defective mismatch repair or homologous recombination deficiency), age, and underlying comorbidities. In NAPOLI 3, NALIRIFOX demonstrated lower rates of haematological

treatment-emergent adverse events than nab-paclitaxel and gemcitabine. In addition, the cost of treatment and its impact on health-related quality of life are important factors in treatment decision making. Future research will be conducted to evaluate cost implications, and analyses of patient-reported quality of life outcomes from NAPOLI 3 are ongoing. Furthermore, ongoing genomic profiling evaluations on tissue and serum collected in the NAPOLI 3 trial might answer additional questions that could inform patient selection, such as whether patients with *BRCA*-mutated pancreatic cancer could have benefited from platinum exposure in the NALIRIFOX group.

Strengths of the NAPOLI 3 study include the large sample size, randomised design, and the global recruitment of patients from academic and community sites in North and South America, eastern and western Europe, Asia, and Australia. Limitations of the study include the following: the open-label study design and associated potential for outcome bias; the requirement for measurable disease and an Eastern Cooperative Oncology Group performance status score of 0 or 1 at screening; and the absence of somatic or germline profiling information.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship of this Article, take responsibility for the integrity of the work, were involved in drafting, revising, and critical review of the manuscript, and approved the final version for submission. All authors conceived and designed the study, carried out the research, and analysed the data. ZAW, ZX, and HC accessed and verified the underlying data. All authors had full access to the data, final responsibility to submit for publication, and vouch for the accuracy and completeness of the data and fidelity of the trial to the protocol.

Declaration of interests

ZAW has received grants or contracts from Arcus and Bristol Myers Squibb, consulting fees from Amgen, Arcus, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Ipsen, Merck Sharp & Dohme, and Seagen, support for attending meetings or travel from Amgen, Bayer, and Merck Sharp & Dohme, and has participated on a data safety monitoring board or advisory board for Mirati and Pfizer. DM has received grants or contracts from Celgene, Evotec, Incyte, iOnctura, Roche, and Servier, consultancy fees from Incyte, iOnctura, IQVIA, Merck Sharp & Dohme, Servier, and Taiho Pharmaceutical, and has participated on a data safety monitoring board or advisory board for Incyte, Servier, Taiho Pharmaceutical, and Terumo. TM has received grants or contracts (personal) from Merck Sharp & Dohme, Novocure, QED Therapeutics, Roche, Sanofi-Aventis, Servier, and Zymeworks, and received grants or contracts to their institution from AbbVie Farmaceutica, Ability Pharmaceuticals, Agios Pharmaceuticals, Amgen, Aslan Pharmaceuticals, AstraZeneca, Basilea Pharmaceutica International, Bayer, BeiGene, BioKeralt Research Institute, BioLineRx, Blueprint Medicines, Boston Biomedical, Bristol Myers Squibb, Cantargia, Celgene, Eisai, Eli Lilly and Company, Erytech Pharma, FibroGen, Halozyne, Incyte, Ipsen, Loxo Oncology, MedImmune, Merck Sharp & Dohme, Nelum, Novartis, Novocure, OncoMed Pharmaceuticals, QED Therapeutics, Roche, VCN Biosciences, and Zymeworks, payment or honoraria from Janssen and Lilly, support for attending meetings or travel from AstraZeneca, Incyte, Merck Sharp & Dohme, Sanofi, and Servier, and has participated on a data safety monitoring board or advisory board for Ability Pharmaceuticals, AstraZeneca, Basilea Pharma, Baxter, BioLineRX, Celgene, Eisai, Incyte, and Ipsen. RPC has received consulting fees from AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eisai, Eli Lilly and

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Data sharing

Qualified researchers can request access to patient-level study data that underlie the results reported in this publication. Additional relevant study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan, and data set specifications can also be made available. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of study participants. When applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the USA and EU or after the primary manuscript describing the results has been accepted for publication, whichever is later. Further details on Ipsen's sharing criteria, eligible studies, and process for sharing are available online at <https://vivli.org/members/ourmembers/>. Any requests should be submitted to <https://vivli.org> for assessment by an independent scientific review board.

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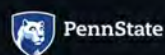
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Appendix WANG02

ORIGINAL ARTICLE

Open Access



The efficacy and safety of modified FOLFIRINOX as first-line chemotherapy for Chinese patients with metastatic pancreatic cancer

Zhi-Qiang Wang^{1†}, Fei Zhang^{1†}, Ting Deng², Le Zhang², Fen Feng³, Feng-Hua Wang¹, Wei Wang³, De-Shen Wang¹, Hui-Yan Luo¹, Rui-Hua Xu¹, Yi Ba^{2*} and Yu-Hong Li^{1*}

Abstract

Background: Oxaliplatin, irinotecan, 5-fluorouracil, and L-leucovorin (FOLFIRINOX) has become one of the first-line treatment options for advanced pancreatic cancer (PC). However, the relatively high rate of grade 3 or 4 adverse events associated with the standard dosage of FOLFIRINOX limits its widespread use in clinical practice. In this study, we were to evaluate the efficacy and safety of a modified FOLFIRINOX regimen as a first-line chemotherapy for Chinese patients with metastatic PC.

Methods: Patients with histologically confirmed primary metastatic pancreatic adenocarcinoma with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 were recruited to receive the modified FOLFIRINOX regimen (intravenous infusion of oxaliplatin, 65 mg/m²; irinotecan, 150 mg/m²; L-leucovorin, 200 mg/m²; and 5-fluorouracil, 2400 mg/m², repeated every 2 weeks). The treatment was continued for 12 cycles unless the patient had progressive disease (PD), stable disease (SD) with symptom deterioration, unacceptable adverse events, or requested to terminate the treatment prematurely. The primary endpoint was objective response rate (ORR).

Results: Sixty-five patients were enrolled from July 2012 to April 2017 in three institutions, and they all received at least one cycle of chemotherapy, with a median of 8 cycles (range 1–12 cycles). No complete response was observed. Twenty-one (32.3%) patients had partial responses, and 27 (41.5%) had SD. The ORR and disease control rate of the study cohort was 32.3% and 73.8%. The estimated median overall survival and progression-free survival were 11.60 (95% confidence interval [CI] 8.76–14.44) and 5.77 (95% CI 5.00–6.54) months. Major grade 3 or 4 adverse events included neutropenia (12.3%) and diarrhea (6.2%). No treatment-related death was observed.

Conclusions: Modified FOLFIRINOX was well-tolerated and might be a promising option as first-line therapy for Chinese patients with metastatic PC.

Trial registration ClinicalTrials.gov, NCT02028806. Registered 7 January 2014, <https://clinicaltrials.gov/ct2/show/NCT02028806>

Keywords: Pancreatic cancer, Metastatic, Chemotherapy, FOLFIRINOX, Dose modification, First-line, Multicenter, Overall response rate, Efficacy, Safety

*Correspondence: bayi@tjmuch.com; liyh@sysucc.org.cn

[†]Zhi-Qiang Wang and Fei Zhang have contributed equally to this work

¹ Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou 510060, Guangdong, People's Republic of China

² Department of Gastrointestinal Medical Oncology, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, People's Republic of China

Full list of author information is available at the end of the article



Background

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death worldwide [1]. Despite decades of efforts, it is still one of the deadliest solid malignancies, with a 5-year survival rate of less than 5% [2]. Gemcitabine has become the standard care for patients with locally advanced or metastatic PC since 1997 [3]. The addition of albumin-bound paclitaxel (nab-paclitaxel) to gemcitabine has significantly improved the patient's survival rate and has become the newly accepted standard of treatment [4]. However, the combinations of gemcitabine with other cytotoxic or molecularly targeted agents have generally shown no substantial clinical improvement when compared with gemcitabine alone [5–7].

The PRODIGE 4/ACCORD 11 study [5] exploring FOLFIRINOX (a combination chemotherapy regimen of oxaliplatin, irinotecan, 5-fluorouracil, and L-leucovorin) as a first-line treatment in patients with advanced PC was performed by a French consortium study group. When comparing the FOLFIRINOX regimen with single-agent gemcitabine, they found that the FOLFIRINOX regimen was associated with significantly prolonged overall survival (OS, 11.1 months vs 6.8 months, $P < 0.001$) and progression-free survival (PFS, 6.4 months vs 3.3 months, $P < 0.001$). Moreover, the objective response rate (ORR) of patients in the FOLFIRINOX group was higher than that of patients in the gemcitabine group (31.6% vs 9.4%, $P < 0.001$). Furthermore, the observed definitive degradation of the quality of life was significantly lower in the FOLFIRINOX group (31% vs 66%, $P < 0.001$). Thus, FOLFIRINOX became one of the standard options for patients with advanced PC and has demonstrated good performance status in North America and Europe. However, grade 3 or 4 adverse events (45.7% grade 3 or 4 neutropenia, 5.4% febrile neutropenia, 12.7% diarrhea, 9.1% thrombocytopenia, 9.0% sensory neuropathy) were frequently observed in the FOLFIRINOX group even when using the median relative dose intensity of 5-fluorouracil, irinotecan, and oxaliplatin which 82%, 81%, and 78% of the initial dose, respectively [5]. As a result, many dose modifications have been reported and have demonstrated reduced adverse events without compromising the treatment efficacy in both metastatic and adjuvant settings [8–13].

However, data on the efficacy and safety of FOLFIRINOX in Chinese patients with metastatic PC is still limited. Therefore, in this study, we aimed to evaluate the efficacy and safety of a modified FOLFIRINOX as a first-line chemotherapy regimen for Chinese patients with metastatic PC.

Patients and methods

Patient population

Patients who were radiologically and histologically diagnosed with primary metastatic pancreatic

adenocarcinoma between July 2012 and April 2017 were enrolled in this multicenter, single-arm, prospective phase II study. Inclusion criteria included an age of 18 years or older and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2, with at least one measurable metastatic lesion and adequate hematological, liver, and renal functions (hemoglobin ≥ 90 g/L, neutrophil count $\geq 2.0 \times 10^9$ /L, platelet count $\geq 90 \times 10^9$ /L, total bilirubin $\leq 1.2 \times$ upper limit of normal, aspartate transaminase and alanine transaminase $\leq 2.5 \times$ upper limit of normal, and creatinine $\leq 1.25 \times$ upper limit of normal). Prior adjuvant therapy (including adjuvant radiotherapy or chemotherapy > 4 weeks) was allowed. Patients with postoperative recurrence were also enrolled.

Exclusion criteria were an age of 76 years or older, pancreatic malignancies other than adenocarcinoma, a history of other types of cancer, active and uncontrolled medical diseases such as severe sepsis and septic shock, symptomatic peripheral neuropathy $> \text{grade } 2$, a history of palliative radiotherapy/immunotherapy, and pregnancy or breastfeeding women. Written informed consent was obtained from all patients. The study was approved by the independent ethics committees of Sun Yat-sen University Cancer Center, Tianjin Medical University Cancer Institute and Hospital, and The First People's Hospital of Foshan and was performed in accordance with the Declaration of Helsinki.

Treatment and assessment

Patients were given a 30-min intravenous infusion of antiemetic and then treated with modified FOLFIRINOX (a 2-h intravenous infusion of oxaliplatin at 65 mg/m^2 , immediately followed by a 2-h intravenous infusion of L-leucovorin at 200 mg/m^2 , a 1.5-h intravenous infusion of irinotecan at 150 mg/m^2 , and a 46-h continuous infusion of fluorouracil at 2400 mg/m^2 , repeated every 2 weeks). Granulocyte colony-stimulating factor was allowed for those who suffered grade 3 or 4 neutropenia. The treatment was continued for 12 cycles unless the patient had progressive disease (PD), stable disease (SD) with symptom deterioration, unacceptable adverse events, or requested to terminate the treatment prematurely.

Study design

The sample size was estimated by the Simon's two-stage design. The expected ORR for the modified FOLFIRINOX was initially assumed to be 30%. If the ORR was less than 10%, the modified FOLFIRINOX was considered to be ineffective. Due to the possible occurrence of the first type of error ($\alpha = 0.05$) and the possible occurrence of the second type of error ($\beta = 0.10$), 18 patients

were needed in the first stage of the study. If more than 2 patients were responsive to the treatment, the second stage would be initiated, and 17 more patients would be enrolled. Considering a withdrawal rate of 15%, a total of 40 patients were needed in this study.

Evaluation of response

Patients completing at least one cycle of the modified FOLFIRINOX with at least one follow-up tumor assessment were considered evaluable for response. Computed tomography (CT) of the chest, abdomen, and pelvic cavity was repeated every 4 cycles. The treatment response was determined in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) by the investigators. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) on days 1, 8, 15 of the treatment cycle. Second-line treatment was strongly recommended for those who were still with good performance status after PD was observed during the treatment period.

Study endpoints

The primary endpoint of this phase II trial was ORR, and the secondary endpoints were disease control rate (DCR), OS, PFS and the rates of adverse events. ORR was determined as the percentage of patients who had a complete (CR) or partial response (PR). DCR was defined as the percentage of patients who had a CR, PR, or SD. In addition, OS was calculated from the date of enrollment to death from any cause. PFS was defined as the time interval from recruitment until radiological or clinical progression or death from any cause.

Follow-up

All patients received regular blood tests including tumor markers detection and CT scans of the chest, abdomen, and pelvic cavity every 2 months unless they had PD. Patients with PD after modified FOLFIRINOX treatment were followed-up every 3 months by telephone until death. The end of follow-up period was December 20, 2018.

Statistical analysis

Descriptive statistical analysis was used to determine the ORR and DCR. The OS and PFS were estimated using the Kaplan–Meier method. Log-rank test was used for statistical comparisons between survival curves. All statistical analyses were carried out using the SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA). A two-sided *P* value of less than 0.05 was considered significant.

Results

Patient characteristics

Between July 2012 and April 2017, a total of 65 patients with histologically confirmed primary metastatic PC from three centers (Sun Yat-sen University Cancer Center [*n* = 38], Tianjin Medical University Cancer Institute and Hospital [*n* = 21], and The First People's Hospital of Foshan [*n* = 6]) were included in this study. There were 43 men (66.2%) and 22 women (33.8%) with a median age of 56 years (range 23–74 years). Thirty-two (49.2%) patients had tumors located in the head of the pancreas, while there were 13 (20.0%) and 6 (9.2%) patients with tumors located in the body and tail of the pancreas, respectively. Fourteen (21.6%) patients had multicentric PC. Six patients had an ECOG performance score of 2, and the remaining 59 patients had a score of 0 or 1. The baseline clinicopathologic characteristics are summarized in Table 1.

Responses

A total of 469 cycles of chemotherapy were delivered, with a median of 8 cycles per patient (range 1–12 cycles).

Table 1 Demographic and baseline characteristics of the enrolled patients

Clinicopathological	No. of patients
Characteristics	<i>n</i> , (%)
Gender	
Male	43 (66.2)
Female	22 (33.8)
ECOG performance status score	
0	21 (32.3)
1	38 (58.5)
2	6 (9.2)
Primary tumor location	
Head	32 (49.2)
Body	13 (20.0)
Tail	6 (9.2)
Multicentric	14 (21.6)
No. of metastatic sites involved	
Median	1
Range	1–4
Metastatic tumor sites	
Liver	53 (81.5)
Lung	14 (21.5)
Lymph nodes	19 (29.2)
Peritoneum	15 (23.1)
Others	7 (10.8)
Cycles of mFOLFIRINOX	
Median	8
Range	1–12

ECOG Eastern Cooperative Oncology Group, mFOLFIRINOX modified 5-fluorouracil, irinotecan, leucovorin, and oxaliplatin

Table 2 Objective responses and survival of the study population

Variable	No. of Patients [cases (%)]	Median PFS (95% CI, months)	Median OS (95% CI, months)
Best response			
Complete response	0	–	–
Partial response	21 (32.3)	7.80 (4.86–10.74)	18.17 (12.89–23.45)
Stable disease	27 (41.5)	7.00 (4.43–9.57)	13.00 (9.68–16.32)
Progressive disease	16 (24.6)	1.93 (1.59–2.28)	4.30 (3.58–5.02)
Could not be evaluated	1 (1.5)	–	–
Objective response rate ^a	21 (32.3)	–	–
Disease control rate ^b	48 (73.8)	–	–

OS overall survival, PFS progression free survival, CI confidence interval

^a The rate of objective response was defined as the percentage of patients who had a complete response or a partial response

^b The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease

The responses to therapy are summarized in Table 2. Of the 65 patients, 21 (32.3%) achieved PR, and 27 (41.5%) had SD; no CR was observed, leading to an ORR and DCR of 32.3% (21/65) and 73.8% (48/65). One case could not be evaluated due to the lack of CT scan after receiving 3 cycles of treatment. No CR or PR was observed in patients with an ECOG performance score of 2.

Survival

The median follow-up time was 16.70 (range 1.43–45.13) months. At the end of the study, 59 (90.8%) of the 65 patients had PD, and 57 (87.7%) died. The estimated median PFS and OS of the entire study cohort were 5.77

(95% confidence interval [CI] 5.00–6.54) and 11.60 (95% CI 8.76–14.44) months (Fig. 1).

In addition, the estimated median PFS for patients with an ECOG performance score of 0, 1, and 2 were 7.57 (95% CI 7.37–7.77), 4.73 (95% CI 3.55–5.92) and 1.93 (95% CI 1.41–2.45) months, respectively (ECOG 0 vs 1 vs 2: $P < 0.001$; Fig. 2a), and the estimated median OS were 16.17 (95% CI 12.03–20.30), 11.07 (95% CI 9.57–12.57) and 3.17 (95% CI 2.68–3.65) months, respectively (ECOG 0 vs 1 vs 2: $P < 0.001$; Fig. 2b).

Safety

The common treatment-related hematologic and nonhematologic adverse events are summarized in Table 3. The most common adverse events were neutropenia, anemia, loss of appetite, nausea, vomiting, fatigue, and alanine aminotransferase elevation. Major grade 3 or 4 adverse events included neutropenia in 8 (12.3%) patients and diarrhea in 4 (6.2%) patients. Eight patients needed dose reduction due to severe diarrhea ($n = 4$) or neutropenia ($n = 4$). 5-Fluorouracil and/or irinotecan infusion were the most commonly adjusted agents. Of the 6 patients with an ECOG performance score of 2, only one developed grade 4 neutropenia and recovered after 1 week of hospitalized treatment. No treatment interruption or treatment-related death occurred.

Second-line therapy

Second-line therapy was recommended for patients with good performance status and adequate organ functions who had PD after the modified FOLFIRINOX chemotherapy ($n = 20$). Gemcitabine plus nab-paclitaxel was the most commonly used second-line regimen and was prescribed in 14 patients. Other patients received gemcitabine ($n = 3$) or S1 ($n = 3$) monotherapy. No patients

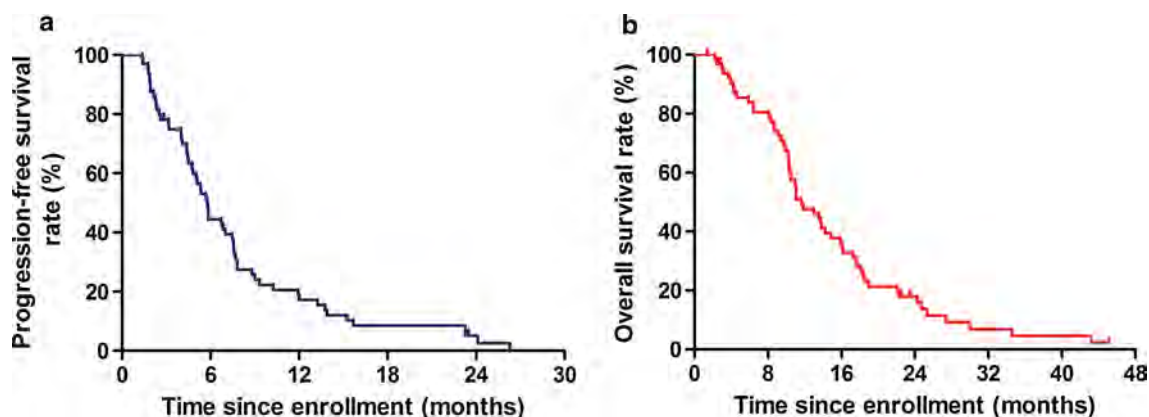


Fig. 1 Kaplan-Meier survival curves of **a** progression-free survival (PFS) and **b** overall survival (OS) of the 65 enrolled patients

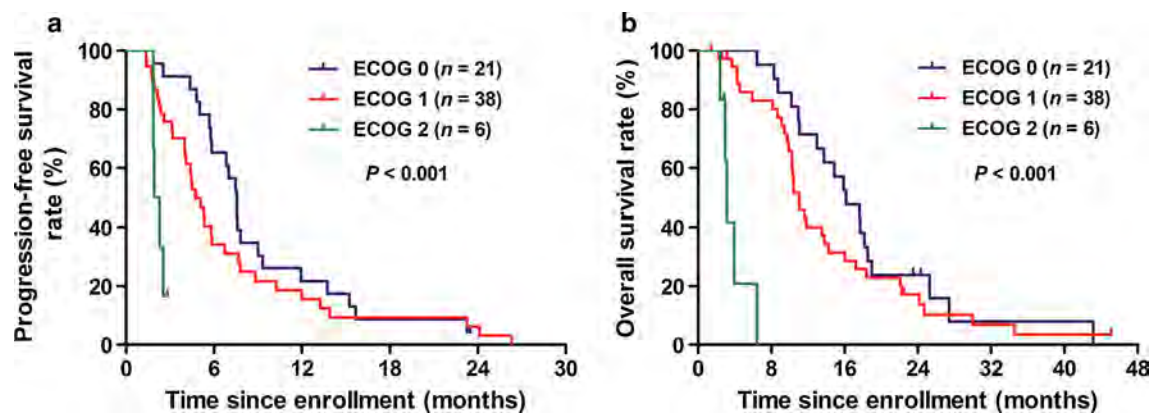


Fig. 2 Kaplan-Meier survival curves of **a** progression-free survival (PFS) and **b** overall survival (OS) of the 65 enrolled patients stratified by the Eastern Cooperative Oncology Group (ECOG) performance status scores (log-rank test of ECOG 0 vs 1 vs 2)

underwent third-line therapy due to a decrease in ECOG performance status after the second-line chemotherapy.

Discussion

In the present study, in an attempt to reduce the risk of adverse events of the FOLFIRINOX regimen, dose modification was performed by using 65 mg/m² and 150 mg/

m² of oxaliplatin and irinotecan based on their median relative dose intensities of their initial prescribed dosage used in the PRODIGE 4/ACCORD 11 study [5], and removed the intravenous bolus of 5-fluorouracil due to its notable myelosuppression. Based on such modifications, we found that our modified FOLFIRINOX regimen demonstrated encouraging anti-cancer activity in

Table 3 The rate of treatment-related adverse events of the study cohort

Adverse event	Frequency [cases (%)]			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Neutropenia	20 (30.8)	15 (23.1)	4 (6.2)	4 (6.2)
Thrombocytopenia	9 (13.8)	2 (3.1)	0	0
Anemia	24 (36.9)	3 (4.6)	0	1 (1.5)
Nonhematologic				
Loss of appetite	34 (52.3)	18 (27.7)	0	0
Nausea	26 (40.0)	18 (27.7)	0	0
Vomiting	14 (21.5)	19 (29.2)	1 (1.5)	0
Mucosal inflammation	14 (21.5)	1 (1.5)	0	0
Diarrhea	20 (30.8)	4 (6.2)	4 (6.2)	0
Alopecia	52 (80.0)	13 (20.0)	–	–
Fatigue	25 (38.5)	10 (15.4)	0	0
Sensory neuropathy	18 (27.7)	3 (4.6)	0	0
Weight loss	7 (10.8)	0	0	0
Constipation	7 (10.8)	1 (1.5)	0	0
Alanine aminotransferase elevation	22 (33.8)	7 (10.8)	1 (1.5)	0
Aspartate aminotransferase elevation	12 (18.5)	4 (6.2)	0	0
Bilirubin elevation	4 (6.2)	0	0	0
Allergic reaction	1 (1.5)	0	0	0
Rash	1 (1.5)	0	0	0
Hand-foot syndrome	1 (1.5)	0	0	0
Singultus	1 (1.5)	0	0	0

Chinese patients with metastatic PC. The ORR and DCR were reported to be 32.3% and 73.8%. Moreover, the estimated median OS and PFS were 11.60 and 5.77 months, which were consistent with those treated with the full-dose FOLFIRINOX [5].

Other reported modified FOLFIRINOX regimens were usually established by removing the intravenous bolus of fluorouracil and reducing the oxaliplatin and irinotecan dosages to 78%–88% and 64%–81% of the full dose (Table 4) [11, 14, 15]. Stein et al. [14] reported the efficacy of a modified FOLFIRINOX (the doses of irinotecan and bolus 5-fluorouracil reduced by 25%) with an ORR of 35.1% and median OS and PFS of 10.2 and 6.1 months. Meanwhile, Li et al. [15] evaluated the efficacy and safety of a modified FOLFIRINOX (the doses of oxaliplatin and irinotecan adjusted to 85% and 75% of the full

doses, without intravenous bolus of 5-fluorouracil) in 62 metastatic PC patients treated at a single institution. They found that a DCR of 60% was achieved of which 13 patients had CR or PR, leading to an ORR of 32.5%, and the median OS and PFS were 10.3 and 7.0 months. Thus, combined with the results from these previous studies, we strongly suggest that a modified FOLFIRINOX regimen can have comparable treatment efficacy as to that of the original regimens reported in the PRODIGE 4/ACCORD 11 study [5].

In regard to the therapeutic safety, our results showed that this modified FOLFIRINOX regimen was well-tolerated, had a relatively low number of adverse events (grade 3 or 4 neutropenia 13.4%, no febrile neutropenia; grade 3 diarrhea 6.2%, grade 2 sensory neuropathy 4.2%), without treatment-related death. In comparison with

Table 4 The efficacy and safety of standard and modified FOLFIRINOX regimen in advanced pancreatic cancer patients

Events	Standard regimen	Modified regimen			
	Conroy et al. [5]	Yoshida et al. [11]	Stein et al. [14]	Li et al. [15]	Present study
Patients (n)	171	31	68	62	65
Disease (n)					
Locally advanced	0	0	31	0	0
Metastatic	171	31	37	62	65
ECOG performance score (n)					
0	64	25	17	38	21
1	106	6	20	24	38
2	1	0	0	0	6
Dose (mg/m ²)					
Oxaliplatin	85	85	85	68	65
Irinotecan	180	150	135	135	150
5-Fluorouracil	2400	2400	2400	2400	2400
Survival (months)					
Median OS	11.1	14.9	10.2	10.3	10.9
Median PFS	6.4	7	6.1	7	6.7
Response (n)					
Complete response	1	0	0	0	0
Partial response	53	12	13	13	21
Stable disease	66	11	19	11	27
Progressive disease	26	8	5	16	16
Objective response rate (%)	31.6	38.7	35.1	32.5	32.3
Disease control rate (%)	70.2	74.2	86.5	60	73.8
Adverse event (%)					
Neutropenia (grade 3/4)	45.7	83.9	12.2	29	12.4
Fatigue (grade 3/4)	23.6	NE	12.2	0	0
Diarrhea (grade 3/4)	12.7	6.5	16.2	0	6.2
Vomiting (grade 3/4)	14.5	3.2	2.7	0	1.5
Sensory neuropathy (grade 3/4)	9	9.7	2.7	0	0
Sensory neuropathy (grade 1/2)	NE	58.1	NE	0	32.3

NE not evaluated

other modified FOLFIRINOX regimens [11, 14], the rates of adverse events were different in Chinese PC patients. The rate of grade 3 diarrhea in this study was significantly higher than that reported by Li et al. [15], which might be attributed to the relatively higher dose of irinotecan in the present study (150 mg/m² vs 135 mg/m²) (Table 4). Moreover, the median number of cycles of modified FOLFIRINOX delivered per patient in this study were 8 (oxaliplatin with a cumulative dosage of 520 mg/m²), which could explain why there were more patients suffering from grade 1 or 2 sensory neuropathy (21 cases, 32.3%) compared to those in Li et al.'s study [15].

Furthermore, in the present study, patients were included regardless of their ECOG performance scores. Among them, 6 patients had an ECOG performance status score of 2 and showed good tolerance of treatment with the modified FOLFIRINOX regimen, except for one patient who developed grade 4 neutropenia but recovered after 1 week of hospitalized treatment. In addition, the estimated median PFS and OS were 1.93 (95% CI 1.41–2.45) months and 3.17 (95% CI 2.68–3.65) months. This preliminary result showed that although the adverse events of modified FOLFIRINOX in ECOG performance status 2 patients were manageable, their PFS and OS were short, which might be attributed to the unwillingness of the patients to receive subsequent treatment. For these patients, further studies might be needed to compare the efficacy and safety of the modified FOLFIRINOX with the standard monotherapy regimen.

There are some limitations of the present study that needs to be addressed. First, although the patients were recruited from three hospitals, only 65 patients were enrolled and the study period was relatively long, nearly 5 years. Second, the small sample size may have partly affected the observed results of this study. Third, we could not evaluate the patients' quality of life due to insufficient data. Therefore, we suggest that further studies on a larger cohort of patients are needed to confirm the efficacy and safety of this regimen.

Conclusions

The efficacy of this modified FOLFIRINOX was comparable to that of the original regimen but with a notably lower rate of adverse events. This modified FOLFIRINOX regimen might be a promising first-line chemotherapy option for Chinese patients with metastatic PC.

Abbreviations

FOLFIRINOX: oxaliplatin, irinotecan, fluorouracil and L-leucovorin; PC: pancreatic cancer; ECOG: Eastern cooperative oncology group; ORR: objective response rate; CI: confidence interval; OS: overall survival; PFS: progression-free survival; PD: progressive disease; SD: stable disease; RECIST: response evaluation criteria in solid tumors; CT: computed tomographic; CTCAE: common

terminology criteria for adverse events; DCR: disease control rate; PR: partial response; CR: complete response.

Authors' contributions

HYL, YB, and RHX conceived and designed this study. TD, LZ, FF, WW, FHW, DSW and HYL were involved in data collection and statistical analysis. ZQW, FZ, HYL and YB were involved in the interpretation of results and manuscript writing. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

Author details

¹ Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou 510060, Guangdong, People's Republic of China. ² Department of Gastrointestinal Medical Oncology, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, People's Republic of China. ³ Cancer Center, The First People's Hospital of Foshan, Foshan 528000, Guangdong, People's Republic of China.

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None.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data are fully available without restrictions. The authenticity of this article has been validated by uploading the key raw data to the Research Data Deposit public platform (<http://www.researchdata.org.cn>) with Approval RDD Number RDDA2019000966.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Written informed consent was obtained from all included subjects. The study was approved by the independent ethics committee at Sun Yat-sen University Cancer Center, Tianjin Medical University Cancer Institute and Hospital and The First People's Hospital of Foshan, and the study was performed in accordance with the Declaration of Helsinki.

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Appendix WEI02

Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer



Tao Wei^{1,2}, Qi Zhang^{1,2}, Xiang Li^{1,2}, Wei Su^{1,2}, Guogang Li^{1,2}, Tao Ma^{1,2}, Shunliang Gao^{1,2}, Jianying Lou^{1,2}, Risheng Que^{1,2}, Lei Zheng³, Xueli Bai^{1,2}, and Tingbo Liang^{1,2}

Abstract

We aimed to explore the application of circulating cell-free DNA (cfDNA) profiling in monitoring tumor burden in patients with pancreatic ductal adenocarcinoma (PDAC). Thirty-eight patients with advanced PDAC receiving first-line FOLFIRINOX chemotherapy were prospectively enrolled. Next-generation sequencing for a panel of 560 genes covering a wide range of cancer-related loci was performed to profile cfDNA. In total, 25 patients (65.8%) had at least one common driver gene alterations (*KRAS*, *TP53*, *SMAD4*, *CDKN2A*) detected within cfDNA. In contrast, no above tumor-related recurrent mutations were found in plasma from 13 healthy individuals. Concordant alterations in plasma cfDNA and tumor tissue DNA was confirmed in two of three patients

with available tissues. Further analysis showed that mutant allele fraction (MAF) for altered loci in cfDNA correlated with tumor stage, metastatic burden, and overall survival. Serial blood samples were collected from 17 patients after chemotherapy. We found that allele fraction for specific altered loci declined in chemotherapy-responding subjects. For cases who were resistant to this therapeutic regimen, increased ctDNA MAF was observed at the time of disease progression. Meanwhile, the dynamics of total cfDNA concentration correlated with tumor burden following chemotherapy. Collectively, we provide evidence that pretreatment ctDNA level correlates with tumor burden in PDAC, and serial cfDNA analysis is a robust tool for monitoring cancer response to chemotherapy.

Introduction

Cancer arises through accumulation of genomic aberrations. Numerous evidence has revealed complicated mutational landscape in various types of cancer and genetic heterogeneity among patients (1, 2). These somatic alterations are almost exclusively present in tumor cells, and thereby serve as specific biomarkers for cancer patients. However, tumor tissue sampling is usually not convenient in clinic in particular for those who cannot undergo surgical resection. It has been shown that mutant DNA within tumor cells can be released into blood, and sequencing of circulating nucleic acids in plasma represents a way of liquid biopsy. Besides the ease of blood sample acquirement, the profiling of cell-free DNA (cfDNA) in plasma is more likely to recapitulate the whole genetic spectrum of tumor compared with tissue sequencing (3). Abundant evidence has confirmed that quantification of

mutant circulating tumor DNA (ctDNA) is valuable in cancer diagnosis, prognostication, monitoring therapy response, and postoperative recurrence (4–6). Emerging studies are also reported its application in tracking clonal evolution and elucidating treatment-resistant mechanisms (7, 8).

Currently, ctDNA can be measured with distinct techniques and strategies. Digital PCR and other allele-specific PCR offer a high sensitivity for detecting individual loci like hotspot mutations (9, 10). Genome-wide analysis through next-generation sequencing (NGS) like whole-exome sequencing was also adopted, but the sensitivity is inadequate with detection limit of 5% to 10% of allele fraction (11, 12). In addition, targeted sequencing for specific DNA regions of interest constitutes a way to interrogate a broad range of loci. This strategy has the advantage to design multiplex patient-specific panels, and the sensitivity can be improved by increased sequencing depth and even ultra-deep sequencing (13).

The aim of this study was to explore the application of cfDNA profiling in monitoring tumor burden change following treatment. Instead of focusing on a few genes, we performed targeted NGS with a customized panel covering 560 cancer-related genes. To this end, a cohort of advanced pancreatic cancer patients receiving FOLFIRINOX (5-fluorouracil, Irinotecan, and Oxaliplatin) regimen was followed. The result showed a high degree of concordance between therapy response and dynamics of ctDNA allele fraction. Applying a broader panel provided additional value as infrequently mutated genes in pancreatic cancer can be detected in selected cases for tracking tumor burden, but this may limit to a small number of patients. Furthermore, we found that the total cfDNA concentration was also useful in monitoring tumor response for selected cases.

¹Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, China. ²Zhejiang Provincial Key Laboratory of Pancreatic Disease, Hangzhou, China. ³Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

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T. Wei and Q. Zhang contributed equally to this article.

Corresponding Authors: Tingbo Liang, The Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, China. Phone: 86 571 87315006; Fax: 86 571 87315006; E-mail: liangtingbo@zju.edu.cn; and Xueli Bai, shirleybai@zju.edu.cn

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Materials and Methods

Study patients

Between October 2015 and April 2018, treatment-naïve patients with pancreatic ductal adenocarcinoma (PDAC) were enrolled from the Second Affiliated Hospital of Zhejiang University, School of Medicine, China. Informed consent was obtained from all patients for participation in the study. The study was approved by the institutional review board of the Second Affiliated Hospital of Zhejiang University, School of Medicine. Clinical information included age, gender, smoking status, tumor staging, tumor location, carbohydrate antigen 19-9 (CA19-9) level, number of FOLFIRINOX therapy cycles, and chemotherapy response. Diagnosis of pancreatic adenocarcinoma was confirmed by pathologic examination of either primary or liver metastasis biopsy for all enrolled subjects. The staging of PDAC was evaluated using American Joint Committee on Cancer (AJCC) criteria. Proximal location was defined as tumor in pancreatic head or neck, whereas distal tumor refers to location in body or tail. All included patients received FOLFIRINOX therapy as first-line treatment except one undergoing initial surgery. This regimen was modified by reducing Oxaliplatin and Irinotecan to 85% and 75% of their full dose, respectively, and omitting the Fluorouracil intravenous bolus (14). Assessment of treatment response was performed every four cycles of chemotherapy via abdominal enhanced CT and enhanced MRI of the liver. According to the Response Evaluation Criteria in Solid Tumors version 1.1 (15), the imaging measurement of tumor response was qualitatively classified into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). This work was conducted in accordance with the guideline of the Declaration of Helsinki.

Sample collection

Five to ten milliliters of peripheral blood was collected from each patient before treatment and at time when therapy response was assessed. Plasma was extracted within 3 hours of blood collection and was immediately frozen in -80°C freezer or liquid nitrogen. Peripheral blood from eight healthy donors was obtained for the same manipulation. Peripheral blood monocytes (PBMC) were obtained synchronously before chemotherapy. Fresh resected tumor tissues or biopsies were collected when possible.

Targeted sequencing of circulating mutant DNA

cfDNA was extracted using the QIAamp Circulating Nucleic Acid Kit. DNA from fresh frozen tissue and peripheral blood mononuclear cells (PBMC) were extracted using the DNeasy Blood & Tissue Kit. Purified DNA was quantified by Qubit DNA Assay Kit in Qubit 2.0 Fluorometer. The size distribution of cfDNA was analyzed then (Supplementary Fig. S1A). Sequencing libraries were prepared using the Agilent SureSelect XT Custom Kit with an optimized manufacturer's protocol. Different libraries with unique indices were pooled together, and hybridized with SureSelect biotin labeled probes targeting 9,762 exons of 560 cancer-relevant genes (Supplementary Table S1). The target exons of genes were captured by streptavidin-coated magnetic beads. Captured libraries were enriched in a PCR reaction to add index tags. Library fragment size was confirmed then (Supplementary Fig. S1B). The clustering of the index-coded samples was performed on a cBot Cluster Generation System using HiSeq PE

Cluster Kit. Then, the DNA libraries were sequenced on Illumina HiSeq4000 NGS platform. For cfDNA and tumor tissues, we intended to generate an average of $1,000 \times$ sequencing depth. Reads from each sample were mapped to the reference sequence hg19. Somatic variant calls presenting at less than 1% mutant allelic frequency (MAF) in the paired PBMC, but with over 0.5% allelic frequency and at least four reads supporting variant alleles in cfDNA or tumor tissue samples, were retained. Raw sequence data have been deposited at the Sequence Read Archive (SRA) under accession number PRJNA491473.

Statistical analysis

Mann-Whitney *U* test was used for comparison of continuous parameters including total cfDNA concentration and MAF. Correlation analysis was performed using Pearson correlation method. Survival analysis was performed using Kaplan-Meier method and multivariate Cox regression analysis. All statistical calculations were performed using SPSS 22.0 (SPSS) and Prism 6.0 (Graphpad). Two-sided *P* value less than 0.05 was considered as significant.

Results

Patient characteristics

The demographics and clinical characteristics for included 38 patients are shown in Table 1. The majority of patients are male (71%). The median age is 62 years-old, and 11 patients are over 65 years of age. Twenty-eight cases were diagnosed with stage IV disease, of whom 26 had liver metastasis and 2 had peritoneal metastasis. For other 10 subjects, stage III disease was diagnosed due to unresectable tumor and absence of metastatic lesions. All cases were treatment-naïve at the time of diagnosis in our center, and FOLFIRINOX therapy was given as initial treatment except one patient. The last patient underwent curative resection first. However, liver metastasis was found 1 month postoperatively, and FOLFIRINOX regimen was given. A median of four cycles of

Table 1. Patients characteristics

Variables	All patients (<i>n</i> = 38)	ctDNA MAF		<i>P</i> value
		<1.5% (<i>n</i> = 17)	>1.5% (<i>n</i> = 21)	
Age, median (range)	62 (42–74)	61	62	0.893
Gender, <i>n</i>				0.721
Male	27	13	14	
Female	11	4	7	
Smoking status, <i>n</i>				0.181
No	27	13	14	
Yes	11	4	7	
Tumor location, <i>n</i>				1.000
Proximal	18	9	9	
Distal	20	8	12	
Stage, <i>n</i>				0.023
III	10	8	2	
IV	28	9	19	
CA19–9, median (range)	1,964 (2–12,000)	879	4496	0.204
FOLFIRINOX cycles, median (range)	4 (2–13)	7	6	0.413
FOLFIRINOX response ^a , <i>n</i>				0.542
PR	6	2	4	
SD	10	4	6	
PD	14	8	6	

^aEight patients did not finish four cycles of therapy and thus were not evaluated for response. The response showed here is the outcome after all cycles of therapy for each case.

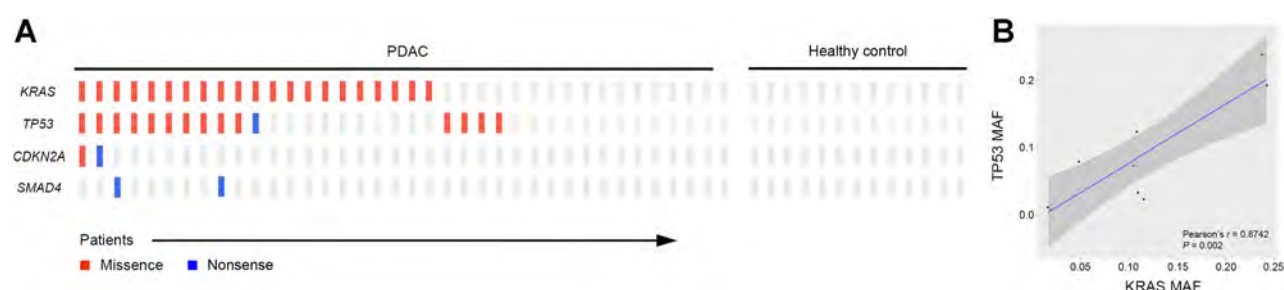


Figure 1. cfDNA profiling in patients with advanced pancreatic cancer. The distribution of detected ctDNA in selected genes among included patients with PDAC and healthy individuals (A). The correlation between *KRAS* and *TP53* cfDNA MAF was analyzed (B).

chemotherapy were performed for all cases, and eight patients did not complete four cycles. For two subjects with stage III disease, remarkable shrinkage of primary tumor was observed after neoadjuvant treatment, and curative resection was performed thereafter.

cfDNA profiling

For cfDNA samples, a median of 987× sequencing depth was acquired after excluding duplication, and 95% of exons were at coverage >100× for all samples. We initially focused on the mutations in common driver genes for PDAC including *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*. Twenty-five of 38 included subjects (65.8%) had at least one alteration for above genes in plasma (Fig. 1A). *KRAS* and *TP53* mutation were present in 84% and 60% of these cases, respectively. G12D ($n = 13$) was the most frequently observed alteration at *KRAS* followed by G12V ($n = 5$), G12R ($n = 3$), and G13D ($n = 1$). The MAF for altered *KRAS* varied between patients reflecting distinct tumor burden (median: 3.4%, range: 0.66–32.6%). One patient had simultaneous *KRAS* G12D and G13D mutation with comparable allele frequency (10.3% vs. 10.5%). For the remaining 13 cases without detection of the four driver gene alterations, we noted three patients harbored hotspot mutation in other loci including *GNAS* and *SF3B1*. The altered codon in all these genes have been reported in PDAC, and cause functional impact. In contrast, none aforementioned hotspot variants were detected in plasma from 13 healthy individuals (Fig. 1A). Noteworthy, 11 patients with PDAC had detectable amounts of *KRAS* and *TP53* mutation concomitantly, and they are presumably to be quantitative correlated as both of them are presented in early clone. Indeed, there was a significant correlation between MAF of them (Pearson's $r = 0.8742$; Fig. 1B). This provides yet another validation of the reliability of our assay and its quantitative nature.

Concordance of alterations in plasma and tumor tissue could be evaluated in three patients. The time interval of acquisition between tumor biopsy or tissue and synchronous blood sample was within 3 days for all cases. In the first patient, liver metastatic biopsy was obtained for analysis, and all four somatic nonsynonymous mutations at *KRAS*, *TP53*, *SMAD4*, and *C8orf34* presented in biopsy was also found in the plasma cfDNA (Table 2). *KRAS*^{G12V} alteration detected in this patients' tumor was validated by Sanger sequencing (Supplementary Fig. S2). Other two patients underwent curative resection after neoadjuvant chemotherapy, and thus primary tumors were available. In one case, same hotspot variant at *TP53* was detected in tissue and plasma (Table 2). For another patient, *SF3B1*^{R625C} was detected in plasma, whereas there were

no alterations found in tumor tissue possibly due to extremely low viable tumor cell fraction after FOLFIRINOX therapy.

Correlation of ctDNA level and tumor burden

The median total cfDNA concentration for patients with PDAC was significantly higher than those of healthy donors (28.4 ng/mL vs. 10.3 ng/mL plasma, $P < 0.001$; Fig. 2A). Moreover, stage IV patients tended to have increased cfDNA concentration compared with stage III cases, although the difference was not significant (Fig. 2B). Then we determined the relationship between ctDNA allele fraction and tumor staging. For cases with multiple alterations detected, the one with highest allele fraction was used to represent the ctDNA MAF. Elevated MAF was observed in stage IV metastatic patients compared with stage III cases (Fig. 2C, $P < 0.01$). We further divided 21 stage IV patients with liver metastasis into two groups with either limited metastatic lesion (≤ 2 lesions) or disseminated lesions (> 3 lesions). Patients with multiple isolated liver metastasis had markedly higher ctDNA MAF compared with those having fewer lesions (Fig. 2D, $P < 0.01$). These results indicated that ctDNA MAF was correlated with disease burden, implying its potential application for tracking tumor response to therapy.

We further divided patients into two groups with either low or high ctDNA MAF using threshold of 1.5%, which is the median value for all subjects. The comparison of clinical parameters for this two groups showed that only stage was significantly different (Table 1). Besides, the overall survival analysis demonstrated that patients with ctDNA MAF $\geq 1.5\%$ had worse prognosis compared with those have lower than 1.5%. But the difference was not significant in multivariate cox regression analysis possibly due to small number of cases included (Supplementary Fig. S3).

Monitoring tumor burden following FOLFIRINOX therapy via cfDNA

The role of ctDNA in monitoring treatment response was studied in 17 patients with PDAC receiving FOLFIRINOX regimen

Table 2. Concordance of altered loci in tumor tissue and plasma.

Patient	Concordant mutations in tumor tissue and plasma
Case 1	<i>KRAS</i> , p.G12V <i>TP53</i> , p.E153K <i>SMAD4</i> , p.E161X <i>C8orf34</i> , p.S262Y
Case 2	<i>TP53</i> , p.C153R

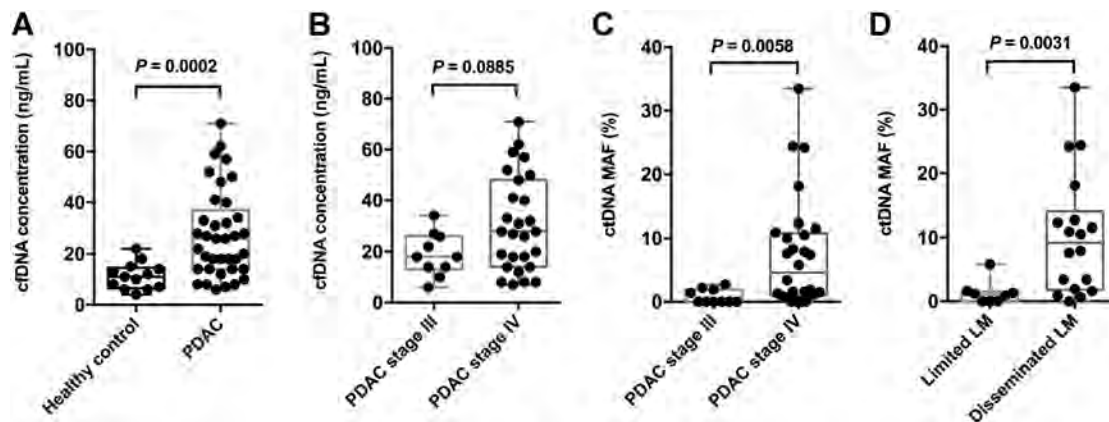


Figure 2.

The correlation analysis of cfDNA concentration and ctDNA MAF with tumor burden. The comparison of total cfDNA concentration was done in PDAC versus healthy individuals (**A**), and AJCC stage III versus stage IV (**B**). ctDNA MAF between patients with PDAC stage III and stage IV was compared (**C**). ctDNA MAF was compared for patients with limited and disseminated liver metastasis (LM; **D**).

who had longitudinal blood samples collected after one course of chemotherapy (Table 3). For 12 subjects responding to chemotherapy with six PR and six SD, the cfDNA MAF reduced concomitantly in 11 patients. Among them, alterations in multiple loci can be detected in four subjects, and all had consistent trend in MAF with tumor burden. One patient exhibited SD, and ctDNA of altered *KRAS* was detectable with MAF of 0.7% after chemotherapy which was not present at baseline. Other five cases showed resistance to chemotherapy, and increased ctDNA MAF was observed at the time of disease progression. In contrast, CA19-9 was not reliable to track disease burden for five cases. Among them, CA19-9 was within normal range throughout the treatment

course in three subjects. For other two cases, the change of CA19-9 level was not in consistent with the clinical scenario (Table 3).

We further highlighted six cases. In case 1, remarkable shrinkage of primary tumor and almost disappearance of multiple liver metastasis were observed after four cycles of FOLFIRINOX therapy. But disease progressed with markedly enlarged lesions in liver when the second course was completed (Fig. 3A). Both cfDNA concentration and MAF for driver gene *KRAS*, *TP53*, and *CDKN2A* were in line with clinical course. The second patient experienced continued response representing as extensive tumor necrosis on imaging, and then curative resection was performed (Fig. 3B). The microscopic examination of resected tumor

Table 3. Dynamics of the ctDNA MAF following FOLFIRINOX therapy

Patient no.	Altered loci in cfDNA	MAF (%)		CA19-9 (U/mL)		Therapy response
		Before therapy	After therapy ^a	Before therapy	After therapy ^a	
1	<i>KRAS</i> (G12D)	10.8	0.82	2	2	PR
	<i>TP53</i> (R172H)	12.3	0.78			
	<i>CDKN2A</i> (H83Y)	8.7	0			
2	<i>KRAS</i> (G12D)	10.3	2.8	51.7	36.7	PR
	<i>KRAS</i> (G13D)	10.5	2.8			
	<i>U2AF1</i> (S34F)	4.6	0.76			
3	<i>KRAS</i> (G12V)	1.9	0	12000	3921	SD
	<i>TP53</i> (E153K)	0.73	0			
	<i>SMAD4</i> (E163X)	0.74	0			
4	<i>TP53</i> (R150W)	0	1.6	162.7	681.5	PD
	<i>SMAD4</i> (R361H)	0	0.75			
5	<i>GNAS</i> (R201S)	3.4	2.2	512	235.7	SD
6	<i>SF3B1</i> (K700E)	1.6	0	1261.2	374.2	SD
7	<i>KRAS</i> (G12D)	0.66	0	12000	12000	PR
8	<i>TP53</i> (C153R)	1.2	0	43	10.9	PR
9	<i>KRAS</i> (G12D)	1.2	0	2	2	SD
10	<i>SF3B1</i> (R625C)	2.9	0.63	121.8	61.9	PR
11	<i>TP53</i> (R175H)	0	1.3	4018.9	3569.1	PD
12	<i>KRAS</i> (G12R)	4.6	59.6	134.1	12000	PD
13	<i>TP53</i> (I195T)	1.0	37.0	12000	3746.7	PR
	<i>KRAS</i> (G12D)	32.6	0			
14	<i>TP53</i> (Q165X)	33.5	12.8	1594.5	1161.1	SD
	<i>KRAS</i> (G12C)	0	0.7003			
15	<i>TP53</i> (G295V)	0	5.9	587.3	1287.1	PD
16	<i>KRAS</i> (G12D)	3.4	11.2	108.5	884.2	PD
17	<i>TP53</i> (R175H)	5.8	5.1	2	2	SD

^aThree to four cycles of chemotherapy.

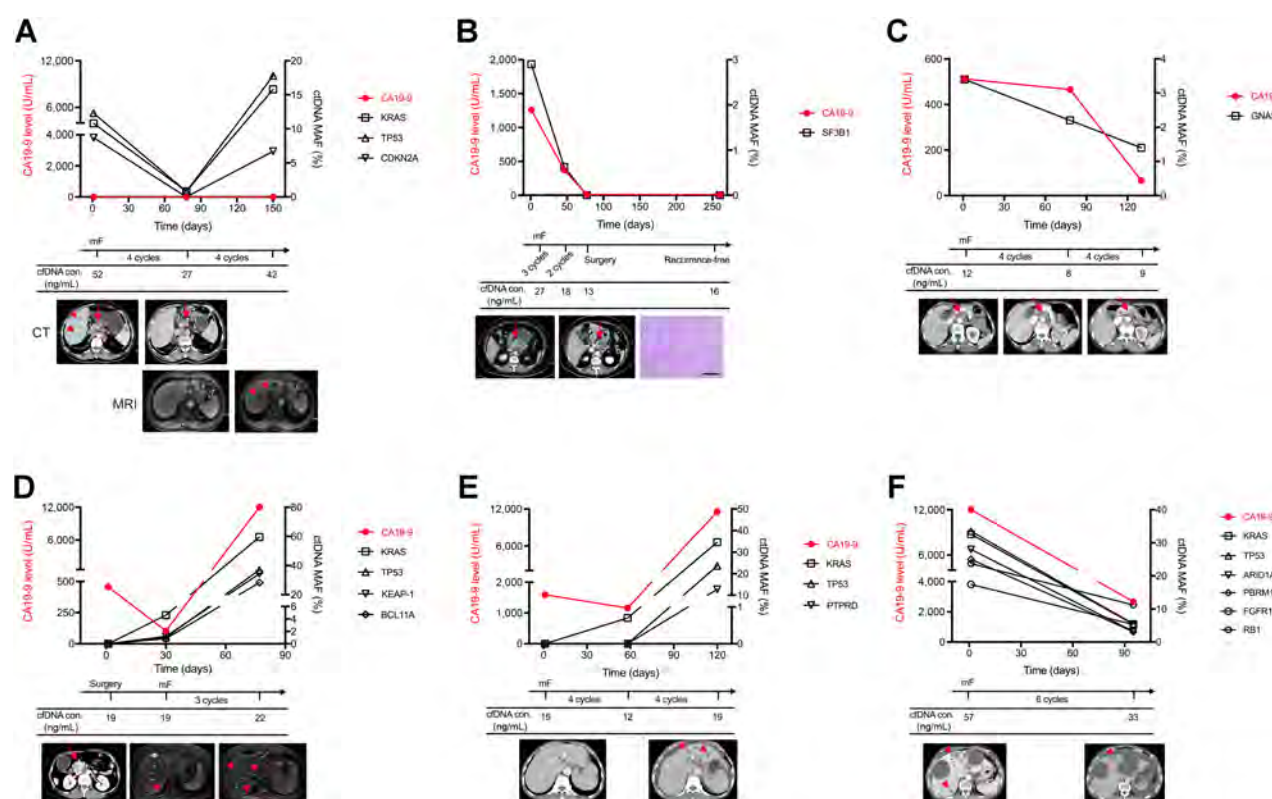


Figure 3. Representative cases of ctDNA dynamics and correlation with treatment response (A-F). Arrows represent primary pancreatic tumors. Arrowheads represent liver metastatic tumors. Low tumor fraction and necrosis was shown by H&E staining, and there were typical cholesterol-like crystals with multinuclear giant cell reaction after chemotherapy (B). cfDNA con. denotes cfDNA concentration. The scale bar is 200 μ m.

specimen showed typical post-chemotherapy structure and massive necrosis (Fig. 3B). *SF3B1*^{R625C} alteration was detected before chemotherapy, and in parallel, its MAF gradually decreased along with treatment course. The kinetics of cfDNA concentration was also consistent with tumor burden change. In case 3 with localized tumor, moderate response was noted, which correlated with decline of *GNAS*^{R201S} MAF and stable level of cfDNA concentration after the first and second course of therapy (Fig. 3C). In the fourth subject, surgical resection was first performed. Emerging liver metastatic lesions were found one month postoperatively, and ctDNA of *KRAS* and *TP53* was detectable concomitantly. Metastasis progressed despite multiple times of FOLFIRINOX treatment, along with the dramatic increase of ctDNA MAF (Fig. 3D). Interestingly, we observed that two other somatic alterations at *KEAP1*^{R483H} and *BCL11A*^{R141H} exhibited consistent dynamics as *KRAS* and *TP53*. These two mutations have not been reported in pancreatic cancer and the functional impact remains to be defined. In case 5, disease continuously progressed with multiple emerging liver metastasis following chemotherapy (Fig. 3E). In line with the clinical findings, MAF of ctDNA at multiple loci increased with *KRAS* being up to 10% after two course of therapy. At the same time, a new variant of *PTPRD*^{I972V} was detected. The last patient suffered from disseminated liver metastasis and had high tumor burden, and high MAF for multiple cfDNA loci was noted before treatment (Fig. 3F). This patient exhibited favorable response to the FOLFIRINOX regimen with

substantial reduction of metastatic burden and even disappearance for some lesions. Multiple altered loci in cfDNA were detected at baseline including *KRAS*^{G12D}, *PBRM1*^{T377S}, *RB1*^{Y498C}, *TP53*^{Q165X}, *ARID1A*^{Q564X}, and *FGFR1*^{M390I}. In consistent with clinical scenario, all these detected ctDNA showed decline of MAF. The total cfDNA concentration also decreased concomitantly.

Discussion

In this study, we described the cfDNA analysis as a way to monitor tumor burden in response to treatment. Our cfDNA profiling was based on targeted NGS strategy. Compared with many other studies (16, 17), we designed a larger multigene panel constituted of 560 genes including both high- and low-frequently altered loci reported in PDAC (18). Hybrid capture technique was used in order to cover broad genomic regions of our customized panel. Sensitivity might be compromised given the wide genomic region to be detected. Nevertheless, for well-known driver genes in PDAC including *KRAS*, *TP53*, *SMAD4*, and *CDKN2A*, the results showed that detection rate for at least one of above loci among included patients is 65.6%. Although the sensitivity is lower than a few PCR-based assays, this result is superior to other NGS profiling for ctDNA in pancreatic cancer. By using PCR-amplicon and AmpliSeq platform, Pietrasz and colleagues found 48.1% of patients with unresectable tumor had detectable ctDNA with detection limit of 0.1% (19). Another study reported that

57.7% of patients with advanced pancreatobiliary carcinomas had detectable *KRAS* mutation in cfDNA. Notably, the coverage depth for a 54-gene panel averaged approximately 10,000× in their study (20). However, it has been recognized that the risk of false positive increases with the size of panel owing to multiple hypothesis testing (4). In addition, the mutant cfDNA could be originated from hematopoietic clone and thus lead to false positive detection. However, allele fractions of these nontumor-derived cfDNA are generally low and a threshold of 0.5% MAF defined in the present analysis should avoid these contaminations. Indeed, MAF of ctDNA for most cases was higher than 1% in our analysis. To determine the specificity, plasmas from 13 healthy donors with comparable age to enrolled patients were analyzed with same pipeline, and there were no somatic variants found in PDAC driver genes. It should be noted that only a small population of healthy individuals were included in the control group. Furthermore, the accuracy of ctDNA detection was evaluated in three cases given the available corresponding tumor tissues. The alterations found in tumor tissues were favorably matched to those in cfDNA for two subjects. Finally, as altered *KRAS* and *TP53* are well-characterized drivers for PDAC at an early stage, their MAF among cfDNA is supposed to be correlated quantitatively. This was corroborated in nine patients with concomitant mutation at both genes, which is consistent with other report using digital PCR analysis (21). In one case, mutant codon 12 and 13 of *KRAS* was found with almost same MAF. These results overwhelmingly strengthened the robustness of our sequencing strategy.

One potential clinical utility of ctDNA is to monitor disease longitudinally in response to therapy given the ease of repeated blood drawing (22, 23). This is rationalized by the relationship between disease burden and circulating mutant DNA level. Here we included a highly-selected group of patients with advanced PDAC with uniform first-line treatment of FOLFIRINOX chemotherapy. FOLFIRINOX regimen has been recommended as a first-line treatment choice for advanced PDAC (24). We confirmed that ctDNA level could mirror tumor burden at baseline as higher cfDNA MAF was associated with liver metastasis. The serial blood analysis showed that ctDNA dynamics in allele frequency was consistent with therapy response in all 12 patients evaluated. In comparison, as the standard clinical biomarker for PDAC, CA19-9 remained undetectable in three cases and thus was futile for tumor monitoring. Indeed, certain percentage of patients are negative for Lewis antigen (25). Therefore, ctDNA could be a useful compensate for conventional serum biomarker in tracking therapy response. Although we noted a generally consistency between change of CA19-9 level and tumor burden, other studies found superiority of ctDNA over standard biomarker. In colorectal cancer, researchers revealed that ctDNA outperformed carcino-embryonic antigen in predicting recurrence and tracking disease (26).

PDAC has remarkable genetic heterogeneity with a large number of low-frequently mutated loci, and importantly, a fraction of patients does not harbor mutations in *KRAS* and *TP53* (27). For three patients, we detected alterations at *GNAS* and *SF3B1* in plasma but not at those high-frequently altered driver genes. *GNAS* has been characterized as an oncogene in pancreatic cancer, and the hotspot mutation can be found in about 5% to 10% of cases (28). *SF3B1* encoded the protein involving in RNA splicing, and both R625C and K700E variant detected here resulted in

functional change. The frequency for *SF3B1* mutation in PDAC was reported to be around 5% (29). In addition, a few detected somatic mutations in cfDNA have not been reported in pancreatic cancer before including *ARID1A*^{Q564X}, *PBRM1*^{T377S}, and *KEAP1*^{R483H}. These data supported the additional value of application of large gene panel in ctDNA analysis.

Besides the ctDNA level, total cfDNA concentration was also clinically relevant in selected patients. A significantly higher cfDNA concentration was present in PDAC patients in contrast to healthy donors. Meanwhile, stage IV patients tended to have elevated concentration. Indeed, the correlation between tumor staging and cfDNA concentration has been well characterized. It is thus presumably that tumor would give rise to a considerable percentage of cfDNA in plasma. Goodall and colleagues reported that decline of total cfDNA concentration was able to predict the progression-free and overall survival in prostate cancer patients treated with PARP inhibitor. Moreover, the change of cfDNA concentration was consistent with that of allele frequency of somatic mutation in plasma (30). Another recent study also demonstrated that total cfDNA concentration was a surrogate marker for tumor burden and is prognostic for overall survival (31). Compared with mutation profiling, measurement of cfDNA concentration has the distinct advantages being faster, easier, and cheaper. Its clinical application warrants further investigation.

In this cohort, a few patients exhibited initial response to FOLFIRINOX therapy, but secondary resistance occurred after the next course of treatment. It would be clinically significant to interrogate resistant mechanisms though analysis of genomic evolution via cfDNA (32). In fact, several piece of emerging evidence indicated that serial cfDNA analysis informed the underlying mechanisms for acquired therapy resistance. Two recent studies uncovered that acquired *BRCA2* or *PALB2* reversion mutations conferred insensitivity to PARP inhibitor olaparib or talazoparib in prostate cancer (30, 33). Another study reported polyclonal secondary *FGFR2* mutations drove resistance to *FGFR* inhibitor in patients with cholangiocarcinoma who initially responded due to *FGFR2* fusion-positive (34). FOLFIRINOX regimen is a combination of three cytotoxic drugs. The genomic alterations associated with therapy sensitivity are lacking except that DNA repair genes status predicts response to platinum-based drugs like oxaliplatin. Nevertheless, there were no detected pathogenic variants in genes regulating DNA damage response like *BRCA1*, *BRCA2*, *ATM*, and *PALB2*. It is worthwhile for further investigation as a significant proportion of patients develop acquired drug tolerance (14).

Clinically, the widely-used circulating protein biomarker for pancreatic cancer is CA19-9, and CA125 and CEA are useful in a small fraction of patients. It is proposed that ctDNA has greater dynamic range and shorter half-life than protein biomarkers (4). This should enable ctDNA to be more sensitive in monitoring tumor burden following treatment. In particular, the current method like ultra-deep sequencing allows extremely low abundance ctDNA to be detected. Meanwhile, ctDNA-based markers might be more specific than proteins. Increased CA19-9 has been seen in other nontumor contexts like pancreatitis and cholestasis. However, we believe that ctDNA suffers from some drawbacks similar as protein-based blood diagnosis. For instance, for early-stage cancer and those with minimum residual disease after resection, the detection sensitivity remains low as ctDNA level tightly correlate with tumor burden.

Conclusions

In summary, we provide evidence that ctDNA level constitute as an indicator for tumor burden. Serial cfDNA analysis is a noninvasive and robust tool for tumor monitoring in patients with pancreatic cancer receiving FOLFIRINOX chemotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T. Wei, Q. Zhang, L. Zheng, X. Bai, T. Liang

Development of methodology: T. Wei, Q. Zhang, X. Li, T. Liang

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Wei, Q. Zhang, X. Li, W. Su, G. Li, T. Ma, S. Gao, J. Lou, R. Que

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T. Wei, Q. Zhang, W. Su, G. Li

Writing, review, and/or revision of the manuscript: T. Wei, Q. Zhang, X. Bai, T. Liang

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Liang

Study supervision: Q. Zhang, T. Liang

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Zhe-Sheng Chen,
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REVIEWED BY

Chen Jue,
Yangzhou University, China
Harsh Patel,
St. John's University, United States

*CORRESPONDENCE

Yingzhou Fu,
✉ fuyingzhou@hnca.org.cn
Yong Pan,
✉ panyong@hnca.org.cn

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Cost-effectiveness analysis of first-line combination chemotherapy regimens for metastatic pancreatic cancer and evidence-based pricing strategy of liposomal irinotecan in China

Zuojuan Xiang¹, Ling Ma², Zhengxiong Li³, Yingzhou Fu^{1*} and Yong Pan^{1*}

¹Department of Pharmacy, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Hunan Cancer Hospital, Changsha, China, ²Department of Clinical pharmacy, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, China, ³School of Medical Informatics and Engineering, Xuzhou Medical University, Xuzhou, China

Background: The phase III NAPOLI-3 trial, which upgraded FOLFIRINOX (leucovorin, fluorouracil, irinotecan and oxaliplatin) to NALIRIFOX (liposomal irinotecan, oxaliplatin, leucovorin, and fluorouracil), demonstrated the superiority of NALIRIFOX over GEMNABP (gemcitabine and nab-paclitaxel) as the first-line treatment for metastatic pancreatic ductal adenocarcinoma. The purpose of this study was to assess the cost-effectiveness of NALIRIFOX, FOLFIRINOX, and GEMNABP, and to simulate the price of liposomal irinotecan at which NALIRIFOX could achieve cost-effectiveness.

Methods: A partitioned survival model was performed to evaluate the cost-effectiveness of NALIRIFOX, FOLFIRINOX and GEMNABP from the perspective of the Chinese healthcare system. Survival data was obtained from a recently published network meta-analysis (NMA). Drug prices were collected from the database of the Hunan Province Drug and Medical Consumables Procurement Management Subsystem. Other cost and utility values were sourced from established literature. Cumulative costs, LYs (life-years), quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs), net monetary benefits (NMBs) and incremental net monetary benefits (INMBs) were the main outputs. Furthermore, the variations in ICER were analyzed as the price of liposomal irinotecan gradually decreased when comparing NALIRIFOX with FOLFIRINOX or GEMNABP. The robustness of the model was assessed by sensitivity analysis and scenario analysis.

Results: At the willingness-to-pay (WTP) threshold of \$38,223.34, GEMNABP was the favored treatment. NALIRIFOX was associated with the highest LYs, QALYs, and cost. The cost-effectiveness of NALIRIFOX would be obtained if the price of liposomal irinotecan was less than \$3.36/mg and \$2.08/mg compared to FOLFIRINOX and GEMNABP, respectively, without considering the patient assistance program (PAP). Sensitivity analysis and scenario analysis revealed that the results of the model were stable.

Conclusion: From an economic standpoint, GEMNABP represents the favored choice in the prevailing market conditions among these three first-line combination chemotherapy regimens. The price simulation of liposomal irinotecan conducted in this study could provide valuable evidence for healthcare decision-making. Further evidence regarding the budget impact is still needed.

KEYWORDS

metastatic pancreatic cancer, cost-effectiveness, FOLFIRINOX, NALIRIFOX, GEMNABP, liposomal irinotecan

1 Introduction

Pancreatic cancer, a highly malignant digestive system cancer, poses a serious threat to human health. It ranks twelfth in the world in terms of newly diagnosed cases among all malignant tumors, but ranks sixth in terms of mortality rate (Bray et al., 2024). In China, the estimated number of new confirmed cases was 118,700, and the number of deaths was 106,300 in 2022 (Han et al., 2024). Pancreatic cancer typically onsets insidiously and progresses rapidly, leading to a diagnosis at an advanced stage for most patients. Less than 20% of patients have the chance for surgical intervention, and the 5-year survival rate for patients with metastatic pancreatic cancer is a mere 3% (Wainberg et al., 2023; Golivi et al., 2024).

The dense stroma matrix surrounding pancreatic cancer cells hinders the delivery of therapeutic drugs and immune cells to the target site, leading to diminished drug effectiveness (Luo and Zhang, 2024). The targeted and immunotherapy approaches, which have made significant strides in the treatment of other types of tumors, have demonstrated poor efficacy when applied to pancreatic cancer (Liu et al., 2022). For patients with metastatic pancreatic cancer, gemcitabine monotherapy was proved to be more effective than fluorouracil (Burris et al., 1997). Therefore, in the past two decades, clinicians have endeavored to identify drugs or combination therapy regimens capable of surpassing the effectiveness of gemcitabine. In this context, the combination of leucovorin, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) (Conroy et al., 2011) and the combination of gemcitabine and nab-paclitaxel (GEMNABP) (Von Hoff et al., 2013) have demonstrated favorable outcomes in clinical trials, establishing them as the gold standard first-line chemotherapy regimens. Recently, the phase III NAPOLI-3 clinical trial upgraded FOLFIRINOX to NALIRIFOX, which included liposomal irinotecan, oxaliplatin, leucovorin, and fluorouracil. The findings indicated that both progression-free survival (PFS) and overall survival (OS) of NALIRIFOX were superior to GEMNABP (Wainberg et al., 2023). Based on the positive results, NALIRIFOX has been recommended as a new first-line treatment for metastatic pancreatic cancer in the 2023 edition of National Comprehensive Cancer Network (NCCN) guidelines and the 2024 edition of Chinese Society of Clinical Oncology (CSCO) guidelines.

Only NALIRIFOX and GEMNABP were head-to-head compared in the NAPOLI-3 trial, and to date, neither of these two regimens has been directly compared with FOLFIRINOX. Recently, Nichetti F et al. conducted a network meta-analysis (NMA) comparing these three treatments in terms of PFS, OS, and toxicity (Nichetti et al., 2024). The results revealed that the

median PFS for NALIRIFOX and FOLFIRINOX was 7.4 months and 7.3 months, respectively, showing no significant difference. In contrast, GEMNABP demonstrated a significantly poorer median PFS of 5.7 months. Similarly, the OS of NALIRIFOX and FOLFIRINOX was 11.7 months and 11.1 months, respectively, whereas GEMNABP displayed a poorer OS of 10.4 months. In comparison to the other two treatments, NALIRIFOX was linked to a lower occurrence of grade 3 or higher hematological toxicity. However, it exhibited a higher risk of severe diarrhea compared to GEMNABP.

Clinical data serves as a critical basis for the evidence-based use of drugs in clinical practice. However, to the best of our knowledge, there is a dearth of pharmacoeconomic evaluations of these three treatments, which are also essential for promoting rational drug use. Although NALIRIFOX has demonstrated favorable clinical outcomes, its use involves a relatively expensive drug, liposomal irinotecan, which encapsulates irinotecan in pegylated liposomal particles to achieve improved pharmacokinetics and has been approved for metastatic pancreatic cancer (Melisi et al., 2024). In fact, among the drugs used in these three treatments, only liposomal irinotecan has not been included in the Chinese Basic Medical Insurance Drug List. Therefore, drawing from the NMA, this study conducted a cost-effectiveness assessment of these three regimens from the perspective of the Chinese healthcare system and a price simulation of liposomal irinotecan to inform the pricing strategy. It aimed to provide decision-makers with valuable references for optimizing the allocation of healthcare resources and offering doctors important economic evidence for selecting appropriate chemotherapy regimen for their patients.

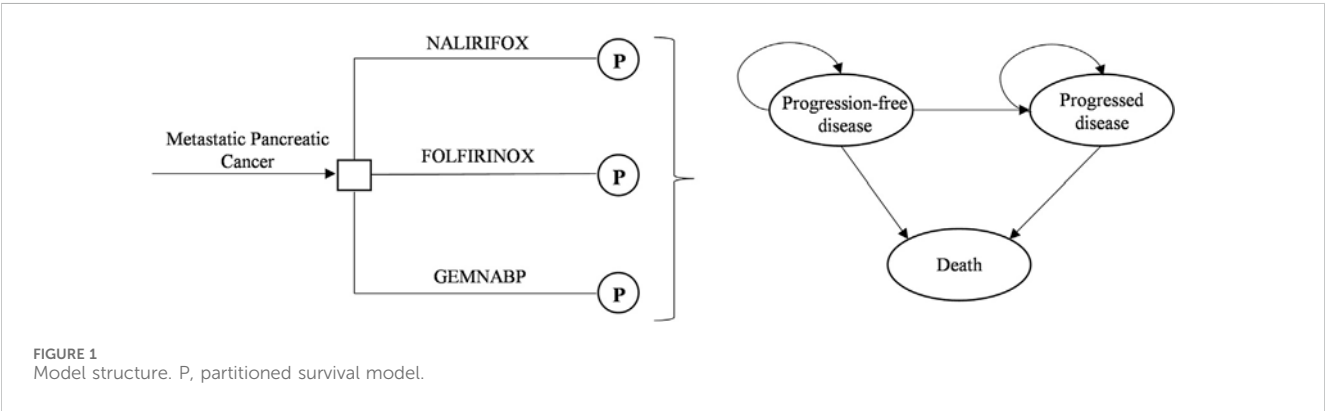
2 Methods

This cost-effectiveness analysis was conducted according to Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and from the perspective of Chinese healthcare system (Supplementary Table S1). Total costs, LYs (life-years), QALYs (quality-adjusted life-years), incremental cost-effectiveness ratios (ICERs), net monetary benefits (NMBs) and incremental net monetary benefits (INMBs) were the main outputs. According to the 2020 version of the China Guidelines for Pharmacoeconomic Evaluations (CGPE), whether cost-effectiveness of the treatment was determined by comparing the ICER value with the willingness to pay (WTP) threshold of \$38,223.34, which was three times the gross domestic product (GDP) *per capita* of China in 2022, or by evaluating the INMB.

TABLE 1 Specific dosing regimens.

First-line chemotherapy regimen	Dosing schemes	Second-line chemotherapy regimen	Dosing schemes
NALIRIFOX	Liposomal irinotecan 50 mg/m ² + oxaliplatin 60 mg/m ² + LV 400 mg/m ² + fluorouracil 2,400 mg/m ² over 46 h; every 14 days	GEMNABP	GEM 1000 mg/m ² + NABP 125 mg/m ² ; Days 1, 8, 15, and every 28 days
FOLFIRINOX	Irinotecan 180 mg/m ² + oxaliplatin 85 mg/m ² + LV 400 mg/m ² + fluorouracil bolus 400 mg/m ² +2,400 mg/m ² over 46 h; every 14 days	GEMNABP	GEM 1000 mg/m ² + NABP 125 mg/m ² ; Days 1, 8, 15, and every 28 days
GEMNABP	GEM 1000 mg/m ² + NABP 125 mg/m ² ; Days 1, 8, 15, and every 28 days	FOLFOX	Oxaliplatin 85 mg/m ² on day 1 +LV 200 mg/m ² +2,400 mg/m ² over 46 h every 14 days

GEM, gemcitabine; LV, leucovorin; NABP, nab-paclitaxel.



INMB = WTP*(E2 - E1) - (C2 - C1). INMB >0 indicates cost-effective.

2.1 Patient population and regimen

This model was conducted based on the NMA, which involved the reconstruction of individual patient data from 7 phase III clinical trials (Conroy et al., 2011; Von Hoff et al., 2013; Philip et al., 2019; Van Cutsem et al., 2020; Tempero et al., 2021; Bekaii-Saab et al., 2023; Wainberg et al., 2023). Aligned with the NMA, the hypothetical cohort in this study comprised patients with metastatic pancreatic ductal adenocarcinoma who received NALIRIFOX, FOLFIRINOX, or GEMNABP as their first-line treatment planned at standard dose intensity. Prior adjuvant treatment was allowed. Patients were adults aged 18 years or older, with an Eastern Cooperative Oncology Group performance status score (ECOG PS) of 0 or 1.44% of patients were male. Since this study was based on previously published data and did not involve patient recruitment or a retrospective analysis of primary patient data, ethical approval was not required.

All medications involved in this model were administered intravenously. Specific dosing regimens and doses were collected from the corresponding clinical trials and detailed in the Table 1. When determining the dosage, an average body surface area of 1.72 m² was used (Qiao et al., 2021).

2.2 Model structure

We employed the TreeAge Pro 2019 software to construct a partitioned survival model comprising three distinct health states: PFS, progressed disease (PD), and death. The model structure was shown in Figure 1. The partitioned survival model calculates the proportion of patients in different health states based on the area under the OS and PFS curves. This approach yields results that closely approximate the actual observed data. Given the highly aggressive nature of metastatic pancreatic cancer, the time horizon for the model was established at 5 years, within which 99% of the patients in the model had died. The cycle length was set at 28 days to align with the dosing regimen.

Survival data used in this model were derived from the reconstructed and validated survival curves in the NMA. WebPlotDigitizer was used to extract PFS and OS data points from the Kaplan-Meier curves, followed by curve reconstruction using the R software (version 4.3.2). As shown in Supplementary Figure S1 and Supplementary Table S2, the median PFS and median OS values of the reconstructed curves were very close to the original ones. Based on Guyot et al.'s algorithm, we extrapolated survival curves and used exponential, Weibull, log-normal, log-logistic, Gompertz, and generalized gamma parametric survival functions to fit the survival data. These standard parametric models are the most commonly used method in existing studies, despite their potential limitations in capturing survival curve inflection points compared to more flexible parametric models. However, given the

TABLE 2 Key parameters.

Parameters	Baseline value	Minimum	Maximum	Distribution	References
Kaplan Meier survival curve					
NALIRIFOX-OS	Shape 1.4047, rate 0.1006	-	-	Gamma	Nichetti et al. (2024)
NALIRIFOX-PFS	Shape 1.3473, rate 0.1479	-	-	Gamma	Nichetti et al. (2024)
FOLFIRINOX-OS	Shape 1.3484, scale 0.0261	-	-	Weibull	Nichetti et al. (2024)
FOLFIRINOX-PFS	Shape 1.5054, rate 0.1730	-	-	Gamma	Nichetti et al. (2024)
GEMNABP-OS	Shape 1.6851, rate 0.1311	-	-	Gamma	Nichetti et al. (2024)
GEMNABP-PFS	Shape 1.7450, rate 0.2355	-	-	Gamma	Nichetti et al. (2024)
Cost (\$)					
Biochemical and blood routine examination/cycle	29.21	23.37	35.05	Gamma	Li et al. (2021)
Radiological examination/cycle	95.53	76.42	114.64	Gamma	Li et al. (2021)
Best supportive care	118.29	94.63	141.95	Gamma	Li et al. (2021)
Terminal care	1,967.95	1,574.36	2,361.54	Gamma	Li et al. (2021)
Cost of drugs					
Liposomal irinotecan/1 mg	24.88	19.90	29.86	Gamma	Local charge
Irinotecan/100 mg	10.01	8.01	12.01	Gamma	Local charge
Oxaliplatin/100 mg	65.13	52.10	78.16	Gamma	Local charge
Leucovorin/100 mg	2.43	1.94	2.92	Gamma	Local charge
Fluorouracil/100 mg	3.28	2.62	3.94	Gamma	Local charge
Gemcitabine/1000 mg	5.01	4.01	6.01	Gamma	Local charge
Nab-paclitaxel/100 mg	22.24	17.79	26.69	Gamma	Local charge
Cost of grade ≥3 AEs					
Anemia	42.42	33.94	50.90	Gamma	Cui et al. (2021)
Neutrophil count decreased	113.32	90.66	135.98	Gamma	Cui et al. (2021)
Febrile neutropenia	279.40	223.52	335.28	Gamma	Cui et al. (2021)
Platelet count decreased	378.48	302.78	454.18	Gamma	Cui et al. (2021)
Diarrhea	5.10	4.08	6.12	Gamma	Cui et al. (2021)
Peripheal neuropathy	58.76	47.01	70.51	Gamma	Cui et al. (2021)
Vomit	28.33	22.66	34.10	Gamma	Cui et al. (2021)
Fatigue	84.54	67.63	101.45	Gamma	Cui et al. (2021)
Utility					
PFS	0.85	0.68	1.00	Beta	Li et al. (2021)
PD	0.73	0.58	0.88	Beta	Li et al. (2021)
Disutility due to grade ≥3 AEs					
Anemia	0.07	0.06	0.08	Beta	Zhu et al. (2023)
Neutrophil count decreased	0.09	0.07	0.11	Beta	Zhu et al. (2023)
Febrile neutropenia	0.13	0.10	0.16	Beta	Coyle et al. (2017)
Platelet count decreased	0.65	0.52	0.78	Beta	Zhu et al. (2023)
Diarrhea	0.21	0.17	0.25	Beta	Coyle et al. (2017)

(Continued on following page)

TABLE 2 (Continued) Key parameters.

Parameters	Baseline value	Minimum	Maximum	Distribution	References
Peripheal neuropathy	0.23	0.18	0.28	Beta	Coyle et al. (2017)
Vomit	0.13	0.10	0.16	Beta	Liu et al. (2023)
Fatigue	0.47	0.38	0.56	Beta	Coyle et al. (2017)
Risk of grade ≥ 3 AEs (%)					
NALIRIFOX					
Anemia	10.5	8.40	12.60	Beta	Nichetti et al. (2024)
Neutrophil count decreased	23.8	19.04	28.56	Beta	Nichetti et al. (2024)
Febrile neutropenia	2.4	1.92	2.88	Beta	Nichetti et al. (2024)
Platelet count decreased	1.6	1.28	1.92	Beta	Nichetti et al. (2024)
Diarrhea	20.3	16.24	24.36	Beta	Nichetti et al. (2024)
Peripheal neuropathy	6.8	5.44	8.16	Beta	Nichetti et al. (2024)
Vomit	7.0	5.60	8.40	Beta	Nichetti et al. (2024)
Fatigue	15.1	12.08	18.12	Beta	Nichetti et al. (2024)
FOLFIRINOX					
Anemia	11.2	8.96	13.44	Beta	Nichetti et al. (2024)
Neutrophil count decreased	30.8	24.64	36.96	Beta	Nichetti et al. (2024)
Febrile neutropenia	7.7	6.16	9.24	Beta	Nichetti et al. (2024)
Platelet count decreased	11.8	9.44	14.16	Beta	Nichetti et al. (2024)
Diarrhea	16.8	13.44	20.16	Beta	Nichetti et al. (2024)
Peripheal neuropathy	9.0	7.20	10.80	Beta	Nichetti et al. (2024)
Vomit	14.5	11.60	17.40	Beta	Nichetti et al. (2024)
Fatigue	16.5	13.20	19.80	Beta	Nichetti et al. (2024)
GEMNABP					
Anemia	18.0	14.40	21.60	Beta	Nichetti et al. (2024)
Neutrophil count decreased	34.6	27.68	41.52	Beta	Nichetti et al. (2024)
Febrile neutropenia	3.0	2.40	3.60	Beta	Nichetti et al. (2024)
Platelet count decreased	10.8	8.64	12.96	Beta	Nichetti et al. (2024)
Diarrhea	5.7	4.56	6.84	Beta	Nichetti et al. (2024)
Peripheal neuropathy	12.1	9.68	14.52	Beta	Nichetti et al. (2024)
Vomit	2.4	1.92	2.88	Beta	Nichetti et al. (2024)
Fatigue	14.5	11.60	17.40	Beta	Nichetti et al. (2024)
Body surface area (m ²)	1.72	1.38	2.06	Gamma	Qiao et al. (2021)
Discount rate (%)	5	0	8	Fix	CGPE

OS, overall survival; PFS, progression-free survival; PD, progression disease; AE, adverse events; CGPE, china guidelines for pharmacoeconomic evaluations.

nature of the traditional chemotherapy drugs involved in this study, which were less likely to lead to plateaus or other complex scenarios in survival curves, and because the survival curves were relatively mature, the use of these standard parametric models was considered appropriate. The goodness of fit of the model was assessed using the

Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). Therefore, we ultimately fitted the OS curve of FOLFIRINOX with a Weibull distribution, and the remaining survival curves with a Gamma distribution, based on the lowest AIC and BIC values and consistency with visual inspection. This

approach ensured that the chosen distributions provided the optimal fit to the original curves (Supplementary Figure S2; Supplementary Table S3). Key parameters of the optimal distribution of survival curves were detailed in Table 2. Following the 2020 edition of CGPE, both cost and utility values were discounted at a rate of 5% in this model.

2.3 Cost and utility

Only direct medical costs were taken into account in this model. Biochemical examinations, blood routine tests, radiological examinations, as well as expenses related to the best supportive care and terminal care, were derived from a cost-effectiveness analysis for metastatic pancreatic cancer conducted by Na L et al. in China (Li et al., 2021). The drug price was sourced from the database of the Hunan Province Drug and Medical Consumables Procurement Management Subsystem (<https://healthcare.hnybj.com.cn/>), which could reflect the prices in public hospitals in China. Irinotecan, oxaliplatin, gemcitabine, and nab-paclitaxel were procured through centralized drug procurement, and their prices reflected the winning bid prices. Patients were assumed to receive subsequent treatment after disease progression. GEMNABP and FOLFOX (oxaliplatin, leucovorin, fluorouracil) were found to be the most commonly used regimens for second-line treatment (Hegewisch-Becker et al., 2019). Specifically, GEMNABP was assumed to be the second-line treatment for patients who had previously been treated with NALIRIFOX or FOLFIRINOX, while FOLFOX was employed for patients who had used GEMNABP as first-line treatment. Detailed dosing regimens were provided in Table 1. The cost related to adverse events (AEs) was gathered from a cost-effectiveness analysis for metastatic pancreatic cancer, which was based on a retrospective cohort study in China (Cui et al., 2021). The AE incidences for each treatment were derived from the NMA. Considering the relatively minimal costs and negative effects associated with grade 1–2 AEs, this model only incorporated severe AEs of grade 3 or greater. All AEs were assumed to occur in the initial cycle of the model. Costs were adjusted to the 2022 level using the Consumer Price Index and subsequently converted to U.S. dollars at an exchange rate of 1 USD to 6.7261 CNY. The utility values of PFS and PD, as well as the disutility values associated with AEs, were obtained from previously published literature, as indicated in Table 2.

2.4 Sensitivity analysis

One-way and probabilistic sensitivity analyses (PSA) were conducted to assess the robustness of the model. In the one-way sensitivity analysis, ranges of parameter values were based on published sources or set at $\pm 20\%$ of the base-case value. INMB served as a measure of economic efficiency. Second-order Monte Carlo simulation was used to perform PSA by assigning appropriate distributions to each parameter and sampling them simultaneously for 1,000 iterations. Gamma distribution was selected for costs and the body surface area, beta distribution was used for utility parameters and probabilities, as shown in Table 2.

2.5 Scenario analysis

2.5.1 Scenario 1

According to the opinions of clinical experts, a considerable number of patients with advanced pancreatic cancer receive only best supportive care due to poor physical condition after first-line treatment, consistent with the CSCO guidelines. Therefore, we conducted a scenario analysis, assuming that patients would not receive second-line treatment after disease progression.

2.5.2 Scenario 2

To reduce the toxicity of combination chemotherapy, modified versions of the FOLFIRINOX (mFOLFIRINOX) are frequently employed in clinical practice (Lambert et al., 2017). This modification involves reducing the dosage of irinotecan and omitting fluorouracil bolus. Similarly, the adjusted GEMNABP regimen is achieved by reducing the frequency of drug administration. To assess the impact of these commonly used modified or adjusted chemotherapy regimens on the model's robustness, scenario 2 analysis was conducted. According to the recommendations of the CSCO guidelines, adjusted dosing schemes were presented in Supplementary Table S4.

2.5.3 Scenario 3

To assess the potential cost-effectiveness of NALIRIFOX under current market conditions, we determined the price of liposomal irinotecan in scenario 3 by referencing the cost of the generic drug, which was \$22.82/mg. Additionally, the patient assistance program (PAP) was taken into consideration despite its limitations in suitability for all patients and challenges in ensuring consistent accessibility. Discontinuing the PAP would diminish the cost-effectiveness of the regimen. The PAP for generic liposomal irinotecan enables eligible patients to receive one free dose (43 mg) of medication after purchasing one dose at their own expense. Subsequently, upon purchasing 16 doses at their own expense, patients can continue to apply for free assistance until disease progression.

2.6 Price simulation of liposomal irinotecan

To investigate the impact of liposomal irinotecan pricing on the cost-effectiveness of NALIRIFOX, we conducted an analysis of the variations in ICER when comparing NALIRIFOX with FOLFIRINOX or GEMNABP as the price of liposomal irinotecan gradually decreased. This analysis was carried out in both the base-case scenario and scenario 3. Additionally, a series of cost-effectiveness acceptability curves (CEACs) were developed for each treatment at various prices of liposomal irinotecan in the simulation.

3 Results

3.1 Base-case and subgroup analysis

The cost-effectiveness analysis revealed that NALIRIFOX yielded the highest LYs and QALYs, as well as the highest cost.

TABLE 3 Results of base-case and scenario analyses.

Strategies and scenarios	Total cost (\$)	LYs	QALYs	ICER vs. GEMNABP (\$/QALY)	NMB(\$)	INMB vs. GEMNABP (\$)
Base-case analysis						
GEMNABP	9,217.58	1.01	0.58	-	13,037.05	-
FOLFIRINOX	11,811.68	1.08	0.60	193,629.96	10,955.04	-2,082.02
NALIRIFOX	50,905.5	1.09	0.70	346,330.80	-24,049.91	-37,086.96
Scenario analysis 1						
GEMNABP	6,607.07	1.01	0.58	-	15,647.57	-
FOLFIRINOX	10,964.73	1.08	0.60	325,266.60	11,801.99	-3,845.58
NALIRIFOX	50,097.77	1.09	0.70	365,821.65	-23,242.19	-38,889.76
Scenario analysis 2						
GEMNABP	9,071.66	1.01	0.58	-	13,182.98	-
FOLFIRINOX	11,215.12	1.08	0.60	159,993.13	11,551.60	-1,631.38
NALIRIFOX	50,815.75	1.09	0.70	346,797.52	-23,960.16	-37,143.14
Scenario analysis 3						
GEMNABP	9,217.58	1.01	0.58	-	13,037.05	-
FOLFIRINOX	11,811.68	1.08	0.60	193,629.96	10,955.04	-2,082.02
NALIRIFOX	21,774.45	1.09	0.70	104,318.74	5,081.13	-7,955.92

LYs, life-years; QALYs, quality-adjusted life-years; ICER, increment cost-effectiveness ratio; NMB, net monetary benefit; INMB, incremental net monetary benefit.

In contrast, GEMNABP was linked to the lowest LYs, QALYs, and cost. While FOLFIRINOX produced QALYs close to those of GEMNABP, its relatively higher cost resulted in an ICER of \$193,629.96/QALY, significantly higher than the WTP threshold of \$38,223.34/QALY. In addition, the INMB was \$-2,082.02, indicating that it was not cost-effective. Similarly, NALIRIFOX was also deemed not cost-effective due to its high cost compared to GEMNABP, as evidenced by an ICER much higher than the WTP threshold and an INMB of \$-37,086.96. Overall, GEMNABP was considered the optimal choice. Additionally, based on the NMB values, the cost-effectiveness priority order was as follows: GEMNABP > FOLFIRINOX > NALIRIFOX. Details were shown in [Table 3](#).

3.2 Sensitivity analysis

The tornado diagram of one-way sensitivity analysis indicated that the results were stable, showing that both FOLFIRINOX and NALIRIFOX lacked cost-effectiveness compared to GEMNABP when the parameters varied within the defined range, as shown in [Figure 2](#). When comparing FOLFIRINOX with GEMNABP, the model results were primarily impacted by PFS utility value, as well as the risk of AEs including fatigue and decreased platelet count. While in the analysis of the cost-effectiveness of NALIRIFOX versus GEMNABP, body surface area and the price of liposomal irinotecan were the parameters that had the greatest impact on the results. CEACs of the PSA were shown in [Figure 3](#). With the increase of the WTP

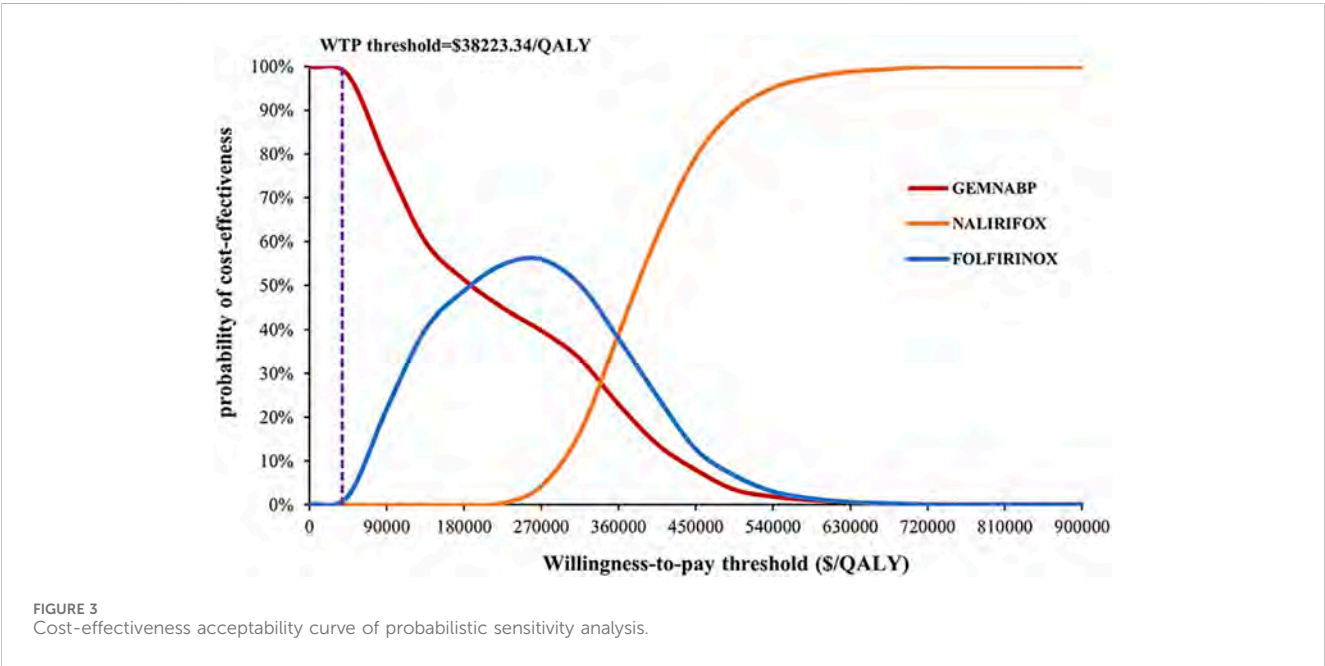
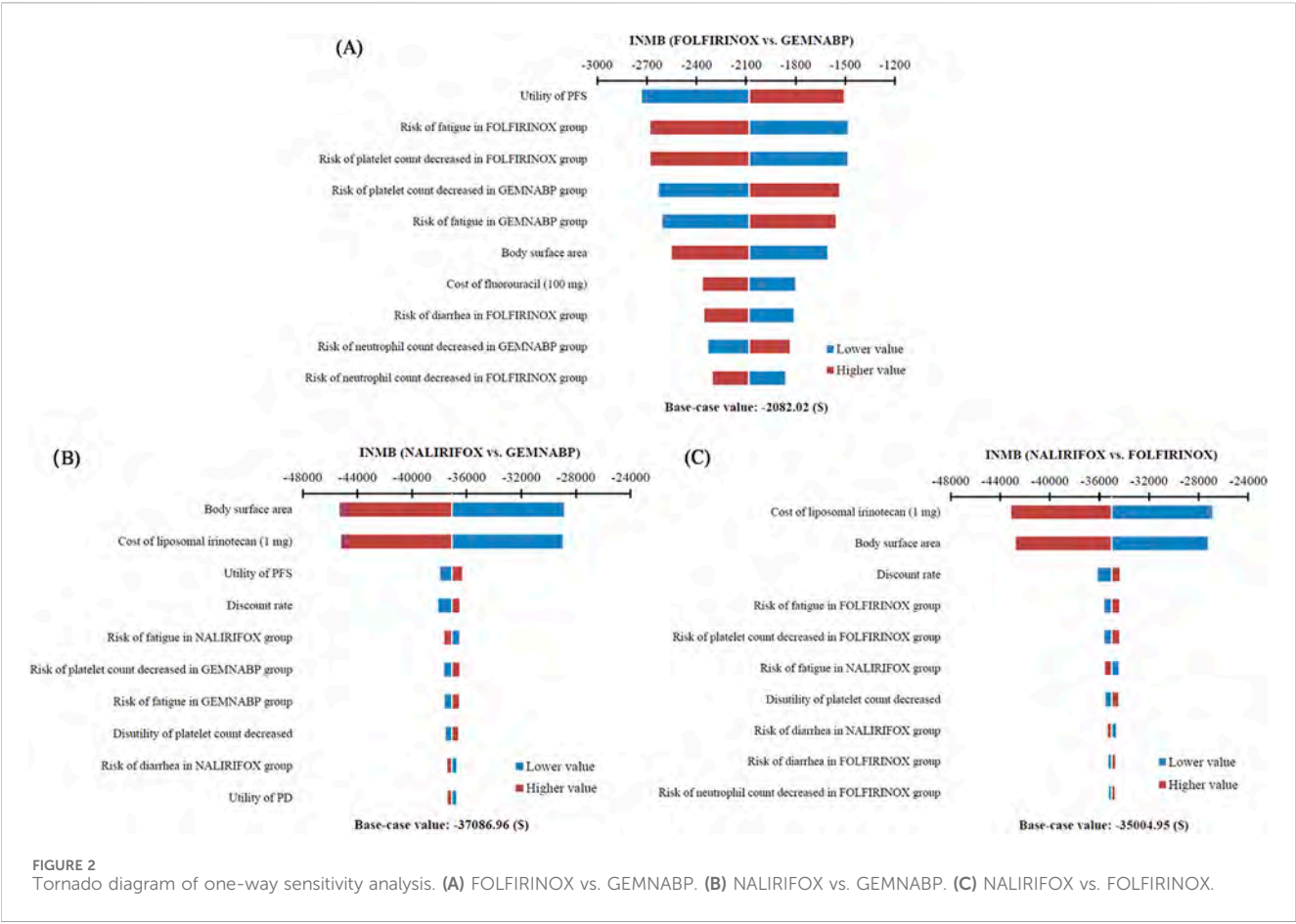
threshold, the probability that GEMNABP was more cost-effective gradually decreased. Incremental cost-effectiveness scatter plots could be found in [Supplementary Figure S3](#).

3.3 Scenario analysis

The results of the scenario analysis were presented in [Table 3](#), which align with the findings of the base-case analysis. In scenario 3, despite the lower price and more favorable PAP for generic liposomal irinotecan, NALIRIFOX was still not deemed cost-effective in comparison to GEMNABP or FOLFIRINOX.

3.4 Price simulation of liposomal irinotecan

[Figure 4](#) illustrated the outcomes of the price simulation. As the price of liposomal irinotecan decreased, the ICER value of NALIRIFOX compared to GEMNABP or FOLFIRINOX displayed a gradual decline. In the base-case analysis, when the price of liposomal irinotecan decreased by more than 86.5% (less than \$3.36/mg), NALIRIFOX became more cost-effective compared to FOLFIRINOX. Further, when the price reduction surpassed 91.6% (less than \$2.08/mg), NALIRIFOX was more cost-effective compared to GEMNABP. In scenario 3, taking into account the PAP, NALIRIFOX became cost-effective compared to FOLFIRINOX and GEMNABP when the price reduction of generic liposomal irinotecan exceeded 51.8% (less than \$11.00/



mg) and 70.2% (less than \$6.81/mg), respectively. The CEACs at four specific prices were presented in Figure 5. For more information on CEACs presented under a sequence of varying prices (reductions of 0%, 50%, 75%, 85%, 95%) in the base-case analysis, comparing NALIRIFOX with FOLFIRINOX or GEMNABP separately, see Supplementary Figure S4.

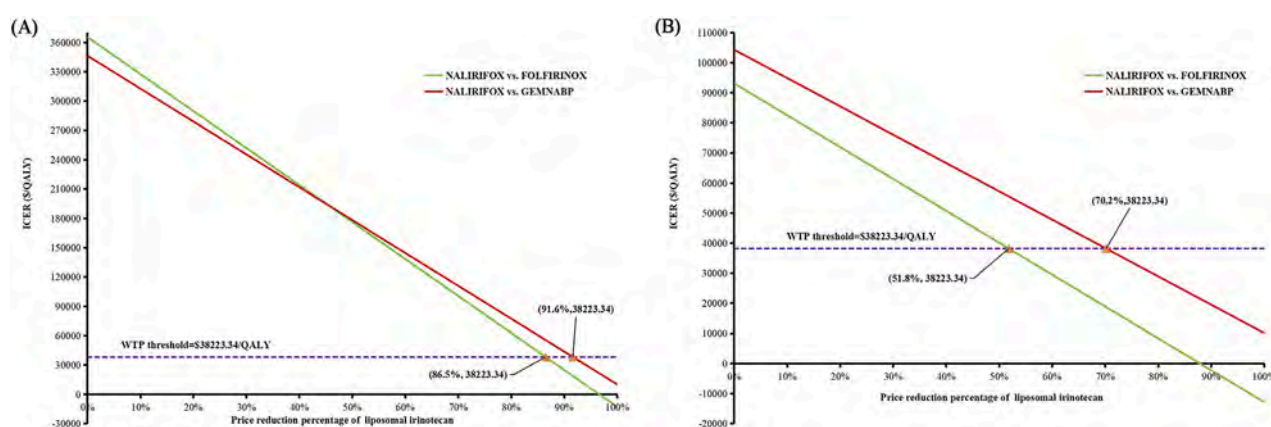


FIGURE 4
Results of price simulation of liposomal irinotecan. (A) Price simulation of liposomal irinotecan in base-case. (B) Price simulation of liposomal irinotecan in scenario 3.

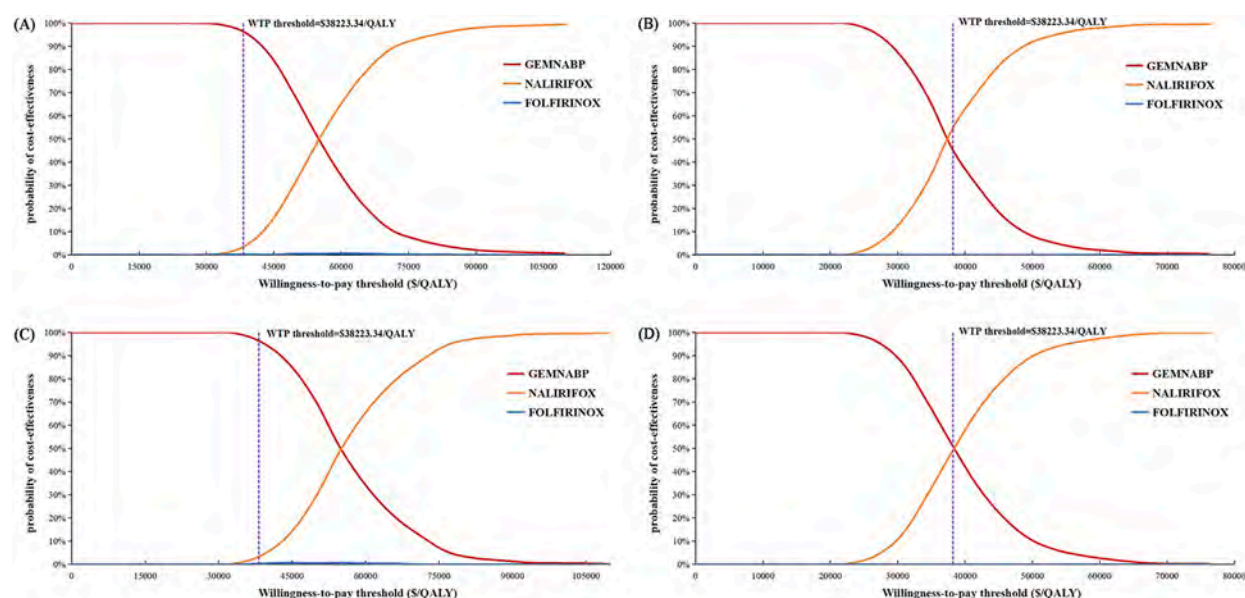


FIGURE 5
Cost-effectiveness acceptability curves in the price simulation of liposomal irinotecan. (A) Liposomal irinotecan is priced at \$3.36/mg in base-case. (B) Liposomal irinotecan is priced at \$2.08/mg in base-case. (C) Liposomal irinotecan is priced at \$11/mg in scenario 3. (D) Liposomal irinotecan is priced at \$6.81/mg in scenario 3.

4 Discussion

When directly comparative clinical trial data is unavailable, indirect comparison and NMA is a commonly used method in health technology assessment (Kim et al., 2019). Based on previously published NMA, this study performed a cost-effectiveness analysis of three first-line combination chemotherapy regimens for metastatic pancreatic cancer. GEMNABP was associated with the lowest LYs, QALYs, and cost, whereas NALIRIFOX yielded the highest LYs, QALYs, and cost. Both FOLFIRINOX and NALIRIFOX generated ICER that was higher than the WTP threshold when compared to GEMNABP. Therefore, GEMNABP was considered

the optimal choice, in line with the results of INMB. However, as NALIRIFOX and GEMNABP could gain more QALYs and LYs, comprehensive evaluation of the patient's circumstances should be conducted when determining whether to prioritize cost-effectiveness or clinical benefits. It also should be noted that tolerance to AEs is a crucial factor influencing chemotherapy outcomes. For instance, caution should be exercised when selecting the NALIRIFOX or FOLFIRINOX for patients who have high risks of diarrhea. And when considering the risk of hematologic toxicity, NALIRIFOX poses a relatively lower risk. Although our economic evaluation model incorporated the costs and disutility values of severe AEs, clinicians are strongly

encouraged to fully consider the risk of AEs when choosing treatment based on individual patient circumstances. Furthermore, upholding the patient's autonomy in medical ethics and providing comprehensive information about potential benefits, drawbacks, and associated costs of the treatment is essential. Several investigations have reported the cost-effectiveness analysis of FOLFIRINOX versus GEMNABP. Our findings were consistent with the findings of two studies carried out in China (Zhou et al., 2016; Cui et al., 2021). On the contrary, studies conducted in Canada and the United Kingdom indicated that GEMNABP yielded lower QALYs and higher costs, making it an inferior option compared to FOLFIRINOX (Coyle et al., 2017; Gharaibeh et al., 2018; Arciero et al., 2022). The centralized drug procurement policy implemented in China may account for this phenomenon, as it has led to a notable reduction in the prices of certain drugs and an enhancement in drug affordability. For instance, the previously expensive nab-paclitaxel in GEMNABP witnessed its price drop from \$401.05 in 2019 to \$22.24 in 2022 after two rounds of price reductions facilitated by this policy, representing a significant decrease of 94.45%. Undoubtedly, this would have a substantial impact on the cost-effectiveness of GEMNABP. So attention should be paid to the fact that drugs in developed countries are often more expensive, and the WTP threshold for pharmacoeconomic evaluation is also higher. For example, the price of liposomal irinotecan in the United States is \$62.93/mg, which is significantly higher than the price in China. The sensitivity and scenario analyses confirmed the robustness of these results.

The cost-effectiveness of NALIRIFOX was limited by its high cost. According to the tornado diagram, the body surface area and the price of liposomal irinotecan had the most substantial impact on the outcomes when comparing NALIRIFOX with GEMNABP or FOLFIRINOX, while the body surface area also affected the drug cost ultimately. Therefore, it is necessary to pay attention to the dosage and price of liposomal irinotecan in clinical application, which may have a significant impact on the cost-effectiveness of the treatment. When analyzing the cost-effectiveness of FOLFIRINOX vs. GEMNABP, the impact of AEs was more significant. The results of scenario 3 analysis indicated that, at present, the lower-priced generic drug still could not make NALIRIFOX cost-effective, even though it reduced the ICER value from \$346,330.80/QALY in the base-case analysis to \$104,318.74/QALY when compared to GEMNABP. Further price simulation of generic liposomal irinotecan showed that NALIRIFOX would be favored when the price was less than \$11.00/mg and \$6.81/mg in comparison to FOLFIRINOX and GEMNABP, respectively. However, when determining the appropriate price for the inclusion of liposomal irinotecan in the Basic Medical Insurance Drug List, it is essential to consider the impact of patients no longer being eligible for the PAP. Consequently, the drug cost should be further reduced to align with the result in the base-case analysis. NALIRIFOX would be cost-effective compared to FOLFIRINOX and GEMNABP if the price is less than \$3.36/mg and \$2.08/mg, respectively. Even though the required reduction is significant, the government will have a chance to achieve appropriate price through negotiation or centralized procurement when there are more manufacturers of generic drugs on the market for liposomal irinotecan. Just like the case with nab-paclitaxel. It is worth noting that although there is currently only one generic liposomal irinotecan available on the

market in China, three other manufacturers' generic drugs are already under review by the China Center for Drug Evaluation (NMPA). So revealing the potential prices of liposomal irinotecan that would make NALIRIFOX cost-effective in comparison to the other two first-line treatments for metastatic pancreatic cancer can offer valuable evidence for manufacturers and decision-makers, since the price fluctuation of liposomal irinotecan may come soon.

There are some limitations of this study. First, this cost-effectiveness analysis model was based on the NMA. The NMA incorporated phase 3 randomized controlled trials with globally comparable inclusion criteria, but heterogeneity in these trials might still affect the pooled results. For example, unlike the GEMNABP, clinical trials related to FOLFIRINOX typically had an age limit for patient enrollment, and the intervals allowed for prior adjuvant therapy to start before first-line treatment varied across studies. Therefore, it is necessary to validate and improve this model with well-designed head-to-head comparison clinical data. In addition, the clinical trials involved in the NMA primarily consist of multicenter trials conducted globally. This may not fully reflect the effectiveness and safety of these treatments in the Chinese population and potentially introduce bias to the model results. Second, utility values were collected from the literature, which may deviate from the actual data. Excluding grade 1–2 AEs when calculating the costs and utilities might result in an underestimation of real-world burden and disutility values. Nevertheless, sensitivity analyses indicated that changes in the related parameters did not alter the model results. Third, the structural uncertainty of the model, brought by the reconstruction and extrapolation of survival curves, should not be ignored. Utilizing parametric models to fit and extrapolate survival curves can introduce uncertainty in capturing complex survival hazards. Additionally, researchers may struggle to determine the best model using statistical indicators. Therefore, enhancing the model's accuracy by validating it with long-term real-world data in the future would be highly beneficial. Fourth, while this study aimed to fully encompass the clinical application characteristics of Chinese patients, such as setting the range of body surface area at $\pm 20\%$ of the base-case value and considering modified versions of the FOLFIRINOX and adjusted GEMNABP regimen in scenario analysis to account for drug tolerances, it is important to acknowledge that these assumptions about patients' demographics might not fully represent the diverse Chinese population and could introduce potential bias. Fifth, further research is required to confirm the validity of these findings in areas with existing income inequality, as the WTP threshold based on GDP *per capita* may not be applicable to certain regions. This study also overlooked potential variations between urban and rural areas within the Chinese healthcare system, which could affect cost-effectiveness.

In conclusion, the findings of this study suggested that GEMNABP was favored among these three first-line treatments thus far from an economic standpoint. Cost-effectiveness of NALIRIFOX would be obtained when the price of liposomal irinotecan was less than \$3.36/mg and \$2.08/mg compared to FOLFIRINOX and GEMNABP, respectively, without considering the PAP. These evidence are valuable for doctors in selecting appropriate treatment protocols and for decision-makers in determining the pricing for liposomal irinotecan. Further investigation is needed to gather additional evidence regarding the budget impact.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#), further inquiries can be directed to the corresponding authors.

Author contributions

ZX: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing—original draft. LM: Data curation, Formal Analysis, Investigation, Software, Writing—original draft, Writing—review and editing. ZL: Methodology, Software, Validation, Visualization, Writing—review and editing. YF: Project administration, Supervision, Writing—review and editing. YP: Conceptualization, Funding acquisition, Project administration, Resources, Writing—review and editing.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2024.1488645/full#supplementary-material>

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Appendix YAMADA01

Article

Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy

Yunami Yamada ¹, Hironori Fujii ^{1,*}, Daichi Watanabe ¹, Hiroko Kato-Hayashi ¹, Koichi Ohata ¹, Ryo Kobayashi ¹, Takuma Ishihara ², Shinya Uemura ³, Takuji Iwashita ³, Masahito Shimizu ³ and Akio Suzuki ¹

¹ Department of Pharmacy, Gifu University Hospital, Gifu 501-1194, Japan; y_yunami@gifu-u.ac.jp (Y.Y.); watayaku@gifu-u.ac.jp (D.W.); hhayashi@gifu-u.ac.jp (H.K.-H.); k_ohata@gifu-u.ac.jp (K.O.); ryo_k@gifu-u.ac.jp (R.K.); akio@gifu-u.ac.jp (A.S.)

² Gifu University Hospital, Innovative and Clinical Research Promotion Center, Gifu University, Gifu 501-1194, Japan; tishiha@gifu-u.ac.jp

³ First Department of Internal Medicine, Gifu University Hospital, Gifu 501-1194, Japan; ueshin550621@gmail.com (S.U.); takuji@w7.dion.ne.jp (Takuji Iwashita); shimim-gif@umin.ac.jp (M.S.)

* Correspondence: h_fujii@gifu-u.ac.jp; Tel.: +81-58-230-6000

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Abstract: While modified FOLFIRINOX therapy is effective for treating advanced pancreatic cancer, it frequently causes severe neutropenia. The present study investigated the effect of severe neutropenia on clinical outcomes in advanced pancreatic cancer patients who received modified FOLFIRINOX. The study subjects were 51 patients (30 males and 21 females) with advanced pancreatic cancer who received modified FOLFIRINOX (2h bolus injection of oxaliplatin at 85 mg/m², 2 h bolus injection of L-leucovorin at 200 mg/m², 90min bolus injection of irinotecan at 150 mg/m², followed by continuous infusion of 5-fluorouracil for 46 h at 2400 mg/m² without bolus 5-fluorouracil) during the period from January 2014 to May 2018. No patients had prior history of chemotherapy. Adverse events, including neutropenia, were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Median overall survival (OS) was the primary endpoint, while median time to treatment failure (TTF), overall response rate (ORR), and the incidence of other adverse events were secondary endpoints. Severe neutropenia (grade ≥ 3) occurred in 39 patients (76.4%), and Cox proportional hazard analysis identified high total bilirubin level as a significant risk factor. Median duration of OS was significantly longer in patients with severe neutropenia than in those without it (21.3 months versus 8.9 months, $p = 0.020$). Moreover, there was a significant correlation between OS and the grade of neutropenia ($r = 0.306$, $p = 0.029$). ORR tended to be higher, though not significantly, in patients with severe neutropenia. In contrast, the incidence rates of other adverse events were not different between the two groups. Severe neutropenia is an independent predictor of prognosis in advanced pancreatic cancer patients received modified FOLFIRINOX therapy.

Keywords: modified FOLFIRINOX; severe neutropenia; overall survival; overall response rate; time to treatment failure; advanced pancreatic cancer

1. Introduction

Pancreatic cancer has extremely poor prognosis and represents the fourth leading cause of cancer-related mortality in the world. Among the various malignancies ten-year (4.6% for males and 4.8% for females) and five-year (7.0% for males and 5.9% for females) survival rates in Japan are the

worst for pancreatic cancer [1,2]. There are few effective therapies for pancreatic cancer, indicating the urgent need for development of more effective chemotherapies to improve the poor outcomes of this malignancy.

FOLFIRINOX, a combination chemotherapy of oxaliplatin, irinotecan, 5-fluorouracil (5-FU), and L-leucovorin, has been shown to significantly prolong survival and is currently a standard chemotherapy for advanced pancreatic cancer. Conroy et al. showed that FOLFIRINOX therapy exhibited clinical superiority over gemcitabine monotherapy with respect to overall survival (OS), progression-free survival (PFS), and tumor response rate (RR) in patients with metastatic pancreatic cancer [3]. However, grade 3–4 neutropenia occurs more frequently in patients treated with FOLFIRINOX than gemcitabine (45.7% versus 21.0%, $p < 0.001$). A high incidence of grade 3–4 neutropenia (77.8%) has also been observed in Japanese patients receiving FOLFIRINOX for metastatic pancreatic cancer [4].

To reduce the incidence of toxicities associated with FOLFIRINOX, the chemotherapy regimen has been modified by omission the bolus injection of 5-FU and/or reducing the dose of irinotecan without reducing the clinical response [5–9]. Modification of the FOLFIRINOX regimen (oxaliplatin 85 mg/m², irinotecan 150 mg/m², 5-FU infusion 2400 mg/m² over 46 h, no bolus 5-FU) reduces the incidence of grade 3–4 neutropenia to 47.8% [7]. More importantly, a meta-analysis showed that the modified FOLFIRINOX regimen is as effective as the original, with a similar tumor response rate (32% versus 33%, $p = 0.879$), rate of 12-month survival (47% versus 50%, $p = 0.38$), rate of 6-month PFS rate (47% versus 53%, $p = 0.38$) and reduced frequency of grade 3–4 adverse events [10].

The occurrence of severe adverse events, including neutropenia [11,12], mucositis [13], neurotoxicity [14] and diarrhea [15], during cancer chemotherapy results in impaired patient quality of life and leads to the therapy interruption or dose reduction. The latter may lead to a reduction in the therapeutic effect due to the decrease in the relative dose intensity (RDI). For example, the incidence of grade 4 neutropenia is significantly higher, while median PFS and OS are significantly shorter in non-small cell lung cancer patients receiving irinotecan with *UGT1A1**6 homozygous mutation compared to the heterozygous mutation or wild-type allele [16]. The incidence rates of diarrhea and neutropenia are significantly higher, while median OS tends to be shorter in metastatic colorectal cancer patients receiving irinotecan with *UGT1A1**28 heterozygous or homozygous mutations compared to the wild-type allele [17].

In contrary, several investigators have shown that the occurrence myelosuppression such as neutropenia is a surrogate for better survival in patients receiving cancer chemotherapy. In patients with metastatic colorectal cancer who receive FOLFOX therapy, the incidences of mild (grade 1–2) and severe (grade 3–4) neutropenia are associated with improved survival [18]. In patients with advanced pancreatic cancer who received gemcitabine alone or in combination with other anticancer drugs, the median OS is significantly longer in patients with early onset of neutropenia than in those without neutropenia [19]. Comparison of the effect of gemcitabine monotherapy on survival among metastatic pancreatic patients with grade 3 neutropenia, those with grade 1–2 neutropenia and those without neutropenia also shows that the median survival time is prolonged with increasing grade of neutropenia [20]. Therefore, the incidence neutropenia may have different effects on the survival period, depending on the cancer type and chemotherapy regimen.

We investigated the relationship between the incidence of severe neutropenia and OS in patients with advanced pancreatic cancer who received modified FOLFIRINOX as first-line chemotherapy to determine whether or not the incidence of severe neutropenia causes favorable survival outcomes in these patients

2. Results

2.1. Patient Demographics

Among the 51 studied patients, 30 (58.8%) were male and 21 (41.2%) were female, and the median age was 64 years (Table 1). The prevalence of heterozygous for *UGT1A1* was 37.3% (Table 1), in which *UGT1A1**6/*1 appeared in 19.6% and *UGT1A1**28/*1 in 17.6%. At the start of chemotherapy, there was no significant difference in body surface area; body mass index; hemoglobin; the numbers of white blood cells, neutrophil, and platelet; or the number of patients with biliary stent or drainage between the two groups.

Table 1. Patient demographics.

Number of patients (male/female)	51	(30/21)
Age, median (mini–max)	64	(49–74)
Heterozygous for <i>UGT1A1</i> *6 or *28 (with/without)	37.3	(19/32)
Height (cm)	162	(156.0–166.5)
Body weight (kg)	57	(49.0–61.5)
Body surface area (m ²)	1.58	(1.51–1.69)
Body mass index	21.3	(19.1–23.7)
Aspartate aminotransferase (IU/L)	20	(16–31)
Alanine aminotransferase (IU/L)	19	(13–34)
Serum creatinine (mg/dL)	0.69	(0.53–0.82)
Total bilirubin (mg/dL)	0.7	(0.5–0.8)
Neutrophil (/μL)	3560	(2955–4455)
White blood cells (/μL)	5460	(4835–6345)
Hemoglobin (g/dL)	12.2	(11.5–13.1)
Platelet (10 ⁴ /μL)	19.7	(16.1–24.6)
HbA1c (%)	6.2	(5.7–6.8)
C-reactive protein (CRP, mg/dL)	0.29	(0.05–1.42)
Carbohydrate antigen 19-9(CA19-9, U/mL)	578.9	(141.5–3983.7)
Biliary stent or drainage (%) (with/without)	29.4	(15/36)
Distant metastasis (%) (presence/absence)	54.9	(28/23)
Neutrophil-lymphocyte ratio (NLR)	2.89	(2.22–3.85)
Modified Glasgow prognostic score (mGPS, 0/1/2)	(33/10/7)	
Initial dose of chemotherapy drug		
Irinotecan (mg/m ²)	150	
Oxaliplatin (mg/m ²)	85	
5-Fluorouracil (mg/m ²)	2400	

All data indicate median, 25–75th percentiles unless otherwise indicated.

The overall incidence rate of severe neutropenia (grade ≥ 3) was 76.5% (39/51). Among the 39 patients, severe neutropenia predominantly occurred during the first cycle (82%, 32 patients), but also occurred during the second cycle (10%, four patients) and during the third cycle (8%, three patients). Demographics were compared between patients with and without severe neutropenia. Granulocyte-colony stimulating factor (G-CSF) was not used for primary prevention of neutropenia in any patients. However, 34 of the 39 patients who developed severe neutropenia were administered G-CSF for recovery from neutropenia. The RDI of irinotecan, oxaliplatin, and 5-FU was 0.73, 0.49, and 0.65 in patients with severe neutropenia, and 0.84, 0.74, and 0.83 in patients without severe neutropenia, respectively. Therefore, the RDI was significantly lower in patients with severe neutropenia than in those without severe neutropenia for irinotecan ($p = 0.034$), oxaliplatin ($p < 0.001$) and 5-FU ($p < 0.001$).

0.65 in patients with severe neutropenia, and 0.84, 0.74, and 0.83 in patients without severe neutropenia, respectively. Therefore, the RDI was significantly lower in patients with severe neutropenia than in those without severe neutropenia for irinotecan ($p = 0.034$), oxaliplatin ($p < 0.001$) and 5-FU ($p < 0.001$).

2.2. Comparison of the Efficacy of Modified FOLFIRINOX between Patients with and without Severe Neutropenia

Following treatment with modified FOLFIRINOX therapy, median OS was significantly longer in patients with severe neutropenia than in those without it (21.3 months [95% CI: 15.2–NA] versus 8.9 months [95% CI: 6.6–NA]; $p = 0.020$, NA indicates calculation impossible (Figure 1).

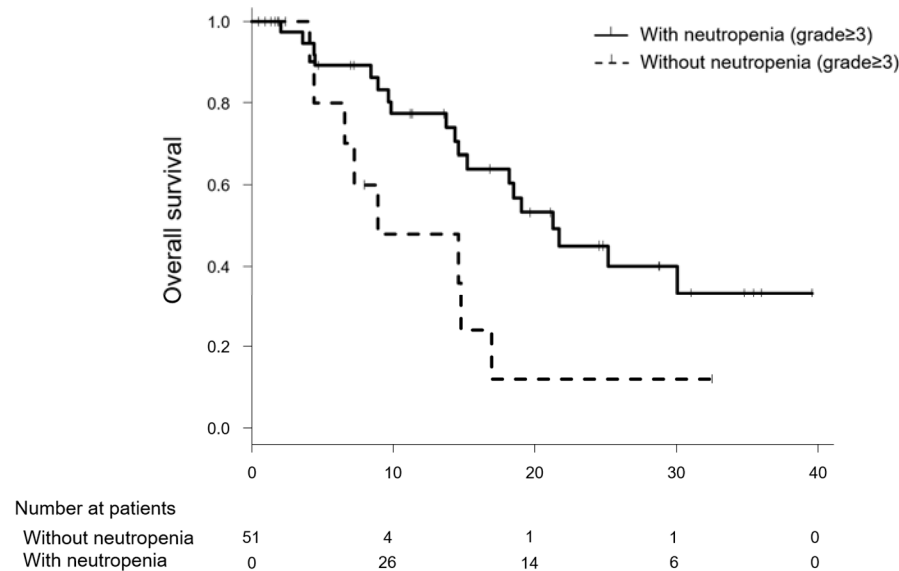


Figure 1. The Simon and Makuch’s modified Kaplan-Meier curves for comparison of overall survival in pancreatic cancer patients who received modified FOLFIRINOX therapy; one curve (solid line) represents patients with neutropenia on any study day, and the other curve (dashed line) represents those without grade ≥ 3 neutropenia on each day.

With time varying Cox proportional hazards regression (Table 2), the relationship between neutropenia and OS was significant (hazard ratio [HR]: 0.40; [95% CI: 0.17–0.95], $p = 0.039$) after adjusting for age and neutrophil-lymphocyte ratio (NLR). The regression model was internally validated and estimated optimism was 0.19, indicating that there was no evidence of overfitting.

Table 2. Cox proportional hazard analysis of time varying neutropenia associated with overall survival in advanced pancreatic cancer patients receiving modified FOLFIRINOX therapy.

Factors	Hazard Ratio (95% CI)	p-value
Neutropenia	0.40 (0.17–0.95)	0.039
Age (IQR: 59–68)	0.90 (0.48–1.69)	0.738
NLR (IQR: 2.3–3.8)	1.25 (1.02–1.52)	0.029

Cox proportional hazards regression with neutropenia as a time varying exposure, with adjustment for age and NLR. Abbreviations: IQR, inter quartile range; CI, confidence interval; NLR, neutrophil-lymphocyte ratio.

The median time to treatment failure (TTF) also tended to be longer in patients with severe neutropenia than in those without it (7.9 months [95% CI: 1.9–24.5] versus 3.7 months [95% CI: 2.0–12.1]; HR: 0.49 [0.22–1.09], $p = 0.079$; Table 3). Interestingly, there was a significant correlation between the grade of neutropenia and OS ($p = 0.029$; Figure 2A), and TTF tended to be correlated with the grade of neutropenia ($p = 0.066$; Figure 2B).

Table 3. Comparison of the median time to treatment failure and tumor response rate between patients with and without neutropenia and those without treatment response and those with treatment response after treatment with modified FOLFIRINOX for advanced pancreatic cancer.

Effect	Without Neutropenia (n = 12)	With Neutropenia (n = 39)	p-value
Median time to treatment failure (months, 95% CI)	3.7 (2.0–12.1)	7.0 (1.9–24.5)	0.079
Tumor response rate (%)	16.7 (2/12)	35.9 (14/39)	0.296
Response rate (CR+PR) (%)	66.7 (8/12)	76.9 (30/39)	0.474
Disease control rate (CR+PR+SD)	66.7 (8/12)	76.9 (30/39)	0.474
One-year survival (%)	41.7 (5/12)	71.8 (28/39)	0.085

Data were statistically analyzed by Fisher's exact probability test. CI: confidence interval; CR: complete response; PR: partial response; SD: stable disease

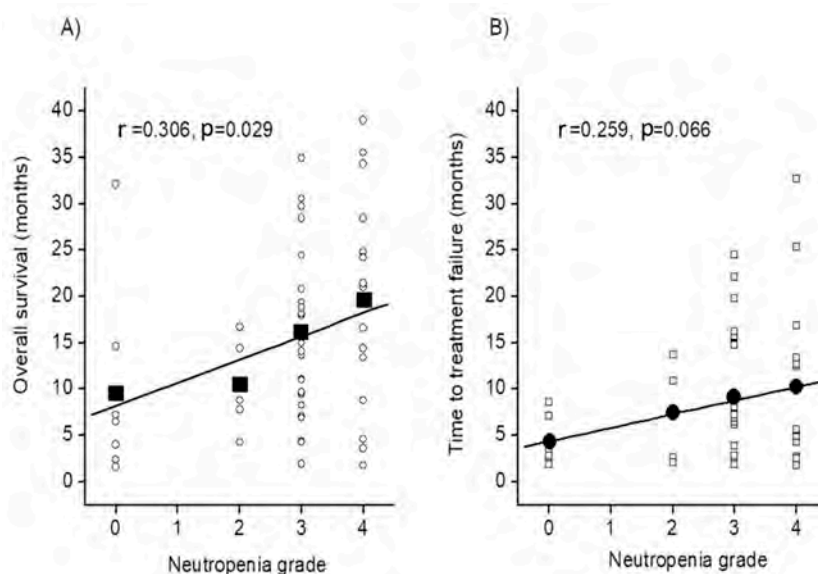


Figure 2. Relationship between the grade of neutropenia and overall survival (A) or time to treatment failure (B) in patients with advanced pancreatic cancer who received modified FOLFIRINOX therapy.

One-year survival was also slightly and not significantly higher in patients with neutropenia than in those without it (71.8% versus 41.7%; OR 3.56 (95% CI: 0.93–13.65), $p = 0.085$). There were no significant differences in the tumor response rates between the two groups (35.9% versus 16.7%; $p = 0.296$ for ORR; 76.9% versus 66.7%; $p = 0.474$ for disease control rate (DCR)) (Table 3).

2.3. Relationship between Other Factor and Prolonging Survival

To assess the relationship between candidate of prognostic factors and OS, multivariable Cox proportional hazard regression analyses were performed. With or without distant metastasis, CRP, CA19-9, NLR and modified glasgow prognostic score (mGPS) were treated as candidate of prognostic factors, and CRP, CA19-9, NLR and mGPS were treated as continuous variables. Multivariable analysis indicated that NLR was significantly associated with prolonged OS in patients with advanced pancreatic cancer who received modified FOLFIRINOX therapy (Table 4).

Table 4. Cox proportional hazard analysis of the risk factors associated with overall survival among various adverse events observed in advanced pancreatic cancer patients receiving modified FOLFIRINOX therapy.

Factors	Univariable Analysis			Multivariable Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
With distant metastasis	2.07	(0.83–5.16)	0.119	2.11	(0.84–5.30)	0.113
CRP	1.01	(0.84–1.22)	0.908	0.99	(0.82–1.21)	0.953
CA19-9	1.00	(0.99–1.00)	0.122	1.00	(0.99–1.00)	0.181
NLR	1.18	(1.02–1.36)	0.030	1.15	(1.00–1.34)	0.048
mGPS	0.90	(0.55–1.47)	0.676	0.92	(0.56–1.53)	0.755

Hazard ratio (HR) and 95% confidence intervals (CI) were indicated. All multivariable analyses were performed adjusting for age and sex.

2.4. Risk Factors for Severe Neutropenia

To assess the relationship between time to neutropenia (grade ≥ 3) and factors which patient had at baseline, multivariable Cox proportional hazard regression analyses were performed. Neutrophil and total bilirubin were treated as continuous variables. Among these factors, Cox proportional hazard analysis showed that total bilirubin (hazard ratio [HR]: 2.65, 95% CI: 1.13–6.19, $p = 0.024$) was a significant risk factor for severe neutropenia (Table 5).

Table 5. Cox proportional hazard analysis of the risk of grade ≥ 3 neutropenia in pancreatic cancer patients receiving modified FOLFIRINOX therapy.

Factors	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Heterozygous for UGT1A1*6 or *28	1.41 (0.74–2.70)	0.300	1.35 (0.69–2.65)	0.373
Neutrophil	1.00 (0.99–1.00)	0.062	1.00 (0.99–1.00)	0.074
Total bilirubin	2.79 (1.30–6.10)	0.010	2.65 (1.13–6.19)	0.024

Hazard ratio (HR) and 95% confidence intervals (CI) are indicated. All multivariable analyses were performed adjusting for age and sex.

2.5. Comparison of the Incidence of Other Adverse Events between Patients with and without Severe Neutropenia

No significant differences in the incidence rates of such adverse events as nausea (grade ≥ 2), vomiting (grade ≥ 1), oral mucositis (grade ≥ 2), dysgeusia (grade ≥ 2), peripheral neuropathy (grade ≥ 2), diarrhea (grade ≥ 2), and thrombocytopenia (grade ≥ 2) were observed between patients with and without severe neutropenia (Table 6).

Table 6. Comparison of the incidence of other adverse events (grade ≥ 2) between patients with and without grade ≥ 3 neutropenia.

Adverse Effect	Without Neutropenia (n = 12)		With Neutropenia (n = 39)		p-value
	%	(presence/absence)	%	(presence/absence)	
Nausea	58.3	(7/5)	53.8	(21/18)	1.000
Vomiting	8.3	(1/11)	10.3	(4/35)	1.000
Oral mucositis	16.7	(2/10)	20.5	(8/31)	1.000
Dysgeusia	8.3	(1/11)	25.6	(10/29)	0.422
Peripheral neuropathy	41.7	(5/7)	28.2	(11/28)	0.481
Diarrhea	33.3	(4/8)	25.6	(10/29)	0.715
Leukopenia	33.3	(4/8)	100	(39/0)	<0.001
Thrombocytopenia	16.7	(2/10)	25.6	(10 / 29)	0.706

Data were statistically analyzed by Fisher's exact probability test.

3. Discussion

FOLFIRINOX or modified FOLFIRINOX is the first-line chemotherapy for advanced pancreatic cancer, however, these regimens cause a number of severe adverse events, including neutropenia. The present study showed that a large portion of patients (76.5%, 39/51 patients) experienced grade 3–4 neutropenia during the course of modified FOLFIRINOX therapy. The occurrence of severe adverse events may cause therapy interruption or a reduction in the dose of chemotherapy drugs, thereby affecting the clinical outcomes. In the present study, the incidence of severe neutropenia led to dose reduction. In particular, the RDIs for irinotecan, oxaliplatin and 5-FU were all significantly lower in patients with severe neutropenia than in those with grades 0–2 neutropenia.

Nevertheless, it was noteworthy that the patients with grade 3–4 neutropenia showed significantly longer survival than those without severe neutropenia in the Simon and Makuch's modified Kaplan-Meier curves, and the relationship between neutropenia and OS was significant after adjusting for age and NLR with time varying Cox proportional hazards regression.

Additionally, severe neutropenia was a significant factor for better survival, and the OS well correlated with the grade of neutropenia. Moreover, there was also a trend towards a correlation between the grade of neutropenia and TTF. Other clinical responses, including OS rate at one-year, ORR, and DCR, also tended to be better in patients with severe neutropenia than in those without it. Therefore, severe neutropenia may be a surrogate marker for better survival outcome due to modified FOLFIRINOX therapy in patients with advanced pancreatic cancer. Our data were generally consistent with a previous report that showed that patients with severe neutropenia after treatment with gemcitabine-containing chemotherapy for advanced pancreatic cancer had significantly longer OS than those without it [19]. The survival effect of gemcitabine monotherapy for metastatic pancreatic cancer is better for patients with grade 3 neutropenia than those with lower grades of neutropenia [20].

A question that the present findings raises is: why does the incidence of severe neutropenia yielded better survival in advanced pancreatic cancer patients receiving modified FOLFIRINOX therapy? One mechanism underlying this finding might be suppression of neutrophils themselves because these cells play a critical role in growth of tumors by promoting the acceleration of angiogenesis and suppressing the antitumor immune response [21,22]. An increase in neutrophils, which reflects systemic inflammation, might promote tumor progression by providing an advantageous environment for invasion and promotion of pancreatic cancer cells. Several studies have revealed that low neutrophil-to-lymphocyte ratio is a good predictor of prognosis in patients with pancreatic cancer [23,24]. Whether modified FOLFIRINOX therapy can also decrease the infiltration of neutrophils in pancreatic tumor tissue in patients with neutropenia should be examined in future studies.

We also presume that myelosuppression occurring in severe neutropenic patients contributes to improve the prognosis of the patients. Myeloid-derived suppressor cells (MDSCs), which reveal immunosuppressive in tumor microenvironment via inhibition of CD4⁺ T cell proliferation [25], accumulate in tumor cells and peripheral blood as the disease is progressed or in advanced stages of pancreatic cancer [26–30]. Reducing the number of MDSCs is a key antitumor mechanisms of some chemotherapy agents, including 5-FU [31], which prevents the accumulation of MDSCs in patients with pancreatic cancer [32]. Taken together, these evidence suggest that the suppressive effect of 5-FU included in FOLFIRINOX regimen on MDSCs in tumor microenvironment is more potent in patients with severe neutropenia than in those without it, where it may act to recover the cytotoxic action of T lymphocytes and prolong survival. Unfortunately, the precise mechanism underlying the 5-FU-induced reduction in the number of MDSC is unknown. Vincent et al. [31] showed that 5-FU induces apoptotic death of MDSCs by activating caspase-3 and caspase-7, and this effect of 5-FU is more potent than that of gemcitabine. They also showed that the suppressive action of 5-FU is more potent as the expression of thymidylate synthase decreases. Therefore, 5-FU in FOLFIRINOX may contribute, at least in part, to reducing the number of MDSCs induced by FOLFIRINOX. Moreover, the reduction in MDSCs may be more potent in patients with severe neutropenia than in those without severe neutropenia due to the more severely depressed thymidylate synthase activity in patients with severe neutropenia.

We found that total bilirubin level was a significant risk factor for severe neutropenia. This suggests that the biological activity of cytotoxic drugs, including irinotecan, is increased in patients with severe neutropenia because elevated bilirubin has critical effects on metabolism of such drugs [33]. Moreover, patients with severe neutropenia may have a genetic predisposition for drug metabolism that is similar to clinical course features [34]. Although the RDIs for irinotecan, oxaliplatin and 5-FU were lower in patients with severe neutropenia, these doses may still exert antitumor effects. Further biological activity and/or blood concentration of cytotoxic agents may be relatively higher in severe neutropenic patients; however, future studies are needed to evaluate these hypotheses.

4. Materials and Methods

4.1. Patients

A total of 69 patients with advanced pancreatic cancer received first-line modified FOLFIRINOX in our outpatient chemotherapy clinic during the period between January 2014 and May 2018. Among them, 18 patients were excluded from the present study because they were treated with reduced initial doses of irinotecan due to harboring a homozygous mutation in *UGT1A1* genes such as *UGT1A1**28/*28, *UGT1A1**6/*6 and *UGT1A1**28/*6 ($n = 2$), poor performance status (≥ 2 according to the Eastern Cooperative Oncology Group) ($n = 9$), or limited duration of therapy less than three cycles ($n = 7$). Data from the remaining 51 patients were analyzed in the present study. Data were obtained from electronic medical record in our hospital and analyzed retrospectively.

The present study was conducted in accordance with the guideline for human studies adopted by the ethics committee of the Gifu University Graduate School of Medicine and notified by the Japanese government (Institutional review board approval No.26-156). In view of the retrospective nature of the study, the need for informed consent from subjects was not mandated.

4.2. Chemotherapy

Patients were treated with modified FOLFIRINOX every 2 weeks, consisting of 2 h bolus injection of oxaliplatin at 85 mg/m², 2 h bolus injection of L-leucovorin at 200 mg/m², 90 min bolus injection of irinotecan at 150 mg/m², followed by continuous infusion of 5-FU for 46 h at 2400 mg/m² without bolus 5-FU. Patients were all administered an initial regular dose of chemotherapy in the first cycle. Dose reduction was performed in the subsequent chemotherapy cycle for patients who suffered from severe adverse events, particularly grade 3–4 neutropenia. In these patients, dose escalation was not performed even if the adverse events disappeared. The criteria for dose reduction was chosen according a Japanese phase II study on modified FOLFIRINOX [6]. Briefly, treatment was delayed when one or more of the following adverse events occurred: grade 3–4 neutropenia or thrombocytopenia, febrile neutropenia, total bilirubin >3.0 mg/dL, aspartate transaminase and alanine transaminase >150 U/L, creatinine >1.5 mg/dL, grade 3–4 peripheral neuropathy, and grade 3–4 diarrhea. Treatment was restarted after recovery from the severe adverse events, but the doses of oxaliplatin, irinotecan, and 5-FU were reduced to 65 mg/m², 120 mg/m², and 1200 mg/m², respectively.

4.3. Assessment of Adverse Events

Adverse events included hematological toxicities such as neutropenia, leukopenia, and thrombocytopenia; and non-hematological toxicities, including nausea, vomiting, oral mucositis, dysgeusia, peripheral neuropathy and diarrhea. The symptoms of adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. [35]. The incidence rates of other adverse events than neutropenia associated with modified FOLFIRINOX therapy were compared between patients with and without severe neutropenia.

4.4. Risk Analysis for Grade ≥ 3 Neutropenia

Heterozygous mutation in *UGT1A1* genes such as *UGT1A1**6/*1 or *UGT1A1**28/*1, low neutrophil count and high total bilirubin concentration have been reported as risk factors for severe neutropenia in advanced colorectal cancer patients who received irinotecan-based regimen [36]. Therefore, these risk factors for severe neutropenia were examined using multivariable Cox proportional hazard analysis with adjustment for age and sex. Neutrophil and total bilirubin were treated as continuous variables.

4.5. Efficacy of Chemotherapy

OS was used as the primary indicator of the efficacy of modified FOLFIRINOX therapy. The tumor response rates and the time to treatment failure (TTF) were used as secondary indicators of the efficacy of modified FOLFIRINOX therapy. OS was defined as the time from the start of therapy to the death. The tumor response was evaluated using patients' computed tomography scan as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors guideline version 1.1. [37]. The overall response rate (ORR) was defined as CR plus PR, while the disease control rate (DCR) as CR+ PR+SD. TTF was defined as the time from the start of therapy to the end of the therapy.

4.6. Risk Analysis for Prolonging Survival

The distant metastasis [38], CRP [38–40], CA19-9 [39,41,42], NLR [40,43–48] and mGPS [43,49] have been reported as prognostic factors in pancreatic cancer patients. To clarify the confounding of these factors with neutropenia on prolongation of survival, multivariable Cox proportional hazard analysis with adjustment for age and sex was performed. CRP, CA19-9, NLR and mGPS were treated as continuous variables.

4.7. Statistical Analyses

Data were analyzed by using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan) and R software version 3.5.1 (www.r-project.org). *p*-values less than 0.05 were considered significant. The characteristics of patients were summarized by median with 25th and 75th percentiles for continuous variables. Frequencies and percentages were shown for categorical variables. The Simon and Makuch's modified Kaplan-Meier survival curves [50] was used to account for time varying exposure. For primary analysis, Cox proportional hazards regression was used to evaluate the association between severe neutropenia as a time varying exposure and OS as an outcome with adjustment for covariates. Covariates were restricted to two variables to avoid overfitting, and included age and NLR on the basis of clinical judgement and previous research, owing to their expected strongly associations with the outcome and severe neutropenia. Secondary multivariable cox regression analyses were performed to assess the association between neutropenia and potential factor with adjustment for age and sex. The reliability of the regression model was internally validated via bootstrap method by measuring of overfitting quantified by optimism parameter in a calibration plot. Bootstrap validation was performed with one hundred fifty resampling. The square of the coefficient of correlation (*r*) was calculated as a measure of the linearity of the relationship between the two variables.

5. Conclusions

Our study presented the first evidence that severe neutropenia is significantly associated with better survival in patients with advanced pancreatic cancer receiving modified FOLFIRINOX therapy. Incidence of severe neutropenia may be a useful index for the survival outcome of pancreatic cancer patients receiving modified FOLFIRINOX therapy.

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original draft, Y.Y., H.F. and T.I. (Takuma Ishihara); Writing – review & editing, Y.Y., H.F., D.W., H.K.-H., K.O., R.K., T.I. (Takuma Ishihara), S.U., T.I. (Takuji Iwashita), M.S. and A.S.

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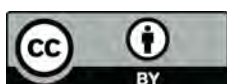
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Appendix YCHOU01

An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors

M. Ychou^{1*}, T. Conroy², J. F. Seitz³, S. Gourgou¹, A. Hua⁴, D. Mery-Mignard⁴ & A. Kramar¹

¹Centre Val d'Aurelle, Montpellier; ²Centre Alexis Vautrin, Nancy; ³Institut Paoli-Calmettes, Marseille; ⁴Aventis, Paris, France

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Background: The aim of this study was to determine the maximum-tolerated dose (MTD) and the recommended dose of irinotecan and oxaliplatin with a fixed 5-fluorouracil (5-FU)/leucovorin (LV) regimen in patients with metastatic solid tumors.

Patients and methods: The trial was designed to evaluate escalating doses of oxaliplatin and irinotecan, starting at 60 mg/m² and 90 mg/m², respectively, given at day 1 with the full-dose LV5FU2 regimen, given on days 1 and 2 as follows: folinic acid 200 mg/m² followed by 5-FU 400 mg/m² bolus and 600 mg/m² 22 h continuous infusion, every 2 weeks. The second cohort of patients was treated at the recommended dose for oxaliplatin and irinotecan with the simplified LV5FU regimen: on day 1, a 2-h infusion of folinic acid (400 mg/m²), followed by a 10-min intravenous bolus of 5-FU (400 mg/m²), followed by a continuous infusion of 5-FU (2400 mg/m²) over 46 h.

Results: Thirty-four patients were treated at the following dose levels (oxaliplatin/irinotecan mg/m²): 60/90, 60/120, 85/120, 85/150, 85/180, 85/200 and 85/220 and seven patients were treated at the recommended dose with the simplified LV5FU scheme. The MTD was reached at dose level 85/220 mg/m² but the recommended dose chosen for the second step was 85/180 mg/m² to keep a better compliance with the biweekly schedule. Main grade 3/4 toxicities per patient included the following: neutropenia in 78% (febrile episodes in 12%), diarrhea in 27%, nausea/vomiting in 24% and peripheral neuropathy in 37% (Lévi's scale). Antitumor activity was observed at almost all dose levels. Most objective responses were observed in digestive malignancies, since 10 out of 11 were obtained in five colorectal cancers, two pancreatic cancers, two cholangiocarcinoma and one gastric cancer.

Conclusion: The recommended dose for the triple association is 85/180 mg/m² of oxaliplatin and irinotecan, respectively, with LV5FU2 or simplified LV5FU. The antitumor activity in gastrointestinal malignancies should be evaluated in phase II studies in different tumor types.

Key words: colorectal cancer, irinotecan, oxaliplatin, phase I trial, triple combination

Introduction

For several decades, the standard treatment for metastatic colorectal cancer (MCRC) has been 5-fluorouracil (5-FU)-based chemotherapy. Optimization of 5-FU-based therapies with different schedules and biomodulation, especially with folinic acid [leucovorin (LV)], has led to improvement in terms of both efficacy and toxicity profile [1]. Among these chemotherapy schemes, the 'LV5FU2' regimen, consisting of high-dose LV administered bimonthly in combination with high-dose 5-FU given as a single bolus together with a continuous infusion, was associated with an improved response rate and progression-free

survival compared with a low-dose LV/5-FU monthly regimen [2, 3].

In recent years, antitumor activity of two novel antineoplastic agents, irinotecan and oxaliplatin, has been shown in several solid tumors and especially in gastrointestinal cell lines, including colorectal cancer. Now, the emergence of these two new drugs allows the consideration of new therapeutic options in the clinical treatment of MCRC.

Irinotecan (Campto[®]) is a semi-synthetic derivative of camptothecin, with evidence of a cytotoxic action via a potent and specific inhibition of the eukaryotic enzyme DNA topoisomerase I [4]. The cytotoxic effect of this agent and of its main active metabolite, SN-38, is specific to the S-phase of the cell cycle. Clinical efficacy of irinotecan monotherapy has been proven in published phase II and III trials, both in chemotherapy-naïve patients and in patients in whom prior 5-FU-based chemotherapy

*Correspondence to: Dr M. Ychou, Centre Val d'Aurelle, 208 Rue des Apothicaires, 34 298 Montpellier Cedex 05, France.
Tel: +33-04-67-61-30-66; Fax: +33-04-67-61-30-22;
E-mail: MYCHOU@valdorel.fncclcc.fr

failed [5–11]. The different mechanisms of action of both irinotecan and 5-FU and their non-overlapping toxicities, except for neutropenia, led to the evaluation of the combination of these two drugs in MCRC. The biweekly irinotecan/LV5FU2 combination was first evaluated in a phase I trial [12]. The association has been shown to be feasible and safe with an encouraging response rate, reaching 22% in pretreated MCRC patients. The recommended dose was 180 mg/m² for irinotecan with the LV5FU2 regimen, although the maximal tolerated dose (MTD) was reached at the 300 mg/m² dose level for irinotecan [12]. More recently, large European and American phase III trials confirmed the clinical benefit provided by the association of irinotecan with 5-FU and folinic acid. This included higher response rate (confirmed objective responses of 39–41%), longer time to progression and increased survival compared with the 5-FU and folinic acid regimen, widely used in patients receiving first-line therapy for MCRC [13, 14]. These trials led to registration of this combination in this indication in both Europe and the USA.

Oxaliplatin, a diaminocyclohexane platinum compound, acts, like cisplatin, through the formation of DNA adducts, but is bulkier and more hydrophobic than cisplatin adducts with activity markedly different from other platinum complexes [15]. Oxaliplatin, especially, has shown consistent clinical antitumoral activity in MCRC treatment. Efficacy of monotherapy was demonstrated in phase II trials, in both 5-FU previously untreated and treated patients, with an overall response rate ranging between 10 and 24% [16–18]. Evidence of oxaliplatin and 5-FU synergism *in vitro* [19] led to numerous clinical trials to assess oxaliplatin in combination with 5-FU/folinic acid. Those trials reported increased response rates reaching 18–51% [20–22], with improvement in time-to-progression but no statistical benefit in overall survival compared with 5-FU/folinic acid chemotherapy alone [22]. The combination has been approved in Europe for first-line treatment of MCRC. In this latter combination, oxaliplatin is administered at a dose of 85 mg/m² every 2 weeks, in combination with 5-FU/folinic acid, according to the LV5FU2 regimen described by De Gramont [21, 22].

In vitro synergism of oxaliplatin and SN-38 was also demonstrated when administered in combination in the human colon cancer cell line HT29 [23]. More cytotoxicity was consistently found *in vitro* when oxaliplatin was given before or concurrently with the camptothecin derivative [23]. Results obtained in a number of clinical trials with the combination of irinotecan and oxaliplatin showed promising efficacy in gastrointestinal malignancies, especially in MCRCs resistant to 5-FU-based therapies (objective responses of 23–64%) [24–28]. The toxicity profile of this combination remained manageable. The recommended dose was 175 mg/m² for irinotecan and 85 mg/m² for oxaliplatin, given every 2 weeks, for patients with performance status (PS) zero or one, and 150/85 for patients with a PS of two [26].

Overall, combining irinotecan or oxaliplatin with 5-FU/LV or the two new drugs together, has provided, in the last few years, new therapeutic approaches for treatment of MCRC patients with proven efficacy.

The different mechanisms of action of 5-FU, irinotecan and oxaliplatin and their relatively non-overlapping toxicities sup-

ported a rationale for evaluating the feasibility of combining the three drugs together.

In the present study, we assessed for the first time the triple combination, given every 2 weeks, with a fixed LV5FU2 regimen and a planned dose escalation for the new drugs, irinotecan and oxaliplatin.

Patients and methods

Patients

Patients were eligible if they had histologically proven non-resectable metastatic solid tumors, or advanced or metastatic disease refractory to conventional therapy and for which no effective therapy was available. Eligibility criteria also included: age between 18 and 75 years; a WHO PS of two or less; adequate hematological, hepatic and renal functions defined by hemoglobin ≥ 10 g/dl, absolute neutrophil count $\geq 2 \times 10^9$ /l, platelets count $\geq 100 \times 10^9$ /l, total bilirubin $\leq 1.25 \times$ the upper normal limit (UNL) of the institution, serum transaminases (aspartate aminotransferase, alanine aminotransferase) and alkaline phosphatase $\leq 3 \times$ UNL (or in cases of liver metastasis, bilirubin $\leq 1.5 \times$ UNL and serum transaminases $\leq 5 \times$ UNL) and serum creatinine level ≤ 125 μ mol/l. Patients must have discontinued previous antitumor treatment for at least 4 weeks (6 weeks in the case of aplasing chemotherapy such as nitrosourea, mitomycin C and carboplatin). Exclusion criteria included: prior chemotherapy regimens with irinotecan or oxaliplatin; symptomatic brain metastasis or carcinomatous leptomeningitis; prior abdomino-pelvic radiation therapy; prior history of severe toxicity with 5-FU; unresolved bowel obstruction or partial bowel obstruction; current uncontrolled infection or serious illness or medical condition (including contraindication to 5-FU); prior history of peripheral neuropathy; concomitant treatment with another anticancer therapy or with another experimental drug; pregnancy or patients with reproductive potential without contraception. All patients had signed a written informed consent before study entry.

Treatment administration

Treatment was given every 2 weeks. Oxaliplatin was diluted in 5% dextrose and administered as a 120-min intravenous (i.v.) infusion at day 1. Irinotecan, diluted in 5% dextrose, was administered as a 90-min i.v. infusion, 1 h after the end of the oxaliplatin infusion. 5-FU and folinic acid were used in commercially available formulations. The LV5FU2 regimen was administered at a fixed dose after the end of irinotecan infusion as follows: on day 1 and day 2 of the 14-day cycle, folinic acid (400 mg/m², DL form) was administered in a 2-h i.v. infusion, followed by 5-FU (400 mg/m²) in a 10-min i.v. bolus, followed by 5-FU (600 mg/m²) in a continuous 22-h infusion.

When the recommended dose had been determined, published data about the 'simplified LV5FU regimen' were available [29–31] and led us to treat a second cohort of patients treated at the recommended dose for oxaliplatin and irinotecan in conjunction with this simplified LV5FU regimen administered as follows: on day 1, a 2-h i.v. infusion of folinic acid (400 mg/m², DL form), followed by a 10-min i.v. bolus of 5-FU (400 mg/m²), followed by a continuous infusion of 5-FU (2400 mg/m²) over 46 h.

For all patients, systematic prophylactic treatment was not recommended at the first cycle except for anti-emetic prophylaxis, which was allowed and left to the investigator's discretion. However, in the case of severe cholinergic syndrome during one cycle, preventive treatment with atropine (0.25 mg subcutaneously) was to be given at subsequent cycles. If patients experienced delayed diarrhea, early prescription of high-dose loperamide was done according to specific guidelines for symptomatic treatment and, if diarrhea persisted >48 h, prophylactic oral fluoroquinolones were given. In the case of

severe neutropenia, defined as grade 4 for ≥ 7 days and/or no recovery to grade ≤ 1 at day 15, further cycles were administered with G-CSF (granulocyte colony-stimulating factor) at a dose of 263 $\mu\text{g/day}$ from day 7 to day 12.

Treatment was continued for up to 12 cycles unless stopped before because of disease progression, unacceptable toxicity or patient's refusal. After the end of treatment, patients were followed up every 3 months until death or cut-off date.

Dose-escalation schedule

Eight dose levels of oxaliplatin/irinotecan were planned for dose escalation: 60/90, 60/120, 85/120, 85/150, 85/180, 85/200, 85/220 and 85/240 mg/m^2 with a fixed dose of the LV5FU2 regimen. In the absence of any dose-limiting toxicity (DLT) observed at the first cycle, a minimum of three patients had to be treated at each dose level. Before escalating to the next dose level, patients at the dose level below had to be observed for acute toxicity during a minimum of 2 weeks (one cycle). When at least one DLT was observed at a dose level, the recommended dose level for all subsequent patients was evaluated by the continual reassessment method (CRM) [32], which provides a method for estimating the dose level nearest to the MTD. The MTD was defined as the dose level for which at least one DLT occurred for 50% of patients during the first cycle.

When the MTD was reached, a minimum of six patients had to be treated at the recommended dose level and a second cohort of patients was also treated at the recommended dose for oxaliplatin and irinotecan with the simplified LV5FU regimen.

DLT was defined as follows: grade 4 neutropenia (absolute neutrophil count $< 0.5 \times 10^9/\text{l}$) for ≥ 7 days; febrile neutropenia or neutropenia grade 3/4 concomitant with infection, any grade 3/4 diarrhea or grade ≥ 2 concomitant with grade 4 neutropenia; symptomatic thrombocytopenia; either grade 4 peripheral sensitive neuropathy or grade 3 necessitating treatment reduction at the 60 mg/m^2 dose level for oxaliplatin—grading according to Lévi's scale [33]; any grade 4 toxicity related to study treatment (except vomiting in the absence of appropriate medication) or any toxicity which necessitated a cycle delay of > 15 days.

Study assessment

Before inclusion, patients were subjected to a pre-trial evaluation including physical examination, assessment of medical history, hematological and biochemical tests and tumor assessment by computed tomography scan. During therapy, a complete blood cell and platelet count was performed weekly. Clinical examination and biochemical tests were required before each cycle. All adverse events experienced during the study were recorded and graded according to the National Cancer Institute common toxicity criteria, or, if not applicable, as mild, moderate, severe or life-threatening. Oxaliplatin neurosensory toxicity was described according to the specific grading proposed by Lévi et al. [33]. Presence of measurable lesions was not required in this study but, in the case of measurable or assessable disease, tumor assessments were performed every four cycles. Responses, as determined by investigators, were recorded according to WHO response criteria.

Statistical analysis

Descriptive statistics (median and range) were provided according to the initial planned dose and for all assessable patients for safety. Percent toxicities are presented per patient and per cycle. Confidence intervals (CIs) for proportions were calculated from the binomial distribution. Response duration was calculated from either inclusion to progression for patients with either partial response or stable disease or from complete response to progression for patients in complete response. Median survival was obtained

from the 50th percentile of the estimated Kaplan–Meier survival rates and presented with the 95% CI.

Results

Patient characteristics

Between April 1998 and January 2000, 42 patients were included in three centers. One patient was not assessable for tolerance because he never received any treatment because of consent withdrawal before the first cycle. A summary of patient characteristics at baseline is presented on the overall population (Table 1). Among the treated population, the median age was 56 years (range 32–73) and most patients had a PS of zero or one (80%). The most common tumors were gastrointestinal tumors (68%) including colorectal, pancreatic, gastric and esophageal cancers and cholangiocarcinoma. More than 60% of patients had at least two organs involved and 69% of patients had visceral involvement with 61% including liver. Seventy-eight percent of patients had received prior chemotherapy.

Study treatment exposure and determination of MTD

A total of 277 treatment cycles were administered with a median number of cycles per patient of six (range 1–12) (Table 2). Eleven patients (27%) received 12 cycles, the maximum number of cycles planned per protocol, and seven patients (17%) received between eight and 11 cycles.

Most patients (78%) had at least one cycle delay ≥ 3 days related to study treatment (35% of cycles). The main reason for delayed administrations was hematological toxicity (56%) but the frequency of cycle delays was not clearly dose-dependent (Table 2), even if all patients who had received more than one cycle at dose levels 85/200 and 85/220 mg/m^2 experienced at least one delay. Only patients treated at the first dose level (60/90 mg/m^2) and in the second cohort (dose level 85/180 with the simplified LV5FU regimen) could have nearly 90% of cycles administered every 2 weeks according to protocol.

To maintain this biweekly schedule, overall, 51% of patients required therapeutic G-CSF during 38% of cycles. However, it is noteworthy that 56% of patients required G-CSF in the first cohort (in 42% of cycles) compared with only 29% of patients in the second cohort (in 18% of cycles). Altogether, dose reductions occurred in 21 patients (51%) and in 13% of cycles and especially at dose levels $\geq 85/150 \text{ mg/m}^2$. Irinotecan was reduced in 15 patients (37%) and in 7% of cycles, mainly for hematological toxicity (more than 70% of irinotecan dose reductions). Nine patients (22%) underwent an oxaliplatin dose reduction in 6% of cycles, primarily (88%) because of peripheral neuropathy experienced at previous cycles. Overall, the median cumulative dose for oxaliplatin was 359 mg/m^2 (range 82–1020). Its administration had to be stopped in three patients after nine, 10 and 11 cycles. Only two patients (5%; three cycles) had a 5-FU dose reduction, both for stomatitis.

The dose level escalation was carried out according to the CRM method based on the observation on DLTs at cycle 1 (Table 3). The DLTs were mainly severe neutropenia. Since two out of four

Table 1. Patient characteristics at study entry

Characteristic	No. of patients	Percent
No. included	42	—
No. treated	41	—
Sex, male/female	24/17	59/41
Age, median (range)	56 (32–73)	—
WHO performance status		
0	12	29
1	21	51
2	8	20
Prior treatment		
Surgery	31	76
Chemotherapy	32	78
Median no. of lines (range)	1 (0–6)	—
Radiotherapy	13	32
Site of primary tumor		
Colorectal	11	27
Pancreas	6	15
Gastric	5	12
Esophagus	3	7
Cholangiocarcinoma	3	7
Kidney	3	7
Breast	2	5
Lung	2	5
Unknown primary site	2	5
Others ^a	4	10
No. of organs involved ^b		
0	1	2
1	14	34
2	13	32
≥3	13	32

^aOne pleural mesothelioma, one thyroid cancer, one carcinoid tumor of bowel and one retroperitoneal sarcoma.

^bOne patient had no metastatic disease at study entry (error of diagnosis).

evaluable patients at dose level 85/220 mg/m² presented a DLT, this dose level was considered as the MTD. Therefore according to the protocol, the recommended dose level should have been the dose level just below, in this case 85/200 mg/m². However, at this dose level, all patients who received more than one cycle had at least a one-cycle delay related to study treatment and three patients out of five had at least one dose reduction of irinotecan. Consequently, the decision was taken to complete the lower dose levels 85/150 and 85/180 mg/m² with the inclusion of three extra patients by dose level. Since no major difference was observed between those two dose levels in terms of drug delivery (dose reductions or cycle delays), the recommended dose chosen for the second step of the study was oxaliplatin 85 mg/m² and irinotecan 180 mg/m².

Table 2. Drug delivery

Dose level, oxaliplatin/irinotecan (mg/m ²)	Total no. of patients/cycles	Median no. of cycles per patient (range)	Dose reductions, no. of patients (percent of cycles)			Delayed cycles (≥3 days) related to study treatment, no. of patients (percent of cycles)	G-CSF support, no. of patients (percent of cycles)
			Oxaliplatin	Irinotecan	5-FU		
First cohort (fixed regimen for LV5FU2)							
60/90	3/22	6 (4–12)	–	–	–	1 (11)	–
60/120	4/45	12 (9–12)	–	2 (4)	–	4 (32)	3 (51)
85/120	2/5	2.5 (2–3)	–	–	–	1 (33)	–
85/150	6/48	9.5 (1–12)	2 (8)	3 (8)	–	4 (52)	3 (48)
85/180	8/45	4 (1–12)	1 (4)	2 (7)	–	5 (49)	5 (44)
85/200	6/25	4 (1–8)	2 (8)	3 (16)	2 (12)	5 (42)	4 (44)
85/220	5/36	7 (3–12)	1 (6)	3 (11)	–	5 (32)	4 (53)
Second cohort [fixed simplified LV5FU scheme (85/180)]	7/51	8 (3–12)	3 (14)	2 (6)	–	4 (11)	2 (18)

LV, leucovorin; 5-FU, 5-fluorouracil; LV5FU2, full-dose LV and 5-FU regimen on days 1 and 2, every 2 weeks; LV5FU, simplified LV and 5-FU regimen; G-CSF, granulocyte colony-stimulating factor.

Table 3. Dose escalation for determination of maximum-tolerated dose (first cohort)

Dose level, oxaliplatin/ irinotecan (mg/m ²)	No. of patients	No. of cycles	No. of patients with at least one dose-limiting toxicity at the first cycle
60/90	3	22	—
60/120	4	45	—
85/120	2	5	—
85/150	3 + 3 ^a	48	2 (diarrhea grade 3, grade 4) ^a
85/180	5 + 3 ^a	45	2 (neutropenia grade 4 ≥ 7 days, febrile neutropenia with diarrhea grade 4)
85/200	6	25	2 (neutropenia grade 4 ≥ 7 days, stomatitis grade 4)
85/220	5	36	2 (neutropenia grade 4 ≥ 7 days, febrile neutropenia grade 4) ^b

^aPatients included after determination of maximum-tolerated dose.

^bTwo dose-limiting toxicities among the first four patients included at this dose level.

Toxicity

All treated patients were assessable for toxicity. No treatment-related death was reported by the investigators during the study. Table 3 lists the DLTs observed during the first cycle of the combination in the dose-escalation part of the study. Table 4 summarizes the main grade 3/4 toxicities encountered during treatment, overall and by dose level. The DLT of the association is clearly neutropenia, which was the most common toxicity in severity. Overall, 85% of patients experienced neutropenia and 78% had at least one grade 3/4 in 23% of cycles. Although the incidence of grade 3/4 toxicity per patient was high, episodes of severe neutropenia, febrile neutropenia or grade 4 lasting ≥ 7 days occurred only above the dose level 85/150 mg/m² and in less than 10% of cycles. It should be noted, however, that no patient received prophylactic G-CSF at cycle one, although overall, 51% of patients required G-CSF in 38% of cycles under treatment. In most cases, G-CSF was used because of no hematological recovery at day 15 with a neutrophil count $<1.5 \times 10^9/l$. It is noteworthy that at dose level 85/180 mg/m² with the simplified LV5FU scheme (second cohort), the incidence of grade 3/4 neutropenia was lower (43% of patients and 10% of cycles) with a lesser use of G-CSF as already stated above: 29% of patients received G-CSF in 18% of cycles compared with 56% of patients of the first cohort (dose escalation) in 42% of cycles (Table 2). Grade 3/4 thrombocytopenia occurred in 6% of cycles and was reported as a serious adverse event for one patient with gastric cancer at two successive cycles. Grade 3/4 anemia was experienced in 5% of cycles and reported as a serious adverse event for one patient. This patient also had a gastric cancer and rapidly recovered after transfusion.

The most frequent and severe non-hematological adverse events were gastrointestinal toxicities, peripheral neuropathy and asthenia with the overall following occurrences of related grade 3/4 by patient: 27% diarrhea (5% of cycles); 24% nausea/vomiting (5% of cycles); 37% peripheral neuropathy (20% of cycles); and 41% asthenia (9% of cycles). All these toxicities are detailed by dose levels in Table 4. Overall, acute toxicity was mild under dose level 85/150 mg/m², except for peripheral neuropathy grade 3 (specific oxaliplatin Lévi scale) observed at almost all dose levels. Its severity was generally preceded by progres-

sively persistent paresthesias between cycles. Severe digestive toxicities, such as grade 3/4 delayed diarrhea, nausea/vomiting, occurred from dose level 85/150 mg/m² and never exceeded 10% of cycles with the exception of the MTD level 85/220 mg/m². Most of these toxicities were only experienced at one cycle per patient (50% at first cycle) and subsequent dose reduction and/or prophylactic anti-emetic therapy improved the gastrointestinal tolerance of these patients. The main other non-hematological toxicity was asthenia, which occurred above the dose level 60/120 mg/m². Of note, the severity of main toxicities appears lower in patients treated in the second cohort with the simplified LV5FU regimen, except for neurotoxicity. At this dose level the median cumulative dose for oxaliplatin was 537 mg/m².

The other frequently reported non-hematological toxicities related to study treatment were alopecia experienced by 61% of patients (27% grade 2), anorexia, which occurred in 59% of patients and 20% of cycles (4% of cycles grade 3/4), and stomatitis in 59% of patients and 23% of cycles, with two patients experiencing a grade 3 and 4, respectively, leading to 5-FU dose reductions. The occurrence and severity of those toxicities were not clearly dose-dependent and seemed rather more patient-related.

Efficacy

Patients were considered to be assessable for response if they had measurable lesions and had received at least four cycles of the study treatment or showed evidence of early progression. Seven treated patients were non-evaluable for efficacy: one patient could not be evaluated because he had no disease (error of diagnosis at study entry) and six came off the study before first evaluation, without evidence of early progression according to the investigator. Of 34 patients evaluable for efficacy, three complete responses (one pancreas, two colorectal cancers) and eight partial responses (three colorectal cancers, two cholangiocarcinoma, one pancreas, one gastric and one renal carcinomas) were observed, resulting in 11 objective responses. Among these responses, 10 concerned gastrointestinal tumors. All responders with CRC had received prior chemotherapy with 5-FU and had liver metastases. Two of them were able to have hepatic resection after response. The five other objective responses observed in

Table 4. Main grade 3/4 toxicities: total and by dose levels (values are no. of patients/cycles)

Dose level, oxaliplatin/ irinotecan (mg/m ²)	Total no. of patients (cycles)	Neutropenia		Diarrhea (grade 3/4)	Nausea/vomiting (grade 3/4)	Asthenia (grade 3/4)	Peripheral neuropathy [grade 3, (specific oxaliplatin Lévi scale)]
		Grade 3/4	With febrile neutropenia or neutropenia ≥7 days				
First cohort (fixed regimen for LV5FU2)							
60/90	3 (22)	2 (9%)	–	–	–	–	2 (32%)
60/120	4 (45)	4 (29%)	–	–	–	–	–
85/120	2 (5)	2 (40%)	–	–	–	1 (20%)	1 (40%)
85/150	6 (48)	5 (28%)	3 (6%)	4 (8%)	2 (6%)	5 (10%)	4 (31%)
85/180	8 (45)	7 (27%)	2 (4%)	2 (4%)	4 (9%)	3 (7%)	1 (9%)
85/200	6 (25)	4 (36%)	1 (4%)	1 (4%)	–	3 (28%)	2 (12%)
85/220	5 (36)	5 (25%)	2 (8%)	2 (11%)	3 (17%)	4 (22%)	2 (22%)
Second cohort [fixed simplified LV5FU scheme (85/180)]	7 (51)	3 (10%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	3 (31%)
Total	41 (277)	32 (23%)	9 (4%)	11 (5%)	10 (5%)	17 (9%)	15 (20%)

LV5FU2, full-dose leucovorin (LV) and 5-fluorouracil (5-FU) regimen on days 1 and 2, every 2 weeks; LV5FU, simplified LV and 5-FU regimen.

digestive malignancies were obtained in diseases with a usually very poor prognosis. In those cases, response duration was ≥5 months except for one patient with one cholangiocarcinoma who went off the study after eight cycles because the response obtained enabled resection of the hepatic tumor. Furthermore, 13 patients (38%) had stable disease among whom four patients had a minor response. Responses were observed at nearly all dose levels (Table 5). With a median follow-up of 16 months, the median duration of response was 9 months (95% CI 6–18 months), the median duration of stabilization was 7 months (95% CI 6–12 months), the median time to progression was 7 months (95% CI 5–9 months) and the survival time ranged from 1.1 to 24.5 months.

Discussion

The objectives of this open-label, non-randomized, dose-escalation study were to determine the MTD, the DLT and the recommended dose for irinotecan and oxaliplatin given together with the LV5FU2 regimen as a triple combination every 2 weeks in patients with advanced solid tumors.

Forty-one patients were treated and evaluated for safety. Thirty-four patients were included in the dose-escalation cohort and the MTD was determined to be the dose level 85 mg/m² for oxaliplatin and 220 mg/m² for irinotecan with the LV5FU2 regimen. The DLT at this dose level was severe neutropenia. Therefore, the recommended dose should have been 85/200 mg/m². However, at this dose level, >30% of cycles had a dose reduction, with 16% of cycles requiring a dose reduction of irinotecan, mainly because of hematological toxicity. Thus, the 180 mg/m² irinotecan dose level was considered the best compromise between dose intensity and safety for designing further multi-center phase II or III studies. Our choice was also supported by the already determined recommended and currently used doses for the bi-therapy associations: irinotecan 180 mg/m² or oxaliplatin 85 mg/m² for combinations with LV5FU2 regimen given every 2 weeks [12, 13, 21, 22] and irinotecan 175 mg/m² or 200 mg/m² plus oxaliplatin 85 mg/m² for the association of the two new drugs given every 2 or 3 weeks [24, 26, 28]. Furthermore, recently published data suggesting the lower hematological toxicity of the simplified LV5FU regimen, alone or in combination with irinotecan [29–31], led us to treat a second cohort of patients at the dose level 85 mg/m² for oxaliplatin and 180 mg/m² for irinotecan with the simplified LV5FU regimen. Results obtained showed that the recommended dose level with this scheme could be safely administered with preservation of a good biweekly dose intensity, since nearly 90% of cycles could be administered every 2 weeks according to the protocol.

Overall, the most frequent adverse events observed were consistent with those expected in patients treated with either irinotecan or oxaliplatin combined with a 5-FU-based regimen, or by the two new drugs given together.

The main grade 3/4 toxicity in this study was neutropenia, observed in 78% of patients and 23% of cycles, with severe neutropenia (febrile neutropenia or grade 4 lasting ≥7 days) observed above the dose level 85/150 mg/m² in less than 10% of

Table 5. Antitumor activity by dose level (values are no. of patients)

Response (<i>n</i> = 34)	Initial planned dose level, oxaliplatin/irinotecan (mg/m ²)							Second cohort	Total
	60/90	60/120	85/120	85/150	85/180	85/200	85/220		
Complete response	1	1	–	–	–	–	1	–	3
Partial response	–	1	–	1	1	2	1	2	8
Stable disease	1	2	–	3	3	1	1	2	13 ^a
Progressive disease	1	–	1	1	2	2	1	2	10

^aIncluding four minor responses.

cycles. In all studies (phase I, II or III) combining every 2 weeks either irinotecan or oxaliplatin with LV5FU2, or the two new drugs together, the occurrence of grade 3/4 neutropenia varied from about 37 to 64% of patients [12, 13, 21, 22, 26, 27]. Furthermore, the occurrence of complicated neutropenia (22% of patients) appears more frequently with the association of the three drugs. These results may be because of the overlapping hematological toxicity of each drug, especially irinotecan and 5-FU. Yet they could also be explained by the patient's characteristics in our study including patients with various solid tumor types who, for the most part, had already been treated before inclusion. One important finding about the hematological safety profile of the association of the three drugs is that the use of growth factors seems necessary in order to allow dose intensity of the biweekly schedule, since, overall, 51% of patients required G-CSF. However, we noticed that at dose level 85/180 mg/m² with the simplified LV5FU scheme, the incidence of grade 3/4 neutropenia was lower (43% of patients and 10% of cycles) with less use of G-CSF: 29% of patients received G-CSF in 18% of cycles compared with 56% of patients of the first cohort (dose escalation) in 42% of cycles. These results are consistent with the already known hematological toxicity of 5-FU bolus compared with 5-FU infusional administration [34, 35] and confirm the lower hematological toxicity of the simplified LV5FU regimen compared with the LV5FU2 regimen [29, 36], which has also been observed in association with oxaliplatin (FOLFOX 6 schedule) or irinotecan (FOLFIRI scheme) [37–39]. Thrombocytopenia was not enhanced either in frequency or in severity with the triple combination as compared with combinations studies of oxaliplatin or irinotecan with LV5FU2 [21–25].

The other principal adverse events were gastrointestinal toxicities, cumulative oxaliplatin-related peripheral neuropathy and asthenia, with the following occurrence of grade 3/4: diarrhea in 27% of patients, nausea/vomiting in 24% of patients and grade 3 peripheral neuropathy in 37% of patients (specific Lévi scale grading). The incidence of these toxicities did not increase significantly in our study compared with the published phase I/II bi-therapy studies. At the recommended dose for combining irinotecan and LV5FU2 (180 mg/m²), grade 3/4 diarrhea occurred in 27% of patients in phase I/II [12] and 13% in phase III [13]. In phase I/II studies combining irinotecan and oxaliplatin every 2 or 3 weeks, grade 3/4 diarrhea was experienced by 17–30% of patients [24–26]. In these studies, the only overlapping toxicity between the two drugs was nausea/vomiting reported in 30–40% of patients overall. As ascertained before and in our

study, this toxicity can be managed by systematic prophylactic anti-emetics at each cycle, and moreover it never led to treatment discontinuation. The occurrence of severe peripheral neuropathy in our study (overall, 37% of patients in 20% of cycles) is of the same order as the one reported in the phase I study of oxaliplatin combined with irinotecan given as a 2-week schedule [26], although the median cumulative dose of oxaliplatin was lower: 359 mg/m² (537 mg/m² at the recommended dose with the simplified LV5FU scheme) compared with 765 mg/m² in the Goldwasser study [26].

Recently, four phase I studies evaluated various schedules of combination of the three drugs, irinotecan, oxaliplatin and 5-FU. All of these trials were conducted in MCRC patients, with a lesser dose intensity of the two new drugs and without 5-FU bolus. However, their preliminary results are consistent with ours, reporting neutropenia and diarrhea as the main DLTs [40–43].

Although tumor response was not the primary end point of this study, it should be noticed that 11 objective responses among 34 evaluable patients were observed at all dose levels and 71% of patients experienced a tumor growth control (complete response plus partial response plus stable disease) according to the investigators' assessment. Most objective responses were observed in digestive malignancies, since 10 of 11 were obtained in five colorectal cancers, two pancreatic cancers, two cholangiocarcinoma and one gastric cancer. With a median follow-up of 16 months, the median duration of responses was 9 months (95% CI 6–18 months) and the survival time ranged from 1.1 to 24.5 months. These results confirm the efficacy of the three drugs in the treatment of CRC, although this had already been demonstrated in bi-therapy studies of either irinotecan or oxaliplatin combined with 5-FU/LV or of the two new drugs combined together. Nevertheless, it is worth noting that two CRC patients who achieved a partial response were able to have hepatic resection after treatment by the triple combination. Furthermore, this also appears of particular interest in gastrointestinal malignancies such as cholangiocarcinoma, pancreatic and gastric cancer, as one patient with cholangiocarcinoma became resectable after eight cycles of treatment. Each patient with one of these diseases that was responsive under treatment (*n* = 5) was still alive 12 months after initial diagnosis.

In conclusion, this phase I study has shown both the lack of clearly overlapping toxicities when the three drugs are combined together and the feasibility of the triple association given every 2 weeks with the simplified LV5FU regimen administered together with the recommended doses of 85 mg/m² for oxaliplatin

and 180 mg/m² for irinotecan. At this dose, it should be noticed that G-CSF was administered in 18% of cycles in cases of severe neutropenia or to maintain a biweekly schedule. Although the use of G-CSF is not recommended in routine palliative chemotherapy, it should be considered in the light of efficacy results. Those obtained in our study warranted further investigation of the regimen, especially in the case of gastrointestinal malignancies, where 10 out of the 11 objective responses were observed. The use of the triple combination with G-CSF support, if necessary, should be justified in front-line therapy for disease where no effective treatment is available, or to allow a secondary radical surgical approach on metastases in colorectal patients. Thus, our results led to two ongoing phase II studies using this combination in advanced pancreatic adenocarcinoma and in metastatic colorectal patients with non-resectable liver metastasis. In this latter case, chemotherapy with the triple association can be justified, since it may increase the proportions of R0 surgical resections, which is the only effective treatment providing long-term survival in this disease [44, 45].

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Appendix YOSHIDA01

A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer

Kensaku Yoshida¹, Takuji Iwashita¹, Shinya Uemura¹, Akinori Maruta¹, Mitsuru Okuno¹, Nobuhiro Ando², Keisuke Iwata², Junji Kawaguchi³, Tsuyoshi Mukai³ and Masahito Shimizu¹

¹First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan

²Department of Gastroenterology, Gifu Prefectural General Medical Center, Gifu, Japan

³Department of Gastroenterology, Gifu Municipal Hospital, Gifu, Japan

Correspondence to: Takuji Iwashita, *email:* takuji@w7.dion.ne.jp

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ABSTRACT

Background: FOLFIRINOX (FX) has been reported as an effective treatment for unresectable advanced pancreatic cancer. However, FX is associated with a high incidence of adverse events (AEs). A previous phase II study in Japan showed high incidences of hematological AEs, including febrile neutropenia (22.2%). A modified FX regimen (mFX) may decrease the rates of AEs and be more effective than FX by improving the treatment compliance.

Aims: To assess the safety and efficacy of first-line mFX for unresectable advanced pancreatic cancer.

Patients and methods: This was as a multicenter prospective phase II study in chemotherapy-naïve Japanese patients with pathologically confirmed unresectable advanced pancreatic adenocarcinoma or adenosquamous carcinoma. Treatment with mFX (85 mg/m² oxaliplatin, 150 mg/m² irinotecan, and 200 mg/m² l-leucovorin, followed by 46-h continuous infusion of 2400 mg/m² 5-fluorouracil) was administered every 2 weeks. The primary endpoint was the response rate. The secondary endpoints were overall survival, progression-free survival, and safety.

Results: Thirty-one patients (18 men; median age, 64 years) were enrolled. A median of 13 treatment cycles were administered during a median follow-up period of 14.2 months. The response rate, median overall survival, and median progression-free survival were 38.7%, 14.9 months, and 7.0 months, respectively. Grade 3 or 4 AEs included neutropenia (83.9%), febrile neutropenia (16.1%), peripheral sensory neuropathy (9.7%), thrombocytopenia (6.5%), diarrhea (6.5%), anorexia (6.5%), and vomiting (3.2%).

Conclusion: Compared to FX, mFX may result in fewer Grade 3 or 4 non-hematological AEs, with a comparable response rate. However, further efforts might be required to reduce hematological AEs.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in Japan, with 31,866 deaths reported

annually [1]. The 5-year survival rate of pancreatic cancer is reported as only 8.3%, owing to the fact that pancreatic cancer is typically found at an advanced stage [2]. At the time of diagnosis, almost 50% of patients have metastatic

lesions and 30% are diagnosed with locally advanced pancreatic cancer [3]. Given the above-mentioned situation, the development of effective and tolerable chemotherapy is highly important for the management of advanced pancreatic cancer.

In 1997, a study comparing gemcitabine (GEM) and 5-fluorouracil (5-FU) for advanced pancreatic cancer showed an improvement in overall survival (OS) with GEM [4]. Since then, GEM has been a key chemotherapy agent for pancreatic cancer. In 2011, a French phase II/III study by Conroy et al. comparing FOLFIRINOX (FX; a combination of 5-FU, oxaliplatin, irinotecan, and leucovorin) versus GEM in metastatic pancreatic cancer showed significant improvements in the median OS (11.1 vs. 6.8 months, $p < 0.001$) and progression-free survival (PFS; 6.4 vs. 3.3 months, $p < 0.001$), as well as an increased response rate (RR; 31.6% vs. 9.4%) [5]. Following this study, a phase II study of FX for metastatic pancreatic cancer in a Japanese cohort was conducted and showed equivalent efficacy as in the original report [6]. However, in terms of its safety profile, the phase II/III study reported that FX was associated with significantly higher rates of grade 3 or 4 neutropenia (45.7% vs. 21.0%), diarrhea (12.7% vs. 1.8%), and sensory neuropathy (9.0% vs. 0%) compared to GEM [5]. The rates of toxicity in the Japanese phase II study of FX was also higher, especially for hematological toxicities such as grade 3 or 4 neutropenia (77.8%) and febrile neutropenia (FN; 22.2%) [6]. These studies reported that the higher toxicity was associated with higher rates of subsequent dose reductions and treatment delays.

Based on these previous two studies, FX can be concluded to represent an effective treatment in patients with metastatic pancreatic cancer; however, its tolerability remains a concern. An initial dose reduction of FX might reduce the toxicity without compromising the efficacy by improving the compliance to the chemotherapy. Thus, we conducted this multicenter prospective phase II study of first-line modified FX (mFX) for unresectable advanced pancreatic cancer in a Japanese cohort.

RESULTS

Patient characteristics

Between October 2014 and March 2016, 31 patients were recruited and enrolled in this study from three tertiary care centers: Gifu University Hospital, Gifu Municipal Hospital, and Gifu Prefectural General Medical Center. The basic characteristics of the study patients are shown in Table 1. Treatment was discontinued in 29 patients (93.5%), owing to progression of primary disease in 24 patients (77.4%), adverse events in 4 patients (12.9%; neutropenia in 2, vomiting in 1 and peripheral sensory neuropathy in 1) and after R0 operation in 1 patient (3.2%).

Efficacy of the modified FOLFIRINOX

The median number of cycles administered was 13 (range, 2-45) in all patients. The median relative dose intensities were as follows: oxaliplatin, 59.6%; irinotecan, 72.8%; 5-FU, 77.9%; and l-leucovorin, 82.5%. A total of 28 (90.3%) and 29 (93.5%) patients required dose reductions and dose delays, respectively, mainly due to neutropenia (Table 2). The median follow-up time was 14.2 months. At the time of analysis, 24 (77.4%) deaths had occurred. Of the 31 evaluable patients, response evaluation showed a partial response in 12 patients (38.7%), stable disease in 11 patients (35.5%), and progressive disease in 8 patients (25.8%). The RR was 38.7% (95% CI, 23.7-56.2) and the disease control rate was 74.2% (95% CI, 56.8-86.3). The estimated 1-year OS rate was 64.5% (95% CI, 46.6-79.1), with a median OS of 14.9 months (95% CI, 9.9-19.2; Figure 1). The estimated 1-year PFS rate was 32.3% (95% CI, 18.3-50.3), with a median PFS of 7.0 months (95% CI, 3.88-11.1; Figure 2, Table 3). The RR, median OS, and median PFS in patients with locally advanced and metastatic pancreatic cancer were 50% (5/10; 95% CI, 23.7-76.3) and 33.3% (7/21; 95% CI, 17.2-54.6), 16.7 months (95% CI, 3.6-26.4) and 14.9 months (95% CI, 9.9-18.5) (Figure 3), and 9.6 months (95% CI, 1.8-17.7) and 7.0 months (95% CI, 3.9-11.0) (Figure 4), respectively.

Second-line chemotherapy and surgical resection

Of the 29 patients who discontinued mFX, 25 patients received second-line chemotherapy with GEM plus nab-paclitaxel ($n=19$), GEM ($n=2$), or S-1 ($n=4$), while 4 patients did not receive any second-line chemotherapy. Two patients proceeded to undergo surgery after treatment with 5 and 13 cycles of mFX, respectively. One patient had R1 resection and the other patient had R0 resection on the final pathological evaluation. Both patients are still alive. One patient is continuing mFX and the other patient is receiving S-1 as adjuvant chemotherapy.

Safety profile

Twenty-seven (87.1%) of the 31 patients experienced grade ≥ 3 adverse events. The most common grade ≥ 3 hematologic adverse events were neutropenia (83.9%), FN (16.1%), and thrombocytopenia (6.5%). G-CSF was administered in 18 patients (58.1%) due to grade ≥ 3 neutropenia. FN occurred only during the first cycle and in 50% (4/8) of patients with biliary drainage whereas the incidence of FN in patients without biliary drainage was 4.3% (1/23). The most common grade ≥ 3 non-hematologic adverse events were peripheral sensory neuropathy (9.7%), diarrhea (6.5%), anorexia (6.5%), and vomiting (3.2%) (Table 4). There were no treatment-related deaths. Four (12.9%) of the 31

Table 1: Baseline characteristics of patients with unresectable advanced pancreatic cancer treated with modified FOLFIRINOX

Age, year-old, median (Range)		64 (49-72)
Sex, n (%)	male	18 (58.1%)
	female	13 (41.9%)
ECOG PS, n (%)	0	25 (80.6%)
	1	6 (19.4%)
CA19-9, µ/mL	median (range)	787.3 (2-24469.2)
Pathological type, n (%)	adenocarcinoma	30 (96.8%)
	adenosquamous carcinoma	1 (3.2%)
Disease extent, n (%)	locally advanced	10 (32.3%)
	metastatic	21 (67.7%)
Site of primary tumor, n (%)	head	15 (48.4%)
	body/tail	16 (51.6%)
Site of metastasis, n (%)	liver	13 (41.9%)
	lung	3 (9.7%)
	bone	3 (9.7%)
	others	3 (9.7%)
Biliary drainage, n (%)	no	23 (74.2%)
	yes	8 (25.8%)
UGT1A1(*6/*28), n (%)	Wild/Wild	21 (67.7%)
	Wild/heterozygous	5 (16.1%)
	Heterozygous/wild	5 (16.1%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1

Table 2: Treatment duration and drug delivery of patients with unresectable advanced pancreatic cancer treated with modified FOLFIRINOX

Median cycles of treatment, number (range)	13(2-37)
Median relative dose intensity, % (range)	
Oxaliplatin	59.59% (13.8-100%)
Irinotecan	72.79% (43.9-100%)
5-FU	77.92% (32.1-100%)
<i>L</i> -Leucovorin	82.5% (48.0-100%)
Dose reduction (total patients), n (%)	
Overall	28 (90.3%)
Oxaliplatin	28 (90.3%)
Irinotecan	24 (77.4%)
5-FU	5 (16.1%)
Delayed cycles, n (%)	
Overall	29 (93.5%)

patients discontinued the treatment due to the following adverse events: vomiting in 2 patients (6.5%), peripheral sensory neuropathy in 1 patient (3.2%), and neutropenia in 1 patient (3.2%). Biliary tract-related adverse events (cholangitis and cholecystitis in 2 patients each) were recognized in 4 patients (12.9%), including 3 patients who already had a biliary stent. Among them, cholangitis was managed with stent exchange and cholecystitis was managed with percutaneous transhepatic gallbladder drainage followed by laparoscopic cholecystectomy.

DISCUSSION

This phase II open label study was carried out to investigate the efficacy and safety of the mFX regimen for unresectable advanced pancreatic cancer, including both locally advanced and metastatic cancers. Overall, the RR was 38.7%, with a median follow-up time of 14.2 months. The median OS and PFS were 14.9 and 7.0 months, respectively. Grade 3 or 4 adverse events included neutropenia (84%), FN (16.1%), peripheral sensory

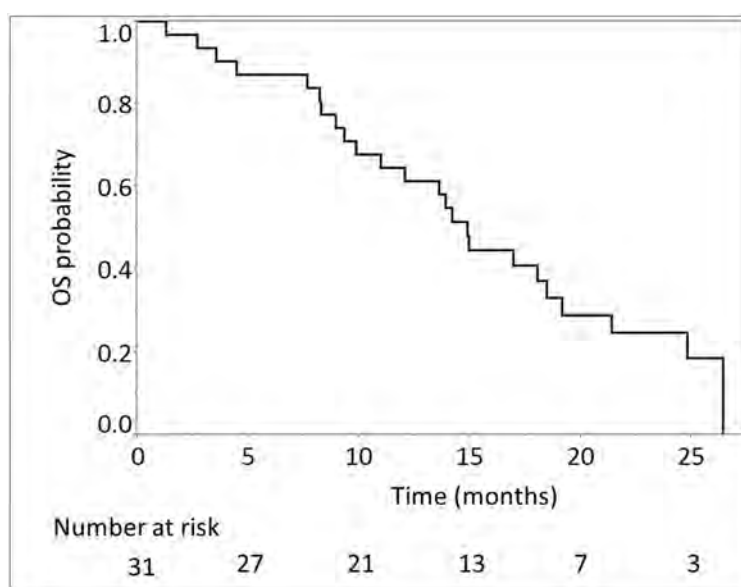


Figure 1: Overall survival (OS) of 31 patients with unresectable advanced pancreatic cancer treated with modified FOLFIRINOX. The median OS was 14.9 months (95% confidence interval, 9.9-19.2).

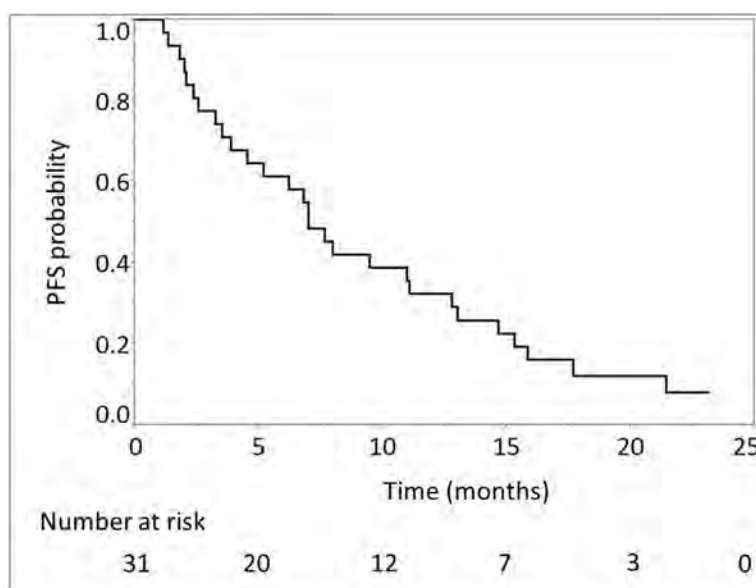


Figure 2: Progression-free survival (PFS) of 31 patients with unresectable advanced pancreatic cancer treated with modified FOLFIRINOX. The median PFS was 7.0 months (95% confidence interval, 3.9-11.1).

Table 3: Efficacy results of patients with unresectable advanced pancreatic cancer treated with modified FOLFIRINOX

Objective response rate	
Complete Response, n (%)	0 (0%)
Partial Response, n (%)	12 (38.7%)
Stable Disease, n (%)	11 (35.5%)
Progressive Disease, n (%)	8 (25.8%)
Response rate, n (%), 95% CI	12 (38.7%, 23.7-56.2)
Disease control rate, n (%), 95% CI	23 (74.2%, 56.8-86.3)
1-year overall survival rate, % (95% CI)	64.5 (46.6-79.1)
Overall survival, months, median (95% CI)	14.9 (9.9-19.2)
1-year progression-free survival rate, % (95% CI)	32.3 (18.3-50.3%)
Progression-free survival, months, median (95% CI)	7.0 (3.9-11.1)

95% CI, 95% confidence interval

neuropathy (9.7%), thrombocytopenia (6.5%), diarrhea (6.5%), anorexia (6.5%), and vomiting (3.2%).

In our study, the mFX regimen was decided based on the result of a phase I study of infusional 5-FU, leucovorin, oxaliplatin, and irinotecan for advanced colorectal cancer in a Japanese cohort, which was designed to determine the maximum tolerated dose. That study showed that the recommended dose in Japanese patients was irinotecan at 150 mg/m², oxaliplatin at 85 mg/m² and 5-FU at 2,400 mg/m² [7]. A few studies reporting the efficacy and tolerability by initial dose reduction of FX as first-line chemotherapy for advanced pancreatic cancer have also been published. Mahaseth et al. performed a retrospective analysis of mFX in which only bolus 5-FU was discontinued [8]. Stein et al. also performed a phase II study of mFX with a 25% reduction of irinotecan and bolus 5-FU (irinotecan intravenously at 135 mg/m² and intravenous bolus 5-FU at 300 mg/m²) [9]. Although no clear rationale was described in the former study, in the latter, the modified regimen was decided based on the authors' retrospective analysis of FX, which showed that the majority of patients received attenuated doses of bolus 5-FU and irinotecan. As a result, the authors suggested that up-front dose attenuation of bolus 5-FU and irinotecan improved the tolerability without compromising the efficacy of the treatment.

The RR of 38.7% (95% CI 23.7-56.2%) in our study was similar to those of the phase II/III study of FX in France and the phase II study of FX in Japan (31.6% and 38.9%, respectively) [5, 6]. The PFS of 7.0 months (95% CI, 3.9-11.1 months) and OS of 14.9 months (95% CI, 9.9-19.2 months) in our study were also comparable with those of the FX of the phase II/III study in France (6.4 and 11.1 months, respectively) and phase II study in Japan (5.6 and 10.7 months, respectively) [5, 6]. Considering these data, our modified regimen of FX maintained its

efficacy even with the dose reduction, although a direct comparison between these studies could not be performed due to the different basic characteristics of the study subjects. The most important difference is that our study cohort included patients with both locally advanced and metastatic pancreatic cancer as unresectable advanced pancreatic cancer. However, even if the results only in the patients with metastasis one were reviewed, the RR of 33.3%, median OS of 14.9 months, and median PFS of 7.0 months were comparable. Thus, in other words, even in the subgroup analyses of locally advanced and metastatic cancers, our results were comparable with those of FX in the previous studies [5, 6]. As expected, the PFS and OS in locally advanced cases tended to be slightly better than those in metastatic cases in this study. Although there were no significant differences in the results between locally advanced and metastatic cancers, this might be due to the small number of patients in the sub-group analyses.

Regarding the toxicity profile in this study, the hematological adverse event rates were not suppressed compared to the rates of the French phase II/III and the Japanese phase II study of FX. The rate of grade 3 or 4 neutropenia was 83.9% (95% CI, 67.4-92.9 %); this was similar to in the phase II study in Japan (77.8 %) and higher than that of the phase II/III study in France (45.7 %) [5, 6]. FN occurred in 16.1% (95% CI, 7.1-32.6 %) of patients in our study, and this was also similar to the rate in the Japanese phase II study (22.2 %) and higher than that in the French phase II/III study (5.4 %) [5, 6]. Although FN occurred only in the first cycle and was successfully treated with administration of antibiotics and G-CSF, with a median recovery time of 3 days (range 2-6), careful observation during the first cycle is considered important to monitor for neutropenia and FN. Another point of view to reduce the rates of neutropenia and FN is

prophylactic usage of G-CSF. The use of G-CSF was not permitted as prophylaxis in this study; however, 69.2 % of the patients were eventually treated with G-CSF due to grade 3 or 4 neutropenia or FN. Similar to in the phase II study of FX in Japan, which reported that severe infection and FN frequently occurred in patients with biliary stents at baseline [6], FN occurred in 50 % of patients with biliary stent placement for biliary obstruction in our study.

These results suggest that careful observation of possible hematological adverse events from neutropenia or FN, especially in the first cycle and in patients with biliary stent placement, is required, even when the FX regimen is modified. Prophylactic administration of G-CSF, including pegylated filgrastim, might be one option to reduce the rates of serious adverse events. For other hematological adverse events, the rates of grade 3 or 4 thrombocytopenia

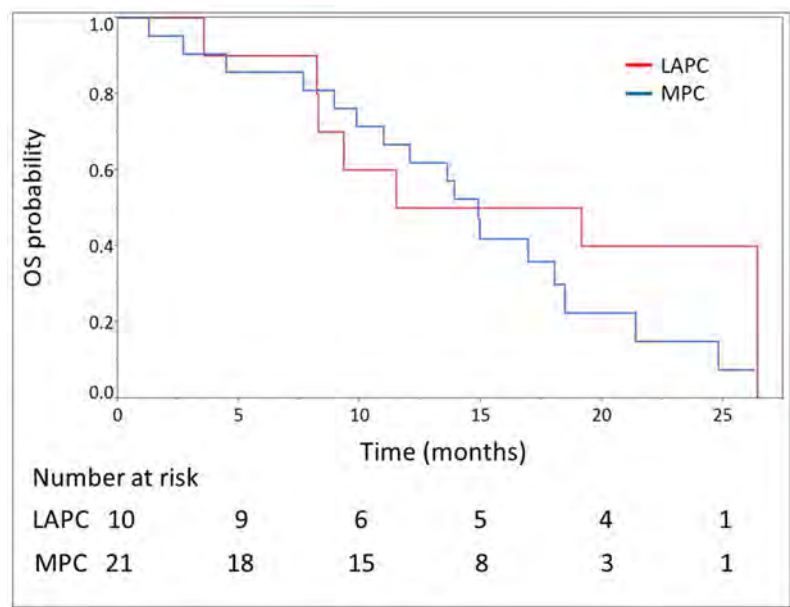


Figure 3: Overall survival (OS) of 21 patients with metastatic pancreatic cancer (MPC) and 10 patients with locally advanced pancreatic cancer (LAPC) treated with modified FOLFIRINOX. The median OS were 14.9 months (95% confidence interval, 9.9-18.5) and 16.7 months (95% confidence interval, 3.6-26.4) in patients with MPC and LAPC, respectively.

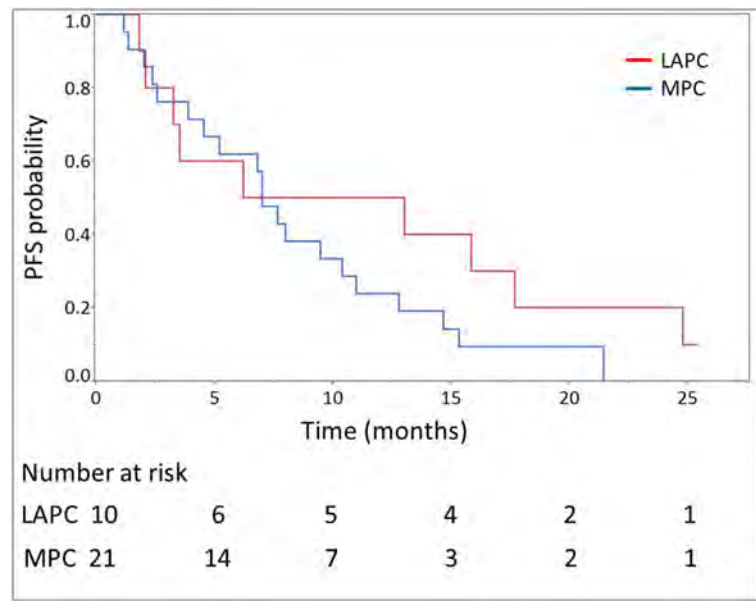


Figure 4: Progression-free survival (PFS) of 21 patients with metastatic pancreatic cancer (MPC) and 10 patients with locally advanced pancreatic cancer (LAPC) treated with modified FOLFIRINOX. The median PFS were 7.0 months (95% confidence interval, 3.9-11.0) and 9.6 (95% confidence interval, 1.8-17.7) in patients with MPC and LAPC, respectively.

Table 4: Adverse events of patients treated with unresectable advanced pancreatic cancer with modified FOLFIRINOX

Adverse events	Total	≥ Grade 3
	n (%)	n (%)
Hematological toxicities,		
Neutropenia	29 (93.5%)	26 (83.9%)
Febrile neutropenia	5 (16.1%)	5 (16.1%)
Thrombocytopenia	6 (19.4%)	2 (6.5%)
Anemia	14 (45.2%)	0 (0%)
Non-hematological toxicities		
Peripheral sensory neuropathy	18 (58.1%)	3 (9.7%)
Diarrhea	13 (41.9%)	2 (6.5%)
Anorexia	6 (19.4%)	2 (6.5%)
Vomiting	5 (16.1%)	1 (3.2%)
Nausea	4 (12.9%)	1 (3.2%)
Malaise	2 (6.5%)	0 (0%)
Mucositis oral	2 (6.5%)	0 (0%)
Erythema	1 (3.2%)	0 (0%)
Cholinergic syndrome	1 (3.2%)	0 (0%)
Interstitial pneumonia	1 (3.2%)	0 (0%)
Elevated AST	1 (3.2%)	0 (0%)

AST, aspartate aminotransferase

and anemia in this study (6.5 % and 0 %) were lower than those in the FX phase II/III study in France (9.1 % and 7.8 %) and phase II study in Japan (11.1% and 11.1%) [5, 6]. The rates of grade 3 or 4 non-hematological toxicities such as diarrhea, anorexia, nausea, vomiting and fatigue in this study tended to be lower in comparison with those in the two previous studies [5, 6]. The lower incidence of non-hematological toxicities, which are directly linked to the patients' symptoms, might be associated with the lower discontinuation rate (12.9%) from adverse events in our study. However, the rate of peripheral sensory neuropathy (9.7%) tended to be higher in this study than in the French (9.0%) and Japanese studies (5.6%) [5, 6]. One possible reason for this finding might be that the total dose of oxaliplatin in our study might have been higher than in the other 2 studies, since the median number of treatment cycles in our study was 13, which was larger than that in the other studies.

In 2013, Von Hoff et al. reported that nab-paclitaxel plus GEM significantly improved the RR, OS, and PFS, compared to GEM in patients with metastatic pancreatic adenocarcinoma (the phase III MPACT study) [10]. However, there have been no clear evidence regarding which regimen, FX or nab-paclitaxel plus GEM, is

more effective as a first-line treatment in patients with unresectable advanced pancreatic cancer. Considering the higher adverse event rates of FX, it might be difficult to perform FX as a second-line treatment, at which time the patient condition is usually not as good as that during the first-line treatment. In that respect, a treatment strategy with FX as first-line treatment followed by nab-paclitaxel plus GEM as a second-line might be recommended, although further evaluation is required.

The UGT1A1 gene is responsible for the metabolism of SN-38, which is an active metabolite of irinotecan, and variants of UGT1A1 have been reported to intensify myelosuppression, such as severe neutropenia [6]. A study by Takahara et al [11], evaluating the associations of variants in the UGT1A1 gene with the safety and efficacy of irinotecan monotherapy for pancreatic cancer in a Japanese cohort showed higher rates of neutropenia and anorexia in patients with UGT1A1 *6 and/or *28. In our study, patients with homozygous UGT1A1*6 or UGT1A1*28, or heterozygous UGT1A1*6 and UGT1A1*28 were excluded, similar to in the Japanese phase II study of FX [6]. Considering insufficient data on the safety of the FX regimen in patients with homozygous UGT1A1*6 or UGT1A1*28, or

with heterozygous UGT1A1*6 and UGT1A1*28, as well as the higher rates of neutropenia-related adverse events in our study evaluating mFX, further modification of the irinotecan dose and intensive observation of the clinical course should be considered in patients with homozygous UGT1A1*6 or UGT1A1*28, or heterozygous UGT1A1*6 and UGT1A1*28, especially in Japanese patients.

This study had several limitations. First, both locally advanced and metastatic pancreatic cancers were enrolled in this study as unresectable advanced pancreatic cancer. Because of that, the OS might have tended to be better than that in the previous studies which included only metastatic pancreatic cancer, although the results of the subanalysis of metastatic cases still showed comparable efficacy with the FX phase II/III study in France [5] and phase II study in Japan [6]. Second, in our study, patients with homozygous UGT1A1*6 or UGT1A1*28, or heterozygous UGT1A1*6 and UGT1A1*28 were excluded, similar to in the Japanese phase II study of FX [6]; this might have affected the rates of adverse events, as compared with those in other studies without exclusion criteria related to the UGT1A1 status. Finally, since there was no comparing arm in this study, further comparison studies between mFX and other regimens including regular FX are required to confirm the efficacy and safety of mFX. On the other hand, the major strength of this study was its prospective multi-center study design.

In conclusion, this open-labeled phase II study showed that the RR, PFS, and OS of mFX in Japanese patients with unresectable advanced pancreatic cancer including both locally advanced and metastatic cancer were comparable to those of full-dose FX, and the rates of non-hematological adverse events were also well-controlled. However, the rates of hematological adverse events, especially neutropenia and FN, were not improved by initial dose reduction. Careful observation of the patients, especially during the first treatment cycle and in those with a biliary stent, is required to prevent the development of severe hematological adverse events. Further comparison studies are required to confirm the efficacy and safety of mFX.

PATIENTS AND METHODS

Study design

This study was designed as an open-label, multicenter prospective phase II study of first-line mFX for unresectable advanced pancreatic cancer. The primary endpoint was the RR. The secondary endpoints were OS, PFS, and the frequency and degree of adverse events. All patients provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board of each participating institution (Gifu University Hospital, 26-200; Gifu Municipal Hospital,

2014-222; Gifu Prefectural General Medical Center, 2014-171) and was registered at the UMIN Clinical Trials Registry (UMIN000015376).

Patient eligibility criteria

Patients were eligible if they had histologically proven adenocarcinoma or adenosquamous carcinoma of the pancreas; unresectable advanced pancreatic cancer, including locally advanced and metastatic cancer; an Eastern Cooperative Oncology Group performance status of 0 or 1; and age of 20-75 years. In this study, locally advanced pancreatic cancer was defined as either i) involvement of the celiac, supra mesenteric, common hepatic, or proper hepatic arteries, or ii) involvement of the portal vein or supra mesenteric vein which was considered as difficult for reconstruction, without clear evidence of distant metastasis based on enhanced computed tomography within 4 weeks of protocol entry. Further, to fulfill the eligibility criteria, patients were required to have an absolute neutrophil count $>2000/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$, hemoglobin $>9.0 \text{ g/dL}$, aspartate transaminase and alanine transaminase $<150 \text{ U/L}$, creatinine $<1.2 \text{ mg/dL}$, creatinine clearance $>50 \text{ mL/min}$, possible oral intake, and no electrocardiographic abnormalities within 4 weeks of protocol entry. The patients were excluded from the study if they met any of the following conditions: pulmonary fibrosis or interstitial pneumonia; watery stools; active infection; serious concomitant diseases; apparent pleural effusion or ascites; history of prior chemotherapy or radiation therapy; UGT genetic polymorphisms (homozygous UGT1A1*6 or UGT1A1*28, or heterozygous UGT1A1*6 and UGT1A1*28); metastasis to the central nervous system; synchronous double cancer or metachronous double cancer with a disease-free period <3 years; patients using atazanavir, flucytosine, phenytoin, or warfarin potassium; patients who were pregnant, lactating, or planning a pregnancy; those with serious mental disorders; and anyone considered ineligible by the investigators.

Treatment

Patients received mFX, consisting of oxaliplatin intravenously at 85 mg/m^2 for 2 hours, leucovorin intravenously at 400 mg/m^2 for 2 hours, irinotecan intravenously at 150 mg/m^2 for 90 minutes, and 5-FU intravenously at 2400 mg/m^2 over 46 hours. To prevent nausea and vomiting, aprepitant 125 mg was administered orally, and dexamethasone 6.6 mg and granisetron hydrochloride 3 mg were administered intravenously on day 1, followed by aprepitant 80 mg and dexamethasone 8 mg administered orally on days 2 and 3. The treatment was continued in repeating 14-day cycles as long as the regimen was tolerated and/or until disease progression, discontinuation decided by the investigators, or patient

refusal. For careful safety evaluation, all patients were admitted to the hospital until the administration of the second round of mFX. Granulocyte-colony stimulating factor (G-CSF) was not administered as prophylaxis against neutropenia or FN.

The treatment was delayed in case of one or more of the following: absolute neutrophil count $<1500/\text{mm}^3$, platelet count $<75,000/\text{mm}^3$, total bilirubin $>3.0 \text{ mg/dL}$, aspartate transaminase and alanine transaminase $>150 \text{ U/L}$, creatinine $>1.5 \text{ mg/dL}$, FN, grade ≥ 3 peripheral sensory neuropathy, and grade ≥ 3 diarrhea. The treatment was resumed upon recovery from these criteria. The dose of oxaliplatin and irinotecan were reduced based on the following criteria: delayed cycle due to absolute neutrophil count (ANC) $<1500/\text{mm}^3$, platelet count $<50,000/\text{mm}^3$, total bilirubin $>2.0 \text{ mg/dL}$, grade 2 peripheral sensory neuropathy, FN, and diarrhea with fever. The dose of oxaliplatin was reduced before that of irinotecan. The dose of 5-FU was reduced in the following cases: grade 3 or higher diarrhea, mucositis and palmar-plantar erythrodysesthesia syndrome. The dose reduction of oxaliplatin, irinotecan, and 5-FU were set to 65 mg/m^2 and 50 mg/m^2 , 120 mg/m^2 , and 1800 mg/m^2 and 1200 mg/m^2 , respectively. If grade 3 or higher peripheral sensory neuropathy occurred, oxaliplatin was omitted until recovery to grade 2 or lower peripheral sensory neuropathy; however, mFX could be continued without oxaliplatin. The dosage adjustment of mFX followed that in the above mentioned Japanese phase II study of FX [6], except for the difference in the initial dose. The treatment also could be delayed by the attending physician based on general condition or convenience of patients.

Assessment

Throughout the whole treatment course, the patients were assessed for their general condition and any possible adverse events by physical and blood examinations including complete blood count and blood chemical tests, generally once a week by the attending physicians. The carbohydrate antigen 19-9 levels were monitored at baseline and every 4 weeks. The treatment response was assessed by the radiologists at each center by comparing the computed tomography scans taken at baseline to scans taken at least every 12 weeks after treatment initiation. Adverse events were scored by using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The radiologic tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.0.

Statistical analysis

The RRs were defined as the best accomplished response rates. OS was calculated from the date of initiation of mFX to the date of death. PFS was

calculated from the date of initiation of mFX to the date of disease progression. The relative dose intensity was calculated as the ratio of the amount of drug actually administered to the amount of the standard regimen during the whole treatment period from the date of initiation to completion of mFX. The outcomes of OS, PFS, and RR were calculated with the corresponding 95% confidence interval (CI). OS and PFS were estimated using the Kaplan-Meier method. All statistical analyses were performed using JMP 10.0 (SAS Institute, Inc, Cary, NC, USA).

The RRs associated with GEM and FX were reported as 9.4% and 31.6%, respectively in the phase II/III study of FX in France [5]. In the phase II study of FX in Japan, the RR associated with FX was reported as 38.9% [6]. From the above results, the threshold RR and the expected RR were set at 9% and 35%, respectively. Subsequently, the sample size was calculated as 25 patients by one-arm binomial sample size calculation, with a power of at least 90% and a one-sided significance level of 2.5%. Accordingly, the target sample size was set as 28 patients to account for an omission rate of 10%.

Abbreviations

FX, FOLFIRINOX; AE, adverse event; mFX, modified FOLFIRINOX; GEM, gemcitabine; 5-FU, 5-fluorouracil; OS, overall survival; PFS, progression free survival; RR, response rate; FN, febrile neutropenia; G-CSF, granulocyte-colony stimulating factor; ANC, absolute neutrophil count; CI, confidence interval; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1.

Author contributions

Kensaku Yoshida and Takuji Iwashita wrote the manuscript. Kensaku Yoshida, Takuji Iwashita, Shinya Uemura, Akinori Maruta, Mitsuru Okuno, Nobuhiro Ando, Keisuke Iwata, Jyunji Kawaguchi, Tsuyoshi Mukai, and Masahito Shimizu managed the patients. Takuji Iwashita took the correspondence.

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CONFLICTS OF INTEREST

Kensaku Yoshida, Takuji Iwashita, Shinya Uemura, Akinori Maruta, Mitsuru Okuno, Nobuhiro Ando, Keisuke Iwata, Jyunji Kawaguchi, Tsuyoshi Mukai, Masahito Shimizu have nothing to declare.

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Appendix ZHANG02

ORIGINAL ARTICLE

Oxaliplatin plus irinotecan vs irinotecan as second-line treatment in pancreatic cancer patients: a randomized-controlled open-label Phase II study

Hangyu Zhang, Zhou Tong, Lulu Liu, Qihan Fu, Xudong Zhu, Xiaomeng Dai, Xuanwen Bao, Weijia Fang, Yi Zheng and Peng Zhao  *

Department of Medical Oncology, School of Medicine, First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, P. R. China

*Corresponding author. Department of Medical Oncology, School of Medicine, First Affiliated Hospital, Zhejiang University, 79 Qingchun Road, Hangzhou, Zhejiang 310000, P. R. China. Tel: +86-571-87235147; Email: zhaop@zju.edu.cn; oncologist@zju.edu.cn

Abstract

Background: Limited second-line therapeutic options are available for metastasis pancreatic cancer (mPC). We aimed to explore the efficacy and safety of oxaliplatin plus irinotecan (IROX) in mPC patients.

Methods: This is an open-label, Phase 2, randomized study of mPC patients (aged 18–75 years) who failed when using gemcitabine plus S-1 as first-line therapy. Block randomization with a block size of four was used to randomly assign patients (1:1) between October 2015 and December 2017 to receive either IROX (oxaliplatin 85 mg/m² and irinotecan 160 mg/m²) or irinotecan monotherapy (irinotecan 180 mg/m²) until disease progression, unacceptable adverse events, or consent withdrawal. The primary end point was overall survival, and the secondary end points were progression-free survival, overall response rate, and adverse event rate.

Results: A total of 74 patients were enrolled in this study, including 44 males and 30 females, with an average age of 61 years. The median overall survival was 10.2 and 6.7 months (adjusted hazard ratio [HR], 0.7; 95% confidence interval [CI], 0.4–1.2; $P = 0.20$) and the median progression-free survival was 5.1 and 2.3 months (adjusted HR, 0.4; 95% CI, 0.2–0.6; $P < 0.01$) in the IROX group and irinotecan group, respectively. The overall response rates were 18.4% (7/38) in the IROX group and 5.5% (2/36) in the irinotecan group ($P = 0.06$). Grade 3–4 adverse events occurred in 34% (13/38) of patients in the IROX group and 19% (7/36) of patients in the irinotecan group ($P = 0.15$).

Conclusions: IROX had no significant survival benefit over irinotecan monotherapy in our study. However, IROX reduced the risk of disease progression by 60%, with acceptable toxicity.

Key words: pancreatic cancer; second-line chemotherapy; randomized control trial; irinotecan; IROX

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer death, and the incidence rises by ~1% per year in both males

and females [1]. The 5-year survival rate of PC patients, ~10% for all stages combined, is poor, which is attributed to its poor biological behavior, difficulty in early detection, and lack of

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targeted therapy and individual therapy options [2]. The median survival time of patients with metastatic pancreatic cancer (mPC) usually ranges from 6 to 11 months [3].

Although various new drugs, including immune checkpoint inhibitors, have been tested in the treatment of PC, they ultimately failed in most studies. Even high microsatellite instability (MSI-H) mPC derives very limited benefit from immunotherapy [4]. The standard first-line therapies are gemcitabine-based chemotherapy and the FOLFIRINOX regimen for mPC patients with good performance status. The GEST study showed that the progression-free survival (PFS) in the gemcitabine plus S-1 (GS) group was significantly longer than that in the gemcitabine monotherapy group (median PFS, 5.7 vs 4.1 months, $P < 0.001$) and showed an overall survival (OS) advantage trend (median OS, 10.1 vs 8.8 months) [5]. Thus, GS is currently one of the first-line treatment regimens recommended by the Chinese Society of Clinical Oncology [6].

Regarding second-line treatments, there are no guideline-preferred treatments; other recommended regimens include liposomal irinotecan plus 5-fluorouracil, FOLFIRI and OFF [7, 8]. Although the Food and Drug Administration of the USA approved nanoliposomal irinotecan as a second-line option [9], it is not available in many countries including China. An appropriate second-line treatment is urgently needed by a large proportion of patients who progressed with GS or gemcitabine combined with capecitabine as an adjuvant or first-line therapy regimen. However, Asian patients are reported to experience more frequent hematologic toxicities than Western patients when treated with FOLFIRINOX [10]; a previous study suggested that a response to repeated use of fluorouracil is highly unlikely [11]. Therefore, we performed this randomized-controlled trial to explore the superiority of oxaliplatin plus irinotecan (IROX) over irinotecan monotherapy as a second-line option for mPC patients.

Patients and methods

Study population

Our study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China). Details about the study are available on ClinicalTrials.gov (NCT02558868). Written informed consents were signed by all patients. The inclusion criteria were as follows: patients with histologically confirmed pancreatic ductal adenocarcinoma who had progressed after first-line GS therapy or had metastasis within 6 months after adjuvant GS treatment; age ranging from 18 to 75 years; Karnofsky performance status of $\geq 70\%$; adequate renal, hepatic, and bone marrow function; and at least one measurable site on computed tomography or magnetic resonance imaging. The exclusion criteria are: prior or concurrent malignant disease within 5 years; prior use of study drugs; the presence of poorly controlled hypertension, diabetes, serious cardiovascular disease, or other chronic diseases; cardiovascular- or cerebrovascular-related events within 4 weeks before randomization; peripheral neurotoxicity more than Grade 2; or pregnancy or breastfeeding.

Study design

This prospective, open-label, Phase II trial assigned patients in a 1:1 ratio to the IROX group or irinotecan monotherapy group through block randomization with a block size of four. The IROX regimen contained both oxaliplatin (85 mg/m², 120 min) and

irinotecan (160 mg/m², 120 min) every 2 weeks. The irinotecan monotherapy regimen involved irinotecan (180 mg/m², 120 min) every 2 weeks. When Grade 3–4 adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) occurred, the dose of chemotherapy was reduced by 20%. Treatment was continued until disease progression or adverse reaction intolerance occurred or until informed consent was withdrawn for any reason.

Outcome measurement

All patients who received at least one cycle of chemotherapy were included in the analysis. We collected demographic data, tumor-site information, serum levels of carbohydrate antigen 19-9 (CA19-9), and surgery information at baseline, and dynamically recorded tumor characteristics.

The primary end point of this study was OS and the secondary end points were PFS, overall response rate (ORR), and AE rate according to CTCAE version 4.0. Tumor response was regularly assessed every 6 weeks and several patients with clinical progression were evaluated earlier according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [12]. An early CA19-9 response was defined as a decrease in the serum CA19-9 level from baseline after one cycle of treatment. PFS was defined as the time from the first treatment after randomization to the date of progression or the date of patient death. ORR was calculated as the ratio of patients with a response (partial response [PR] and complete response [CR]) to all patients. The disease control rate (DCR) was calculated as the proportion of patients with stable disease (SD), PR, and CR out of all patients. For patients lost to follow-up, the last observation time was censored.

Statistical analysis

We analysed the intention-to-treat population (excluding patients who withdrew prior to treatment and had no recorded treatment-related data). A one-sided log-rank test was performed to calculate the sample size of 80 patients (40 per group), with 80% power of a one-sided type I error rate of 0.1. PFS, and OS values were estimated from Kaplan-Meier curves and analysed by using the log-rank test to compare the cumulative survival durations. Univariate analysis was first performed between each variable and PFS/OS, and multivariate analysis was then performed with stepwise Cox proportional hazards regression modeling for variables of interest with a P -value of < 0.10 . Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to express the relative risks. $P < 0.05$ was considered statistically significant for all tests. IBM SPSS Statistics (Version 20.0; IBM Corp, New York, USA) was used for the analyses. Figures were created using GraphPad Prism 7 (GraphPad Software, CA, USA).

Results

Patient characteristics

Between October 2015 and December 2017, a total of 126 patients were screened, of whom 46 did not meet the inclusion criteria because their first-line treatment was not the GS regimen or other reasons, and 6 patients who met the inclusion criteria withdrew their informed consent prior to treatment. Ultimately, 74 patients were enrolled in this study and available for further analysis (Figure 1). At the final follow-up in

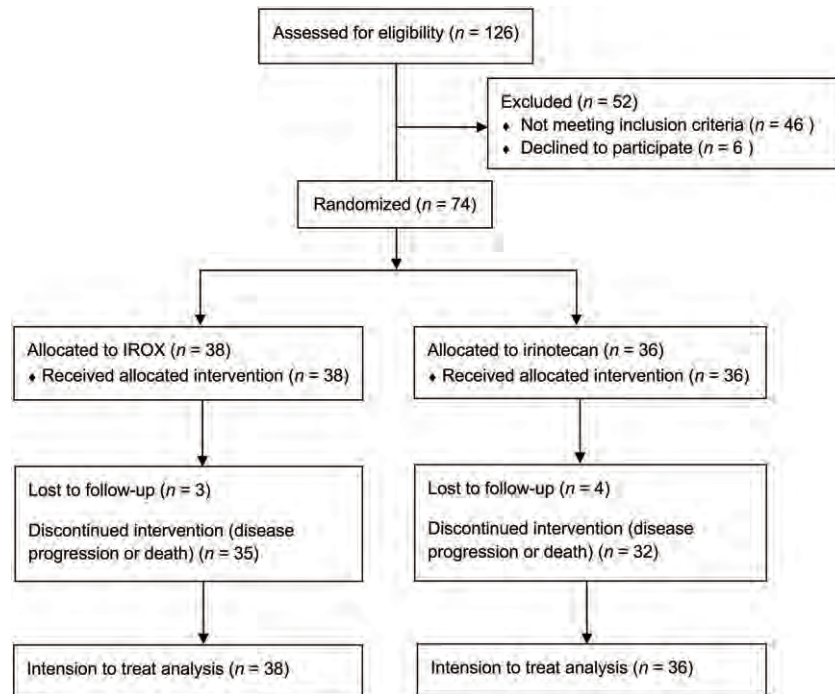


Figure 1. CONSORT flow diagram.

September 2020, all but seven censored patients had died and reached a mature survival time.

Baseline characteristics are shown in Table 1. There were no significant differences in age, sex, primary tumor site, metastatic organ sites, blood type, or baseline serum CA19-9 levels between the two groups. The IROX group had a higher proportion of male patients, although the difference was statistically non-significant. Most patients in both groups had elevated serum CA19-9 levels at baseline (IROX: 84%; irinotecan: 80%). Pancreatic head PC occurred in 42.1% (16/38) of patients in the IROX group and 41.7% (15/36) of patients in the irinotecan group. The proportions of patients who previously underwent PC surgery were 63% (IROX) and 66% (irinotecan). In most patients (65%), metastasis was found in only one organ, which was most commonly the liver or abdominal lymph nodes.

Efficacy and survival

The IROX group and the irinotecan monotherapy group received an average of 6.3 and 5.4 cycles of treatment, respectively. The highest numbers of treatment cycles in the IROX group and monotherapy group were 16 and 17 cycles, respectively. Sixty-five out of 74 patients had complete radiologic assessments; the remainder could not be evaluated due to rapid clinical disease progression or other reasons (Figure 2A and B). The ORRs were 18.4% (7/38) and 5.5% (2/36) in the IROX group and irinotecan group, respectively, and the DCRs were 57.9% and 47.2%, respectively. There were no significant differences in the ORR ($P = 0.06$) or DCR ($P = 0.05$). A greater proportion of early serum CA19-9 responses was observed in the IROX group than in the irinotecan group, but the difference was non-significant (52.6% vs 44.4%, $P = 0.48$).

During the follow-up, 67 of the 74 patients died and 7 patients were lost to follow-up. The median survival time was 9.1 months for all patients, 10.2 months (95% CI, 2.2–11.2 months) for patients in the IROX group, and 6.7 months

Table 1. Baseline characteristics of all enrolled patients

Variable	IROX	Irinotecan	P-value
Age			
Median (IQR), years	59.5 (55–69.5)	62 (54–64.2)	
≤60 years	16 (42%)	17 (47%)	0.65
>60 years	22 (58%)	19 (53%)	
Sex			
Male	26 (68%)	18 (50%)	0.11
Female	12 (32%)	18 (50%)	
Body mass index			
Median (IQR)	20.2 (18.1–20)	20.2 (18.1–22.1)	
Tumor site			
Pancreatic head	16 (42%)	15 (42%)	0.97
Pancreatic body or tail	22 (58%)	21 (58%)	
Metastatic sites			
Single organ	24 (63%)	24 (67%)	0.85
Multiple organs	14 (37%)	12 (33%)	
Prior surgery			
Performed	24 (63%)	22 (61%)	0.85
Not performed	14 (37%)	14 (39%)	
Baseline CA19-9			
≤37 U/mL	6 (16%)	7 (19%)	0.78
>37 U/mL	32 (84%)	29 (81%)	
Blood type			
A	20 (53%)	17 (47%)	0.81
B	6 (16%)	5 (14%)	
O	10 (31%)	10 (39%)	
AB	2	4	
HBV infection			0.94
Yes	3 (8%)	3 (9%)	
No	35 (92%)	32 (91%)	

IROX, irinotecan plus oxaliplatin; IQR, interquartile range.

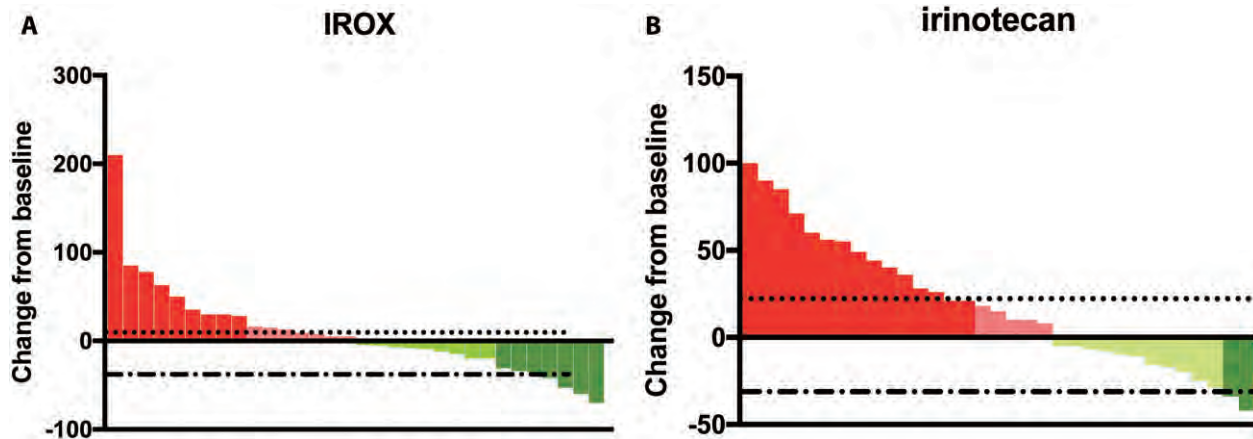


Figure 2. Waterfall plot of the tumor-size change of the IROX group (A) and irinotecan monotherapy group (B). IROX, oxaliplatin plus irinotecan.

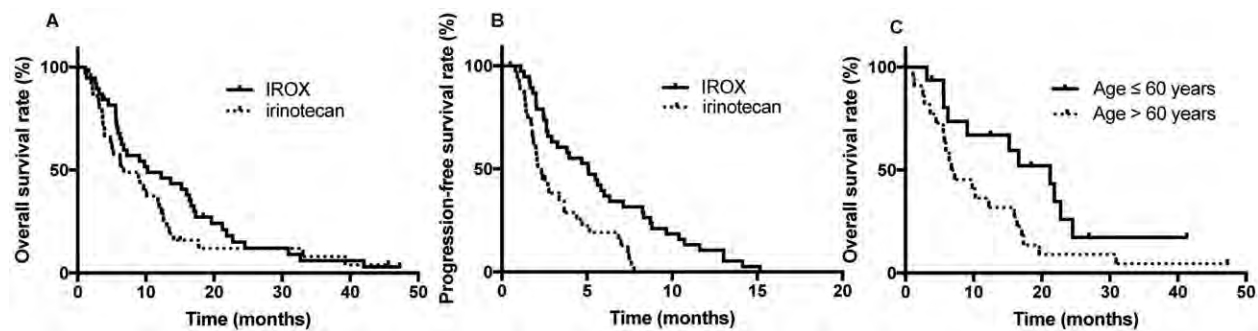


Figure 3. Kaplan-Meier plot for overall survival (A) and progression-free survival (B) according to the treatment arm. Kaplan-Meier plot for (C) IROX group patients according to age (>60 years). IROX, oxaliplatin plus irinotecan.

(95% CI, 2.6–17.8 months) for patients in the irinotecan monotherapy group ($P=0.20$) (Figure 3A). The median PFS was 5.1 months (95% CI, 2.7–7.4 months) in the IROX group and 2.3 months (95% CI, 1.8–2.8 months) in the irinotecan group ($P<0.01$) (Figure 3B).

Early serum CA19-9-responsive patients had an advantageous trend in both PFS (4.4 vs 2.1 months) and OS (10.1 vs 6.2 months). In the irinotecan group, an early serum CA19-9 response was significantly associated with survival ($P=0.07$). The OS of primary pancreatic head PC was significantly shorter than that of pancreatic body or tail PC (5.8 vs 10.2 months, $P=0.04$). In the irinotecan group, the survival benefit was comparable for patients aged >60 years and younger patients (median overall survival (mOS): 10.1 vs 6.2 months, $P=0.17$). In the IROX group, the survival benefit was significantly increased for patients younger than 60 years compared with the patients aged >60 years (mOS: 21.2 months vs 6.7 months, $P=0.04$) (Figure 3C). Regarding metastatic organs, the more metastatic organs there were, the worse the prognosis was, but there was no significant difference (mOS: 6.7 vs 10.1 months, $P=0.39$). Univariate analysis showed that survival was not significantly associated with prior surgery, blood type, or baseline serum CA19-9 levels in all enrolled patients. With the exception of the older patients (>60 years), the survival benefit of IROX was supported in almost all other conditions (Figure 4).

Toxicity and safety

Grade 3–4 AEs were observed in 34% (13/38) of patients in the IROX group and 19% (7/36) of patients in the irinotecan group;

23% (9/38) of patients in the IROX group and 11% (4/36) of patients in the irinotecan group underwent dose reduction during treatment. No treatment-related mortality occurred. The most common AE was neutropenia; febrile neutropenia was found in two patients in the IROX group but was not found in any of the patients in the irinotecan monotherapy group. The rates of fatigue, nausea and vomiting, and other non-hematologic toxicities were relatively higher in the IROX group than in the irinotecan monotherapy group (Table 2).

Discussion

This randomized Phase II study evaluated the efficacy, tolerability, and safety of irinotecan monotherapy or irinotecan combined with oxaliplatin as a second-line treatment in mPC patients. The study did not meet its primary study end point. Efficacy and AEs were assessed in all enrolled patients. In this study, second-line treatment, either irinotecan alone or combined with oxaliplatin, prolonged survival in mPC patients. We found that, compared with irinotecan monotherapy, IROX showed a significant advantage in median progression free survival (mPFS) (5.1 vs 2.3 months), and a survival benefit trend in mOS (10.2 vs 6.7 months). Further analysis showed a significant increase in survival benefit of IROX in younger patients (<60 years). The treatment was well tolerated in both groups, and the occurrence rate of Grade 3–4 AEs was acceptable (8%–23%).

Most PC patients are diagnosed at an advanced stage, so systemic chemotherapy plays an important role in the overall

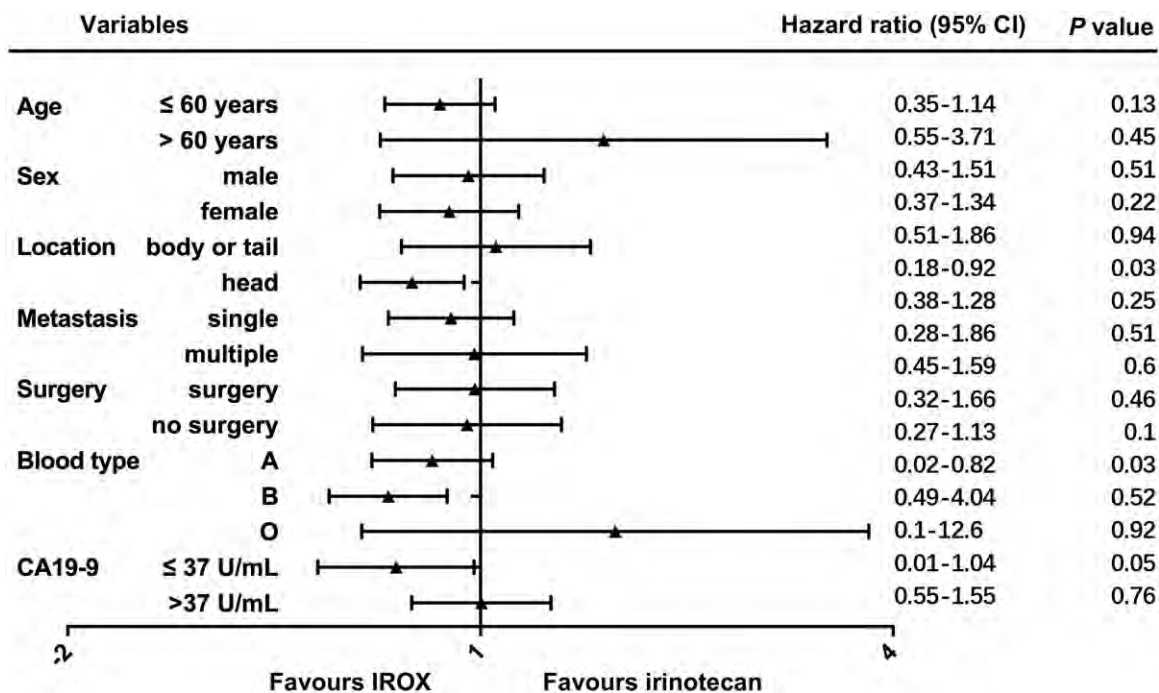


Figure 4. Subgroup analyses of overall survival. CI, confidence interval; IROX, oxaliplatin plus irinotecan.

Table 2 Grade 3–4 adverse events in two treatment groups

Adverse event	IROX group	Irinotecan group	P-value
Hematologic			
Neutropenia	9 (23%)	3 (8%)	0.73
Febrile neutropenia	2 (5%)	0 (0%)	0.16
Thrombocytopenia	6 (15%)	1 (2%)	0.06
Anemia	5 (13%)	3 (8%)	0.50
Non-hematologic			
Fatigue	6 (15%)	3 (8%)	0.32
Vomiting	6 (15%)	4 (11%)	0.55
Nausea	5 (13%)	3 (8%)	0.79
Liver function injury	2 (5%)	1 (2%)	0.59
Peripheral neuropathy	2 (5%)	0 (0%)	0.16
Diarrhea	2 (5%)	1 (2%)	0.59

All values are presented as number of patients followed by percentage in parentheses.

IROX, irinotecan plus oxaliplatin.

management of PC. For second-line treatment, there have been encouraging regimens proven to improve both OS and quality of life [13–15]. The National Comprehensive cancer Network (NCCN) guidelines recommend fluorouracil-based regimens after progression with first-line gemcitabine-based therapy, including FOLFIRI, FOLFOX, and FOLFIRINOX. Second-line FOLFOX or FOLFIRI have a median survival of ~6 months [16, 17]. FOLFIRINOX extends the median survival to 9.2 months, but it is recommended only for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 due to unbearable adverse effects [15]. Therefore, several studies have modified the FOLFIRINOX regimen to reduce its AEs and preserve efficiency. Although various dose-modification regimens exist [18, 19], the regimen without fluorouracil and with only oxaliplatin and irinotecan has not been explored before. In our study, the median OS of patients receiving IROX was 10.2 months, which

was slightly longer than that of patients receiving mFOLFIRINOX (mOS, 9.2 months), possibly due to our increased drug-dose intensity (oxaliplatin 85 mg/m², irinotecan 150 mg/m²) compared with mFOLFIRINOX (oxaliplatin 65 mg/m², irinotecan 135 mg/m²) and the development of support treatment.

Grade 3–4 AEs were more common in the IROX group, with the highest occurrence rate of neutropenia (23% and 8%, respectively). The occurrence rate of AEs in our study was reduced compared with that of mFOLFIRINOX in previous studies, where Grade 3–4 neutropenia accounted for ~28%–29% of cases [20]. This finding indicates that, after the removal of fluorouracil, IROX may be well tolerated in patients with relatively poor physical states.

Our study still has several limitations. First, it was a single-center Phase II clinical study with a small sample size, and the conclusions need further validation. Second, with the increasing application of gemcitabine plus nab-paclitaxel and FOLFIRINOX, the number of patients who received GS as first-line treatment is decreasing, resulting in a limited number of patients fitting our study-inclusion requirements. Third, the AEs of IROX need to be further verified in future observational studies.

Overall, in this prospective controlled Phase II study, we failed to reach our primary end point. However, IROX showed significantly prolonged PFS over irinotecan monotherapy with acceptable AEs as second-line therapy for mPC. IROX might be an alternative option for some selected patients.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by H.Z., Z.T., and L.L. The first draft of the manuscript was written by H.Z. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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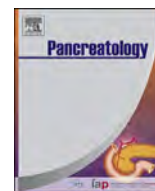
Conflict of Interest

The authors have no conflicts of interest to declare.

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Appendix ZHOU01



Delta HU is a potential marker to predict chemotherapy response for unresectable pancreatic ductal adenocarcinoma

Yizhang Zhou^{a,1}, Song Gao^{a,1}, Bodong Zhou^a, Shuai Yuan^a, He Ren^b, Yifei Wang^a, Xiaofan Guo^a, Jin Ren^c, Zhiqiang Chen^a, Jihui Hao^{a,*}

^a Department of Pancreatic Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China

^b Department of Gastroenterology, Center of Tumor Immunology and Cytotherapy, Medical Research Center, The Affiliated Hospital of Qingdao University, Qingdao, China

^c Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Taiyuan, China

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ABSTRACT

Background: FOLFIRINOX and gemcitabine plus albumin-bound paclitaxel (AG) regimens are recommended as first-line therapy for both locally advanced and metastatic pancreatic cancer. However, there were no specific markers to conduct personalized regimen choice. The research is to assess delta Hounsfield unit (delta HU), which is the difference in CT attenuation value (in HU) between enhanced and nonenhanced phase of region of interest, as a marker for predicting chemotherapy response of unresectable pancreatic cancer.

Methods: A total of 179 unresectable pancreatic cancer patients were enrolled in the study. Kaplan-Meier analysis and COX regression analysis were performed for progression-free survival (PFS) and overall survival. The differences of clinical characteristics were analyzed by χ^2 test. Microvessel density (MVD) was calculated by immunohistochemistry staining of CD34.

Results: Delta HU was an independent risk factor for unresectable pancreatic cancer ($P = 0.017$, HR 0.672, 95%CI 0.485–0.930). Patients with higher delta HU were associated with better PFS ($P = 0.004$). For modified FOLFIRINOX (mFOLFIRINOX) group, delta HU was an independent risk factor ($P = 0.045$, HR 0.571), but not for AG group ($P = 0.473$, HR 0.855). Delta HU was correlated with stroma MVD ($P = 0.000$, $R = 0.483$), not with parenchyma MVD ($P = 0.074$, $R = 0.199$).

Conclusions: Delta HU was a marker predicting chemotherapy response for unresectable pancreatic cancer. Higher delta HU was associated with better survival for patients receiving mFOLFIRINOX rather than AG. The delta HU was positively correlated with stroma MVD, explaining the relationship between delta HU and prognosis.

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Abbreviations: AG, gemcitabine plus albumin bound paclitaxel; CECT, contrast-enhanced computed tomography; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HU, Hounsfield unit; Δ HU, delta HU, delta Hounsfield unit; HR, hazard ratio; mFOLFIRINOX, modified FOLFIRINOX; MVD, microvessel density; NCCN, National Comprehensive Cancer Network; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; ROI, region of interest; TER, tumor enhanced rate.

* Corresponding author. Huan-Hu-Xi Road, Hexi District, Tianjin City, 300060, China.

E-mail address: haojihui@tjmuch.com (J. Hao).

¹ These authors contributed equally to this work and should be considered co-first authors.

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Introduction

Pancreatic cancer is a fatal malignancy with a 5-year survival rate of 10% [1]. Radical surgery is the potential curative treatment, whereas 80%–85% patients cannot undergo surgical resection, in which detected with locally advanced pancreatic cancer or metastatic cancer initially [2]. To prolong survival and improve quality of life, FOLFIRINOX (oxaliplatin, leucovorin, irinotecan and fluorouracil) and gemcitabine plus albumin-bound paclitaxel (AG) are recommended as first-line therapy for both locally advanced and metastatic pancreatic cancer by National Comprehensive Cancer Network (NCCN) guidelines [3]. However, there were no accomplished clinical trials to compare two regimens and no specific

markers to conduct personalized regimen choice. It is urgent to seek a marker predicting chemotherapy response and selecting proper regimen.

Contrast-enhanced computer tomography (CECT) is the most common detection of initial diagnosis and applied to evaluate chemotherapy response. CT value has been used to evaluate chemotherapy response and prognosis for advanced pancreatic ductal adenocarcinoma (PDAC). Shin Il Kim et al. demonstrated that the delta Hounsfield unit (HU) was defined that arterial phase HU of region of interest (ROI) subtracted HU in pre-contrast phase, with cutoff of 31.5 and 18 respectively applied to predict chemotherapy responders in pancreatic tumor (sensitivity 62.8%, specificity 91.3%) and liver metastasis (sensitivity 76.0%, specificity 85.7%) [4]. Zhi-qiang Meng et al. confirmed that locally advanced pancreatic cancer patients with tumor enhanced rate (TER) less than 80.456% had 3.587-fold risk of poorer overall time (OS) than who with TER more than 80.456% [5]. However, in unresectable patients with regular chemotherapy, it was unclear whether prognosis was related to delta Hounsfield unit (delta HU, Δ HU), which is the difference in CT attenuation value (in HU) between enhanced and nonenhanced phase of ROI.

In regard to the correlation between CT value and histology, Xiao-Hua Chen et al. reported that the HU enhancement was negatively related to pathological grade ($P < 0.05$, $R = -0.784$) and tumor microvessel density (MVD, $P < 0.05$, $R = -0.790$) in pancreatic cancer [6]. On the contrary, Yuki Hattori et al. reported that aorta ratio was correlated with MVD positively ($P = 0.033$, $R = 0.649$) [7]. Also, Zhongqiu Wang et al. reported that HU enhancement was correlated with pathological grades ($P = 0.001$, $R = 0.7857$) and MVD ($P < 0.05$, $R = 0.3613$) [8]. The conflicting correlation of delta HU and MVD should be proved by histopathological characteristics explaining the relationship between delta HU and prognosis in different regimens.

The purpose of study was to assess the prognosis prediction value of Δ HU in unresectable pancreatic cancer personalization therapy, exploring the potential underlying mechanisms of the correlation between delta HU and prognosis by histopathology.

Methods and materials

Patients

The retrospective study was approved by the institutional ethics committee of Tianjin Medical University Cancer Institute and Hospital. Written informed consents were obtained from all participants. 179 unresectable PDAC patients between June 2016 and January 2019 were enrolled, who underwent AG or modified FOLFIRINOX (mFOLFIRINOX) chemotherapy at Tianjin Medical University Cancer Institute and Hospital. Following up has continued 18–40 months.

The inclusion criteria included: locally advanced and metastatic stage pancreatic cancer assessed according to NCCN guideline; PDAC pathologically diagnosed by tumor biopsy; treated initially with AG or mFOLFIRINOX; underwent at least three cycles chemotherapy; estimated CECT every three cycles or three months after chemotherapy finished.

Exclusion criteria included: underwent radical resection; diagnosed of other histologic types of pancreatic neoplasms or not with pathological diagnosis; with double primary tumors or other tumors; received palliative surgery or additional radiotherapy or other therapy before; treated with other second-line regimens; treated less than three cycles; cannot examine by CECT due to any reasons; without complete follow-up information or clinical information.

81 patients who were performed pancreatic cancer radical

resection and received adjuvant chemotherapy were enrolled in another group to explore the correlation between MVD and Δ HU. All patients were pathologically diagnosed of PDAC and without neoadjuvant therapy. Following up had continued 18 months–48 months.

Chemotherapeutic regimens

All patients received normative chemotherapy recommended by NCCN guideline. For AG regimen, a 30-min intravenous infusion of albumin bound paclitaxel was given at dose of 125 mg per square meter, following an infusion of gemcitabine at dose of 1000 mg per square meter of body-surface area, on days 1, 8 every 3 weeks. Patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and 1 were adopted mFOLFIRINOX every 2 weeks, which was consisted of oxaliplatin 65 mg, leucovorin 400 mg, irinotecan 150 mg and fluorouracil 2400 mg per square meter. Oxaliplatin delivered as a 2-h intravenous infusion, following leucovorin a 2-h intravenous infusion, after 30 min, following a 90-min intravenous infusion of irinotecan, immediately following by fluorouracil continuously intravenous infusion over a period of 46 h.

Contrast-enhanced CT measurement and delta HU definition

CECT was performed with a 64-slice CT scanner (GE Discovery CT, General Electric, WI, USA) during breath-hold. Using a high-pressure syringe, 90–100 ml (1.0–2.0 ml/kg) of nonionic contrast material (standard iodine concentration, 300 mg/mL, Ultravist 300; Bayer Health Care, Wayne, NJ) was injected intravenously at 2 ml/s. Nonenhanced CT with 1.5 mm section thickness was recorded before enhanced scan. Enhanced phase was recorded at 60sec with a thickness of 1.5 mm.

Three 1 cm $\times$ 1 cm ROIs were chosen in the maximum tumor area to measure the CT value by two experienced radiologists. Cystic areas, necrotic areas and margin near areas were avoided. Both CT value in nonenhanced and enhanced phase of ROIs were measured. Delta HU is the difference in CT attenuation value (in HU) between enhanced and nonenhanced phase of ROI. Two sample graphs were presented in Fig. 1a,b. Average over delta HU of three ROIs was recorded for a patient. In unresectable PDAC group, we set Δ HU median 27 as cutoff value, in addition, we set median 33 as cutoff value in resected group.

Immunohistochemistry and MVD assessment

MVD was calculated by immunohistochemical staining of CD34. Tumor specimens were obtained at the time of surgery. After deparaffination, pathological sections were heated with high pressure for 2min to retrieve antigens in EDTA buffer. The endogenous peroxidase activity was blocked with 3% H_2O_2 for 30 min at room temperature without light. Following PBS washing, primary antibodies were incubated with anti-CD34 antibodies (ab81289, 1:2500; Abcam, Cambridge, MA, USA) overnight at 4 °C. The antibody binding was detected using peroxidase-conjugated secondary antibody at 37 °C for 30 min. A DAB Substrate Kit (ZLI-9019, ZSGB-BIO) was used for the chromogenic reaction.

Parenchyma micro vessels were defined as vessels within malignant ducts less than 100 μ m, while the stroma micro vessels were defined as vessels away from malignant ducts more than 100 μ m. Total MVD was the average of parenchyma and stroma MVD. MVD were calculated according to Weidner correction MVD measure method. Three most vascularized regions, named hot spots, were selected at a low magnification ($\times 100$). MVD was counted in each region at high magnification ($\times 400$) by staining

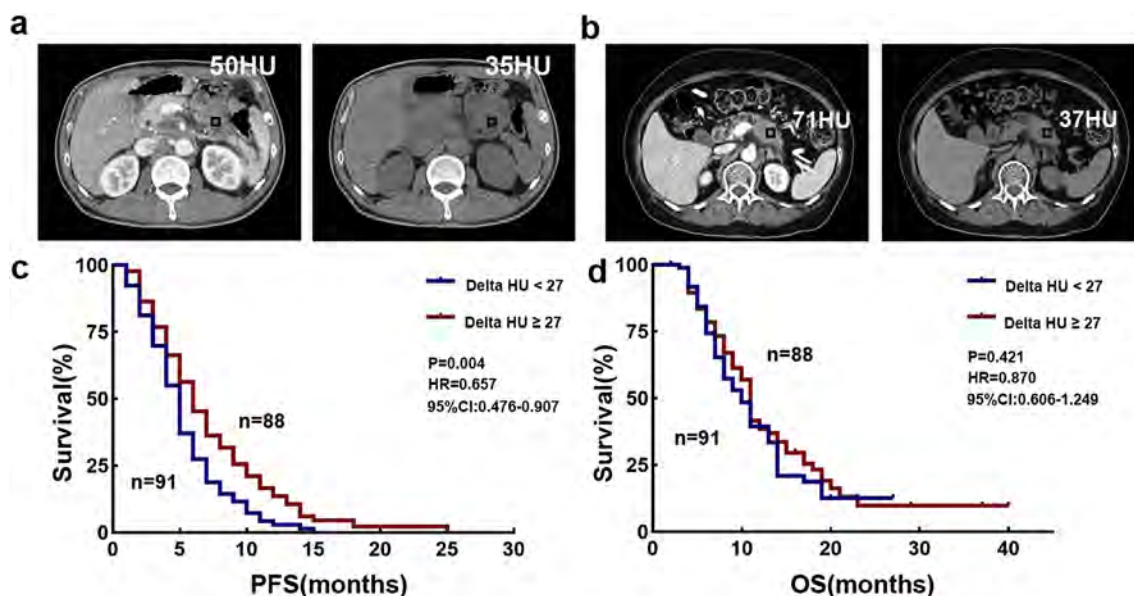


Fig. 1. Delta HU was significantly associated with PFS in unresectable patients. Two samples were presented explaining measurement of delta HU, a 64-year old female advanced PDAC patient with lower Δ HU (a) and a 56-year-old male advanced PDAC patient with higher Δ HU (b), PFS(c) and OS (d) survival curves of Δ HU < 27 and ≥ 27 in 179 patients. delta HU, Δ HU, delta Hounsfield unit; PFS, progression-free survival; PDAC, pancreatic ductal adenocarcinoma.

micro vessels of CD34. The average counts of three views were recorded. Any single endothelial cell or cell mass stained with antibodies, whether or not forming a lumen, was considered a countable micro vessel. Vessels with smooth muscle wall or diameter larger than 8 red blood cells were excluded. All the measurement assessed by two experienced pathologists. We set median as cutoff for each MVD, 26 for stroma MVD (range 11–57), 31 for parenchyma MVD (range 14–63) and 29 for total MVD (range 14–51).

Other factors measurement

Baseline target lesions of all patients were recorded according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) less than 2 weeks before the beginning of chemotherapy by CECT. Gender, age and other characteristic were collected from medical records. ECOG PS was assessed objectively by experienced oncologists before therapy. Baseline CA19-9 was detected by ELISA with the cutoff of 37U/ml. Tumor size, lymph nodes, tumor location and metastasis were assessed by baseline CECT. Clinical TNM stage confirmed according to AJCC TNM staging of pancreatic cancer (8th ed., 2017). Differentiation was confirmed by fine needle aspiration tissue or surgical specimen by pathologists. Therapy response was identified by RECIST 1.1 for regular follow-up.

Statistical analysis

All statistical analyses were performed using SPSS Statistics Program (version 22.0; IBM, Armonk, NY, USA). The clinical characteristics demonstrated with proportion for classified variable, analyzed using χ^2 test between groups. The cutoff of Δ HU was determined by the means of 27 for unresectable group and 33 for resected group. Survival curves were generated by Kaplan-Meier analysis and comparison was analyzed by Log-Rank tests or Breslow tests. Cox regression models for univariate and multivariable analyses were used to identify prognostic factors and estimate hazard ratio (HR) based on progression-free survival (PFS). We considered a two-side P value less than 0.05 to be significant. The P

value of factor in univariate analysis less than 0.2 was considered in multivariate COX analysis. Correlation between MVD and Δ HU were calculated using Spearman correlation analysis. Paired *t*-tests were used for pairwise comparisons in stroma, parenchyma, total MVD.

Results

Delta HU is significantly correlated to prognosis in unresectable PDAC

The baseline characteristics of 179 patients were compared according to the Δ HU, only the factor of age showed significant difference ($P = 0.021$, Table 1). Baseline characteristic of gender, T stage, N stage, M stage and TNM stage, tumor location, differentiation, ECOG PS, chemotherapy regimens, CA19-9 showed no difference in two groups ($P > 0.05$).

On univariate COX analysis among factors (Table 2), gender (HR 1.347, 95% CI 0.971–1.870, $P = 0.075$), clinical T stage (HR 1.354, 95% CI 0.969–1.893, $P = 0.076$), ECOG PS (HR 1.520, 95% CI 1.097–2.106, $P = 0.012$) and Δ HU (HR 0.645, 95% CI 0.466–0.892, $P = 0.008$) were associated with prognosis. ECOG PS (HR 1.458, 95% CI 1.051–2.023, $P = 0.024$) and Δ HU (HR 0.672, 95% CI 0.485–0.930, $P = 0.017$) were independent risk factors for PFS of unresectable PDAC identified by multivariate COX analysis. Gender and clinical T stage did not affect the prognosis. Patients with Δ HU ≥ 27 ($n = 88$) had 0.672-fold risk of shorter PFS compared with those lower than 27 ($n = 91$).

The median PFS of patients with Δ HU < 27 was 5 months, showing poorer survival than 6 months of Δ HU ≥ 27 ($P = 0.004$, HR 0.657, 95% CI 0.476–0.907, Fig. 1c). Although, the significant difference didn't find in OS of two groups ($P = 0.421$, HR 0.870, 95% CI 0.606–1.249, Fig. 1d). Delta HU was significantly associated with PFS in unresectable PDAC.

The relationship between delta HU and prognosis in different regimens

Given to the difference in the chemo regimens, subgroup

Table 1
Characteristics of unresectable patients at baseline.

Characteristic	Delta HU < 27		Delta HU ≥ 27		P Value
	(N = 91)		(N = 88)		
	n (%)		n (%)		
Gender					0.063
female	32	(35.2)	43	(48.9)	
male	59	(64.8)	45	(51.1)	
Age, yr					0.021*
< 60	54	(59.3)	37	(42.0)	
≥ 60	37	(40.7)	51	(58.0)	
Clinical T stage					0.496
T1	1	(1.1)	2	(2.3)	
T2	31	(34.1)	38	(43.2)	
T3	29	(31.9)	26	(29.5)	
T4	30	(33.0)	22	(25.0)	
Clinical N stage					0.920
N0	48	(52.7)	44	(50.0)	
N1	32	(35.2)	32	(36.4)	
N2	11	(12.1)	12	(13.6)	
Clinical M stage					0.898
M0	22	(24.2)	22	(25.0)	
M1	69	(75.8)	66	(75.0)	
TNM stage					0.898
III	22	(24.2)	22	(25.0)	
IV	69	(75.8)	66	(75.0)	
Tumor location					0.519
head/neck	36	(39.6)	39	(44.3)	
body/tail	55	(60.4)	49	(55.7)	
Differentiation					0.407
moderately	30	(33.0)	24	(27.3)	
poorly	61	(67.0)	64	(72.7)	
ECOG PS					0.584
0	43	(47.3)	38	(43.2)	
1	48	(52.7)	50	(56.8)	
Chemotherapy regimen					0.777
AG	55	(60.4)	55	(62.5)	
mFOLFIRINOX	36	(39.6)	33	(37.5)	
CA19–9, U/ml					0.924
≤ 37	16	(17.6)	15	(17.0)	
> 37	75	(82.4)	73	(83.0)	

delta HU, delta Hounsfield unit; ECOG PS, Eastern Cooperative Oncology Group performance status; AG, gemcitabine plus albumin bound paclitaxel; mFOLFIRINOX, modified FOLFIRINOX.

analyses were performed. The group of AG (n = 110, [Supplementary Table 1](#)) and mFOLFIRINOX (n = 69, [Supplementary Table 2](#)) were separately compared with clinical characteristics by ΔHU < 27 and ≥ 27, no statistically significant differences were detected in AG group, whereas gender (P = 0.041), age (P = 0.044) showed significant difference in mFOLFIRINOX group.

In AG group, after performing univariate Cox regression analysis ([Table 3](#)), data on the variables of clinical T stage (P = 0.132, HR 1.466, 95%CI 0.892–2.410), clinical M stage (P = 0.113, HR 1.499, 95%CI 0.909–2.473), TNM stage (P = 0.113, HR 1.499, 95%CI 0.909–2.473), tumor location (P = 0.114, HR 0.701, 95%CI 0.452–1.089) were entered into multivariate Cox regression analysis of PFS for AG patients. Although it was not related to PFS (P = 0.241, HR 0.780, 95%CI 0.514–1.182), delta HU as the major subject was included in multivariate COX analysis. The result of multivariate COX analysis showed that clinical T stage (P = 0.006, HR 2.150, 95%CI 1.250–3.699), clinical M stage (P = 0.004, HR 2.318, 95%CI 1.316–4.082), TNM stage (P = 0.004, HR 2.318, 95%CI 1.316–4.082), tumor location (P = 0.012, HR 0.551, 95%CI 0.347–0.875) were independent risk factors for AG patients. Unexpectedly, no significant differences were demonstrated in delta HU (P = 0.473, HR 0.855, 95%CI 0.558–1.311).

While the result was diverse in mFOLFIRINOX group ([Table 4](#)). Gender (P = 0.073, HR 1.693, 95%CI 0.952–3.012), differentiation

(P = 0.185, HR 0.702, 95%CI 0.416–1.185), ECOG PS (P = 0.002, HR 2.400, 95%CI 1.379–4.179) and ΔHU (P = 0.009, HR 0.490, 95%CI 0.287–0.836) were associated with PFS in univariate COX analysis. Furthermore, ECOG PS (P = 0.012, HR 2.065, 95%CI 1.169–3.646) and ΔHU (P = 0.045, HR 0.571, 95%CI 0.330–0.988) were independent prognostic factors for mFOLFIRINOX group.

With Kaplan-Meier survival analysis, different results showed in two regimens. In AG group, no significant statistical difference was observed among patients with ΔHU < 27 or ≥ 27 in PFS (5mo vs. 6mo, P = 0.190, HR 0.786, 95%CI 0.521–1.186, [Fig. 2a](#)) and OS (11mo vs. 11mo, P = 0.347, HR 1.246, 95%CI 0.766–2.026, [Fig. 2b](#)). In mFOLFIRINOX group, patients with ΔHU < 27 had a shorter median PFS (4mo vs. 6mo, P = 0.004, HR 0.524, 95%CI 0.313–0.878, [Fig. 2c](#)) and OS (9mo vs. 11mo, P = 0.012, HR 0.538, 95%CI 0.310–0.934, [Fig. 2d](#)). The delta HU was associated with survival in mFOLFIRINOX group, but not in AG group.

Relationship between delta HU and MVD

To investigate underlying reasons for predicting prognosis by delta HU, we focused on histopathological characteristic of PDAC, based on previous results, we verified the relationship between ΔHU and MVD in resectable PDAC group. MVD was calculated by immunohistochemical staining of CD34 in both parenchyma and stroma areas of 81 patients ([Fig. 3a](#)). The stroma MVD was significantly less than parenchyma MVD in PDAC (P < 0.05, [Fig. 3b](#)). Compared the clinical characteristics of these 81 patients according to ΔHU ([Supplementary Table 3](#)), pathology T stage was associated with ΔHU (P = 0.041), meaning that the patients with ΔHU ≥ 33 had smaller masses. Moreover, the stroma MVD (P = 0.000) and total MVD (P = 0.014) were relevant to delta HU. The Spearman correlation between ΔHU and stroma MVD (P = 0.000, R = 0.483, [Table 5](#)) or total MVD (P = 0.001, R = 0.370) was significant, while no significance was indicated in the correlation between ΔHU and parenchyma MVD (P = 0.074, R = 0.199).

In resected PDAC patients, the prognostic significance of ΔHU was identified by Kaplan-Meier analysis in disease-free survival (DFS, 7mo vs. 12mo, P = 0.032, HR 0.609, 95%CI 0.370–1.002, [Fig. 3c](#)), not in OS (35mo vs. 29mo, P = 0.994, HR 1.003, 95%CI 0.487–2.065, [Supplementary Fig 1a](#)). Significant statistical difference of DFS also was observed in stroma MVD (9mo vs. 11mo, P = 0.049, HR 0.736, 95%CI 0.454–1.194, [Fig. 3d](#)) and but not in parenchyma (10mo vs. 11mo, P = 0.760, HR 0.930, 95%CI 0.573–1.510, [Supplementary Fig 1c](#)) and total MVD (10mo vs. 11mo, P = 0.349, HR 0.801, 95%CI 0.494–1.299, [Supplementary Fig 1e](#)). No statistical difference was detected in OS ([Supplementary Fig. 1b, d, f](#)). Delta HU and stroma MVD is associated with prognosis in resected PDAC.

Discussion

The decision of chemotherapy regimen for unresectable PDAC patients was based on performance status recommended by guideline [9]. For individualized therapy, searching for a marker of predicting treatment response would be necessary. Delta HU, which is the difference in CT attenuation value (in HU) between enhanced and nonenhanced phase of ROI, is objectively available in CECT. We validated the relationship between delta HU and prognosis in this study, focused on the group of unresectable PDAC that completely relying on the chemotherapy. Delta HU, as an independent prognosis factor for unresectable PDAC, could be applied to personalized chemotherapy regimen selection. In two regimens subgroups, delta HU was detected merely significant difference in survival for mFOLFIRINOX rather than AG. Therefore, for locally advanced or metastasis PDAC, patients with higher delta HU were

Table 2
Univariate and multivariate analyses of the PFS of unresectable patients.

Variable	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Gender						
female vs. male	1.347	0.971–1.870	0.075	1.273	0.913–1.774	0.154
Age, yr						
< 60 vs. ≥ 60	0.922	0.669–1.271	0.619			
Clinical T stage						
T1/T2 vs. T3/T4	1.354	0.969–1.893	0.076	1.147	0.810–1.627	0.440
Clinical N stage						
N0 vs. N1/N2	1.180	0.856–1.625	0.312			
Clinical M stage						
M0 vs. M1	1.154	0.794–1.677	0.453			
TNM stage						
III vs. IV	1.154	0.794–1.677	0.453			
Tumor location						
head/neck vs. body/tail	0.910	0.657–1.261	0.572			
Differentiation						
moderately vs. poorly	0.876	0.619–1.240	0.455			
ECOG PS						
0 vs. 1	1.520	1.097–2.106	0.012	1.458	1.051–2.023	0.024*
Chemotherapy regimen						
AG vs. mFOLFIRINOX	1.035	0.743–1.441	0.839			
CA19–9, U/ml						
≤ 37 vs. > 37	1.147	0.760–1.729	0.514			
Delta HU						
< 27 vs. ≥ 27	0.645	0.466–0.892	0.008	0.672	0.485–0.930	0.017*

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; AG, gemcitabine plus albumin bound paclitaxel; mFOLFIRINOX, modified FOLFIRINOX; delta HU, delta Hounsfield unit.

Table 3
Univariate and multivariate analyses of the PFS of patients with AG.

Variable	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Gender						
female vs. male	1.198	0.791–1.814	0.395			
Age, yr						
< 60 vs. ≥ 60	1.113	0.736–1.681	0.612			
Clinical T stage						
T1/T2 vs. T3/T4	1.466	0.892–2.410	0.132	2.150	1.250–3.699	0.006*
Clinical N stage						
N0 vs. N1/N2	1.134	0.733–1.754	0.573			
Clinical M stage						
M0 vs. M1	1.499	0.909–2.473	0.113	2.318	1.316–4.082	0.004*
TNM stage						
III vs. IV	1.499	0.909–2.473	0.113	2.318	1.316–4.082	0.004*
Tumor location						
head/neck vs. body/tail	0.701	0.452–1.089	0.114	0.551	0.347–0.875	0.012*
Differentiation						
moderately vs. poorly	1.206	0.732–1.986	0.463			
ECOG PS						
0 vs. 1	1.315	0.834–2.074	0.239			
CA19–9, U/ml						
≤ 37 vs. > 37	1.070	0.621–1.843	0.808			
Delta HU						
< 27 vs. ≥ 27	0.780	0.514–1.182	0.241	0.855	0.558–1.311	0.473

PFS, progression-free survival; AG, gemcitabine plus albumin bound paclitaxel; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; delta HU, delta Hounsfield unit.

supposed be recommended by mFOLFIRINOX as chemo regimen, providing a novel method to select treatment regimen. In this study, there was no difference in both PFS ($P = 0.074$) and OS ($P = 0.467$) in AG and mFOLFIRINOX.

Independent risk factors in AG group included T, M, TNM stage and tumor location, except ECOG PS. Patients with tumor in pancreatic body or tail had better survival. TNM stage was not associated with prognosis in mFOLFIRINOX group, but ECOG PS was significant as independent risk factor. Patients were selected into two groups by ECOG PS before, so the significance of ECOG PS was

different. In all unresectable patients, the difference of ECOG PS in prognosis was significant, either. The results confirmed the reliability of the data that were consistent with identifying regimen by ECOG PS in clinical practice [10]. Whereas, delta HU was superior to ECOG PS in personalization treated choice because of objective record.

Previous researches had indicated the positive or negative correlation between MVD and delta HU, incompatibly [11]. This study verified the positive relationship between delta HU and MVD, emphasizing MVD in stroma rather than parenchyma related to

Table 4
Univariate and Multivariate Analyses of the PFS of Patients with mFOLFIRINOX.

Variable	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Gender						
female vs. male	1.693	0.952–3.012	0.073	1.292	0.694–2.406	0.419
Age, yr						
< 60 vs. ≥ 60	0.740	0.432–1.267	0.272			
Clinical T stage						
T1/T2 vs. T3/T4	1.392	0.824–2.353	0.217			
Clinical N stage						
N0 vs. N1/N2	1.206	0.706–2.061	0.492			
Clinical M stage						
M0 vs. M1	0.897	0.497–1.621	0.720			
TNM stage						
III vs. IV	0.897	0.497–1.621	0.720			
Tumor location						
head/neck vs. body/tail	1.129	0.678–1.880	0.641			
Differentiation						
moderately vs. poorly	0.702	0.416–1.185	0.185	0.665	0.376–1.174	0.159
ECOG PS						
0 vs. 1	2.400	1.379–4.179	0.002	2.065	1.169–3.646	0.012*
CA19–9, U/ml						
≤ 37 vs. > 37	1.157	0.618–2.168	0.648			
Delta HU						
< 27 vs. ≥ 27	0.490	0.287–0.836	0.009	0.571	0.330–0.988	0.045*

PFS, progression-free survival; mFOLFIRINOX, modified FOLFIRINOX; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; delta HU, delta Hounsfield unit.

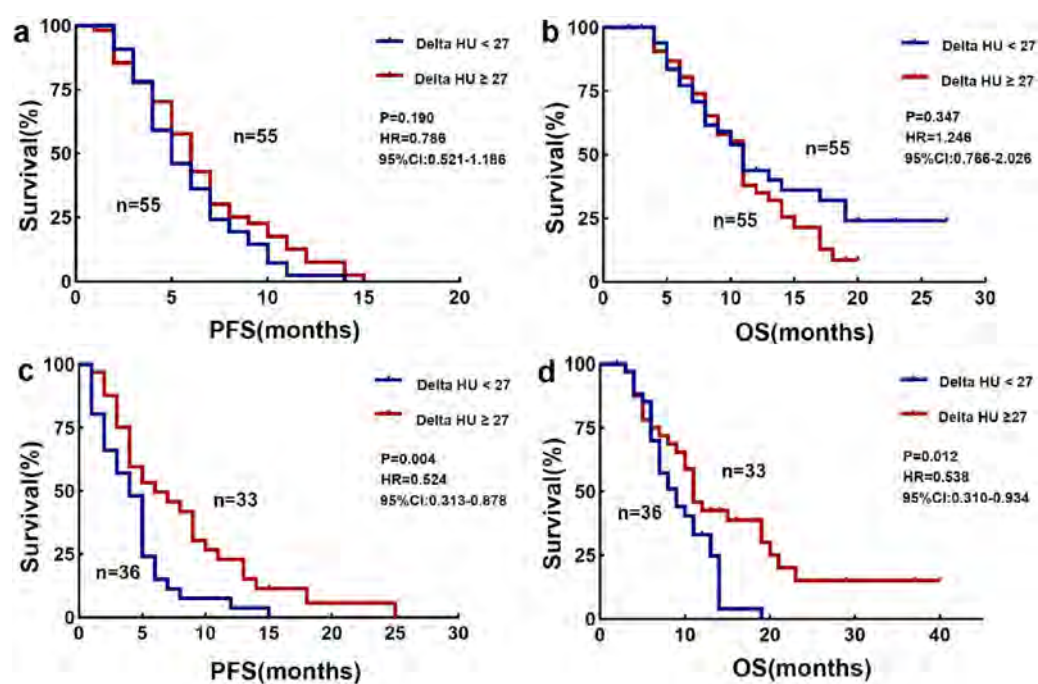


Fig. 2. Kaplan-Meier analysis of survival in AG group and mFOLFIRINOX group. PFS(a) and OS(b) survival curves of Δ HU < 27 and $\geq$ 27 in AG group. PFS(c) and OS(d) survival curves of Δ HU < 27 and $\geq$ 27 in mFOLFIRINOX group. delta HU, delta Hounsfield unit; AG, gemcitabine plus albumin bound paclitaxel; mFOLFIRINOX, modified FOLFIRINOX; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

delta HU. Speculating from this, micro vessels probably played different roles in stroma and parenchyma, stroma compressed vasculature in the tumor resulting in impaired drug delivery, more micro vessels possibly delivered more drug to tumor [12]. We inferred that the chemo response was influenced by stroma micro vessels strongly in mFOLFIRINOX, on the contrary, weakly in AG leading to no significance in analysis of AG regimens.

We announced that higher MVD was associated with poorer

prognosis for resectable PDAC before [13]. Kenji TakagiHigh et al. demonstrated that tumor peripheral MVD assessed by the lumen method was associated with liver metastasis and a poorer survival [14]. MVD was calculated jointly in both stroma and parenchyma in most research, nevertheless, large area of stroma surrounded by pancreatic cancer cells was one of the histology characteristics of PDAC, micro vessels in stroma were much more than in parenchyma [15,16]. Takahiro Nishidamicro et al. indicated that vessels in

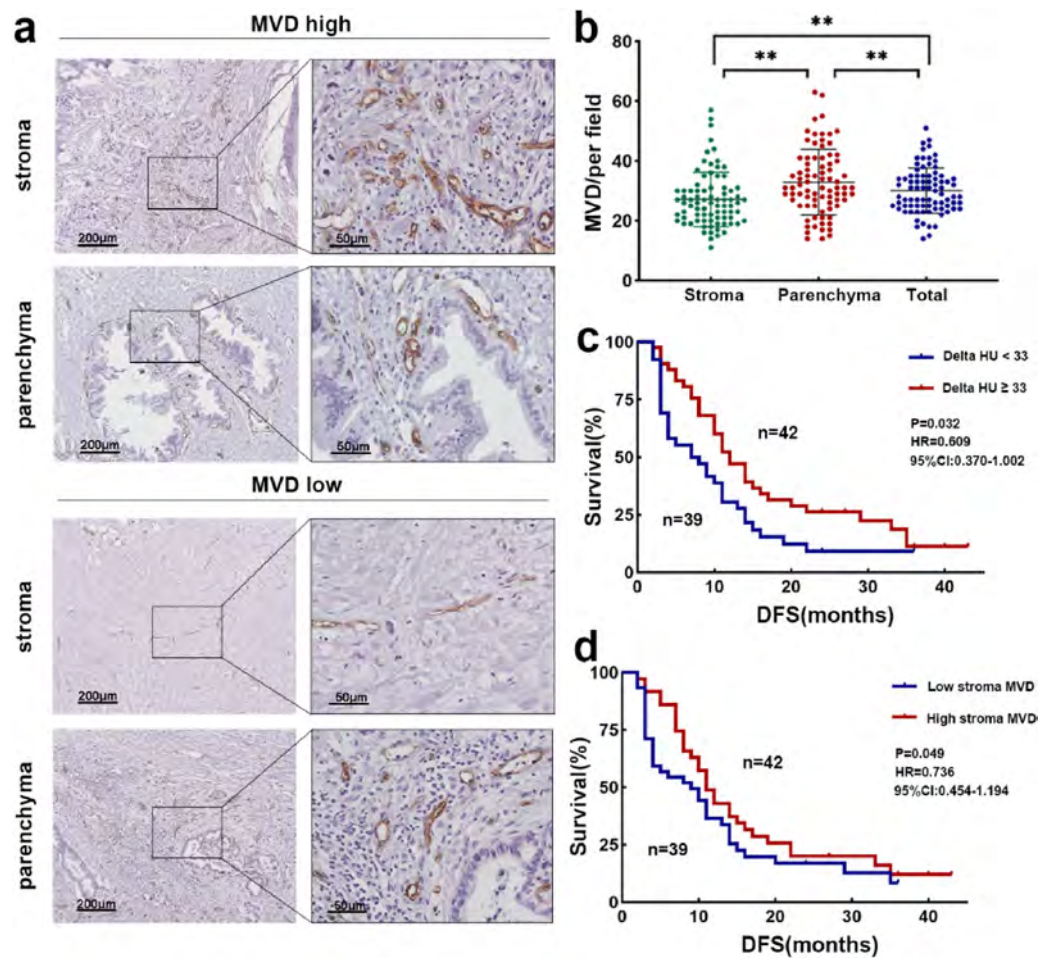


Fig. 3. Delta HU was positively associated with MVD. a, CD34 immunohistochemistry staining of PDAC specimens in stroma and parenchyma. b, Significant difference of MVD in stroma, parenchyma and total. c, DFS survival curves of Δ HU < 33 and $\geq$ 33. d, DFS survival curves of low and high stroma MVD. MVD, microvessel density; delta HU, delta Hounsfield unit; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Table 5
Correlation of delta HU with MVD by Spearman analysis.

		Stroma MVD	Parenchyma MVD	Total MVD
Delta HU	r	0.483**	0.199	0.370**
	P	0.000	0.074	0.001

delta HU, delta Hounsfield unit; MVD, microvessel density.

different areas separately calculated showed differently significance, low stromal area and high stromal MVD predicted poor prognosis in pancreatic cancer [17]. However, in this study, patients with higher stroma MVD had better survival, potentially due to different calculation methods or small sample size. Different results in regimens indicated the clinical significance of stroma MVD [18]. More micro vessels in stroma appear to be better prognosis for unresectable PDAC. It may explain that combined anti-angiogenic therapy and chemotherapy failed in clinical trials for advanced PDAC [19,20]. From now on, the reason was unclear, it was worthy to deeply explore the different function of micro vessels in PDAC.

However, there were some study limitations. Firstly, this retrospective study was performed in only one center, and the sample of groups was small, the results may not apply to other centers. Large scale multicenter prospective clinical trials are needed to confirm these conclusions. Secondly, the mechanism of the difference between regimens is still not clear. The basic research of different

chemo drugs and micro vessels are needed. Thirdly, the correlation between MVD and delta HU was indirectly verified not in biopsy tissue of unresectable group. And the sample of resected group should be enlarged for further study.

In summary, we demonstrated the prognostic value of delta HU for both locally advanced PDAC and advanced PDAC. Delta HU was as a potential marker of predicting chemotherapy response. Patients with higher delta HU will benefit from mFOLFIRINOX treatment. The delta HU was positively correlated with stroma MVD, probably explaining the reason of lower Δ HU associated with worse prognosis.

Author contributions

All authors listed have contributed substantially to the design, data collection and analysis, and editing of the manuscript. Yizhang Zhou and Song Gao contributed equally to this work.

Conception and design: YZ ZHOU, S GAO; statistical analysis: YZ ZHOU, H REN, XF GUO; data acquisition: YZ ZHOU, BD ZHOU, S YUAN, YF WANG, J REN, ZQ CHEN; drafting of the manuscript: YZ ZHOU; critical revision of the manuscript: JH HAO, S GAO; study supervision: JH HAO, S GAO.

Declaration of competing interest

The authors have declared that no competing interest exists.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2021.02.016>.

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