

Original Article

Modified-FOLFIRINOX in metastatic pancreatic cancer: A prospective study in Chinese population



Xiang Li ^{a,b,1}, Tao Ma ^{a,b,1}, Qi Zhang ^{a,b}, Yi-Gang Chen ^{a,b}, Cheng-Xiang Guo ^{a,b}, Yi-Nan Shen ^{a,b}, Pei-Wei Sun ^{a,b}, Guo-Gang Li ^{a,b}, Shun-Liang Gao ^{a,b}, Ri-Sheng Que ^{a,b}, Jian-Ying Lou ^{a,b}, Ri-Sheng Yu ^c, Ying Yuan ^d, Qi-Chun Wei ^e, Shu-Mei Wei ^f, Yun Zhang ^{a,b}, Lei Zheng ^g, Xue-Li Bai ^{a,b,**}, Ting-Bo Liang ^{a,b,*}

^a Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

^b Zhejiang Provincial Key Laboratory of Pancreatic Disease, Hangzhou, China

^c Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

^d Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

^e Department of Radiation Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

^f Department of Pathology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

^g Departments of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Article history:

Received 11 May 2017

Received in revised form

5 July 2017

Accepted 11 July 2017

Keywords:

FOLFIRINOX

Pancreatic cancer

Chemotherapy

Metastatic

Dose modification

ABSTRACT

FOLFIRINOX chemotherapy has shown remarkable responses in patients with metastatic pancreatic cancer (MPC), and has significantly improved prognosis. However, FOLFIRINOX is currently not frequently applied in China because of its high incidence of adverse events, and there is no recognized optimization for this therapy in Chinese population. Modification of FOLFIRINOX may be better for its acceptance in China. In this study, we evaluated the efficacy and safety of modified-FOLFIRINOX in patients with MPC. A total of 62 MPC patients were treated with modified-FOLFIRINOX (no Fluorouracil bolus, 85% Oxaliplatin and 75% Irinotecan) between April 2014 and April 2017 in our institute. 40 of them were evaluated, with a response rate of 32.5% (13/40). The frequent grade 3/4 adverse events are neutropenia (29%) and alanine aminotransferase elevation (14.5%). No treatment-related death was observed. The median overall survival and median progression-free survival are 10.3 months and 7.0 months, respectively. In conclusion, modified-FOLFIRINOX had significantly improved tolerance with similar efficacy to FOLFIRINOX. These findings may provide evidence for the use of FOLFIRINOX in Chinese patients with MPC.

© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death worldwide [1], because of difficulty in diagnosis, early tumor metastasis and tumor resistance to current therapies [2,3]. The incidence in China was approximately 90,100 patients and the mortality was 79,400 in 2015 [4], while the 5-year overall survival (OS) rate remains around 4.1% [5]. Only 15–20% of patients are

eligible for potentially curative surgery, and the remaining patients are defined as locally advanced disease or distant metastasis [6].

Systemic chemotherapy is frequently used to treat patients with metastatic pancreatic cancer (MPC). In the past decade, gemcitabine has replaced 5-fluorouracil and been recognized as the first choice for pancreatic cancer patients, with a 1.2-months increase in median overall survival (OS) [7]. However, the response rate of gemcitabine monotherapy remains low (approximately 10%), and an improved strategy is desperately needed [7,8]. FOLFIRINOX (a combination of fluorouracil, oxaliplatin, irinotecan and leucovorin) achieved much longer median OS in locally advanced pancreatic cancer [9]. Recently, FOLFIRINOX has also been shown to acquire significant longer median OS and progression-free survival (PFS) of 11.1 and 6.4 months, respectively, in MPC as well as an increased

* Corresponding author. 88 Jiefang Road, Hangzhou 310009, China.

** Corresponding author. 88 Jiefang Road, Hangzhou 310009, China.

E-mail addresses: shirleybai@zju.edu.cn (X.-L. Bai), liangtingbo@zju.edu.cn (T.-B. Liang).

¹ These authors contributed equally to this work.

response rate of 31.6% [10]. A meta-analysis, with twenty randomized controlled trials and 6264 patients, was conducted to compare the efficacy of twelve chemotherapy regimens in treating advanced or metastatic pancreatic cancer, and FOLFIRINOX was found to be the best option in terms of better objective response rate (ORR), OS, and PFS [11]. Therefore, FOLFIRINOX has been considered as the first-line chemotherapy regimen for MPC in recent years.

However, the survival gain comes at a cost. Compared to gemcitabine, FOLFIRINOX is reported with a higher rate of grade 3/4 adverse events, including neutropenia (45.7% vs. 21%), fatigue (23.6% vs. 17.8%), vomiting (14.5% vs. 8.3%), diarrhea (12.7% vs. 1.8%), and sensory neuropathy (9% vs. 0%) [10]. For this reason, FOLFIRINOX was only used in patients with very good performance status at full dose, and the tolerability still remains a main concern [12]. As a result, an increasing number of studies have aimed to improve chemotherapeutic or targeted therapy regimens to reduce toxicity without compromising efficacy (Table 1) [13–16]. Using dose attenuation, Mahaseth et al. reported a significantly reduced incidence of adverse events with a similar median OS (9.0 vs. 11.1 months compared to full dose) [14]. Similarly, Stein et al. demonstrated that reduction of irinotecan and bolus 5-fluorouracil by 25% resulted in significantly decreased neutropenia, vomiting, and fatigue, with a relatively high response rate of 35.1% [15].

Compared with Chinese population, Europeans present with physical advantages and show greater tolerance against the adverse effects of chemotherapy. FOLFIRINOX is currently not popular in China because of its safety. Currently, there is no standard regimen for FOLFIRINOX in China. The present study investigated the efficacy of the modified-FOLFIRINOX regimen in patients with MPC. As far as we know, this is the first study to evaluate FOLFIRINOX in Chinese patients with metastatic pancreatic cancer. We hope more Chinese patients can benefit from FOLFIRINOX with dose modification.

Materials and methods

Patients

This was a prospective study involving MPC patients receiving adjuvant modified-FOLFIRINOX from April 2014 to April 2017 at the Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine. Patients who were histologically diagnosed with pancreatic adenocarcinoma and were prescribed modified-FOLFIRINOX, with or without prior treatments, were eligible for inclusion. In all cases, MPC was diagnosed by a multidisciplinary team according to the National Comprehensive Cancer Network definitions. Exclusion criteria were: (1) Eastern Cooperative Oncology Group (ECOG) performance score higher than 1; (2) inadequate bone marrow, liver or renal functions; (3) with additional malignancies; (4) older than 75 years. Our study followed the Declaration of Helsinki, and all included patients provided written informed consent.

Table 1
The efficacy and safety of FOLFIRINOX in advanced pancreatic cancer patients.

Events	Full dose	Modified dose			
	Conroy [10]	Stein [15]	Mahaseth [14]	Rombouts [16]	Our Center
Patients, n	166	68	60	50	62
Stage, %					
Locally advanced	0	45.6	40	36	0
Metastatic	100	54.4	60	64	100
Outcomes					
OS (MPC), months	11.1	10.2	11.1	9.0	10.3
PFS (MPC), months	6.4	6.1	9.0	5.9	7.0
ORR, %	31.6	35.1	30	32	32.5
Grade 3/4 AEs, %					
Neutropenia	45.7	12.2	3	40	29
Fatigue	23.6	12.2	13	8	0
Vomiting	14.5	2.7	8	2	0
Diarrhea	12.7	16.2	13	4	0

Assessments

All patients were evaluated every four cycles of modified-FOLFIRINOX using chest high-resolution computed tomography (HRCT) scan, abdominal enhanced computed tomography (CT), and enhanced magnetic resonance imaging (MRI) of the liver. Physical examination and laboratory tests were performed every time before chemotherapy. Tumor response was categorized into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (version 1.1) [17]. Serum cancer antigen (CA) 19-9 levels were examined at the time of tumor response assessment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). OS was defined as the duration from the beginning of chemotherapy to the date of death of any cause. PFS was defined as the duration from the beginning of chemotherapy to the date of disease progression or death. Patients without event were censored at the last follow-up date (May 1st, 2017). For patients with modified-FOLFIRINOX, information were collected at the moment of admission. While patients who had discharged were followed up every 3 months in clinic with physical examination, laboratory tests, chest HRCT, abdominal enhanced CT and enhanced MRI of the liver.

Treatment

The FOLFIRINOX regimen was modified by reducing oxaliplatin and irinotecan to 85% and 75% of the full dose, respectively, and omitting the fluorouracil intravenous bolus. The detailed treatment plan is as follows: a 2-h intravenous infusion of oxaliplatin (68 mg/m²), followed by another 2-h intravenous infusion of leucovorin (400 mg/m²), concomitantly with an additional 1.5-h intravenous infusion of irinotecan (135 mg/m²), and a subsequent intravenous infusion of fluorouracil (2400 mg/m²) over 46 h. For all patients, anti-emetic agents (ondansetron, azasetron, and metoclopramide), omeprazole, and dexamethasone were used to enhance the tolerance against FOLFIRINOX-related adverse events. All patients in cohort were offered modified-FOLFIRINOX (2-weekly schedule) and evaluated every 4 cycles. Complete blood counts and other necessary blood tests were regularly performed every week. Biliary stenting and drainage procedures were performed in patients with jaundice. In our study, there were 13 patients underwent either chemotherapy or surgical resection before FOLFIRINOX. Six of them underwent tumor resection, four of them received chemotherapy, and the other three patients underwent both operation and chemotherapy. Once chemotherapy resistance or PD was observed, the modified-FOLFIRINOX was stopped. For those patients with SD or PR, the duration of FOLFIRINOX will be as long as 12 cycles and then take S1 orally. When S1 is not strong enough to control the disease, FOLFIRINOX is still the first choice for patients with good performance score.

Statistical analysis

All data were analyzed using SPSS software (version 22). Data were presented as median and range. PFS and OS analyses were performed using the Kaplan–Meier method and log-rank tests. A *P* value less than 0.05 was considered statistical significance.

Results

Patient characteristics

A total of 62 patients were finally included and received the modified-FOLFIRINOX treatment. The baseline characteristics are listed in Table 2. The range of age was 38–75, with a mean age of

Table 2
Patient characteristics at baseline.

Patients Characteristics	All Patients n = 62
Age-Mean (Range)	61.7 (38–75)
Gender-no.(%)	
Male	42 (67.7)
Female	26 (32.3)
Smoke-no.(%)	
No	36 (58.1)
Yes	26 (41.9)
Alcohol-no.(%)	
No	40 (64.5)
Yes	22 (35.5)
Presenting symptoms-no.(%)	
Jaundice	6 (9.7)
Pain	54 (87.1)
Weight loss	31 (50)
Co-morbidities-no.(%)	
Hypertension	17 (27.4)
Diabetes mellitus	12 (19.4)
Coronary heart disease	0
Chronic obstructive pulmonary disease	0
Other malignancy	0
ECOG performance score-no.(%)	
0	38 (61.3)
1	24 (38.7)
2	0
Pancreatic tumor location-no.(%)	
Proximal	22 (35.5)
Distal	40 (64.5)
Metastatic sites-no.(%)	
Liver	49 (79)
Lung	1 (1.6)
Peritoneal	7 (11.3)
Lymph node ^a	10 (16.7)
Others	5 (8.1)
Previous therapy	
Chemotherapy	7 (11.3)
Radiation	0
Curative intent procedures	9 (14.5)
Open-close surgery	1 (1.6)
Biliary stent	6 (9.7)
Lab tests ^b -Mean (Range)	
CA19-9 (U/mL)	5724.7 (2–12000)
Carcino-Embryonic Antigen (U/mL)	72.1 (1–1044)
Alpha-FetoProtein (ng/mL)	33.9 (1–1898)
Albumin (g/L)	39.4 (30–50)
Serum Creatinine (umol/L)	58.8 (30–104)
Total Bilirubin (umol/L)	21.4 (5–138)
Blood Platelet (10 ⁹ /L)	193.6 (40–361)
White Blood Cell (10 ⁹ /L)	6.9 (2.0–14.0)

^a Lymph node located in peri-aortic, caval, SMA and CA.

^b The initial lab test results after admission.

61.7 years old. The majority of the patients (n = 38, 61.3%) demonstrated an ECOG score of 0. Fifty-four (87.1%) patients presented with abdominal pain when diagnosed, and six patients (9.7%) placed biliary stent or catheter before chemotherapy because of jaundice. The liver was the commonest organ with metastases found (n = 49, 79%). The baseline laboratory testing results, including CA19-9, CEA, AFP, albumin, serum creatinine, total bilirubin, blood platelet and white blood cell, after admission are also listed in Table 2. Fifty-four patients (87.1%) were found with elevated CA19-9 levels before chemotherapy.

Response

Forty patients (64.5%) were restaged after modified-FOLFIRINOX treatment. The response of these patients was evaluated and is shown in Table 3. Though no CR was observed, 13 (32.5%) patients showed PR. Unfortunately, 16 out of 40 (40%) had PD. We were able to evaluate CA19-9 response in 32 out of 54 patients with elevated

Table 3
Response to modified-FOLFIRINOX.

Variable	All patients n = 62
Could not be evaluated	22 (35.5)
Response-no.(%)	n = 40
Complete Response (CR)	0
Partial Response (PR)	13 (32.5)
Stable Disease (SD)	11 (27.5)
Progressive Disease (PD)	16 (40)
Rate of Objective Response (OR)-no.(%)	13 (32.5)
Rate of Disease Control (DC)-no.(%)	24 (60)

The Objective Response rate was defined as the percentage of patients with CR or PR.

The Rate of Disease Control was defined as the percentage of patients with CR, PR or SD.

pre-treatment CA19-9 results. A decrease in CA19-9 was observed in 25 patients (25/32, 78.1%) after four cycles of FOLFIRINOX. The median OS of patients with decreased CA19-9 levels was 14.0 months, while that of the others was only 7.0 months ($P < 0.01$; Fig. 1a). A temporary increase in CA19-9 level (more than 1.5 times compared to baseline) was observed in 11 patients from the decreased group. In addition, we found that the pre-treatment level of CA19-9 did not affect OS in patients with MPC (median OS of 10.5 and 10.3 months in CA19-9 normal and elevated groups respectively, $P = 0.78$; Fig. 1b).

Adverse events

In general, the incidence of adverse events was 80.6% (n = 50), and neutropenia was the most frequent one, with an incidence of 64.5%. For severe adverse events, we observed 27 patients (43.5%) with grade 3/4 toxicities, among which 29% (n = 18) was neutropenia, 4.8% (n = 3) was thrombocytopenia, 8.1% (n = 5) was anemia, 4.8% (n = 3) was infection, and 14.5% (n = 9) was elevated level of alanine aminotransferase (ALT; Table 4). Grade 3/4 vomiting was not observed in the present study, probably due to the combination therapy of ondansetron, azasetron and metoclopramide during the chemotherapy and removal of fluorouracil intravenous bolus from the regimen. No patients suffered febrile neutropenia, sensory neuropathy or thromboembolism. Totally, 43 patients (69.4%) received granulocyte-colony stimulating factor treatment before or after chemotherapy. Moreover, five patients (8.1%) required interleukin 11 therapy, and two patients (3.2%) were treated with thrombopoietin.

Survival

All 62 patients were included for survival analysis. The median number of treatment cycles was 5, ranging from 1 to 15. The median duration of follow-up was 7 (range 1–22) months. The median OS was 10.3 months, and a total of 32 (53.2%) patients died at the last follow-up. The median PFS of was 7.0 months (Fig. 2).

Discussion

MPC patients have extremely short survival, and few treatment modalities have been established in such clinical scenario. FOLFIRINOX chemotherapy can produce remarkable efficacy in MPC patients with significantly increased survival, compared to gemcitabine monotherapy [10], and is a promising strategy for these unfortunates. However, the application of FOLFIRINOX is largely limited by its considerable toxicity. As a consequent, clinicians in China hesitate to prescribe FOLFIRINOX for MPC patients, although it may have better efficacy to combat tumor. Very limited MPC

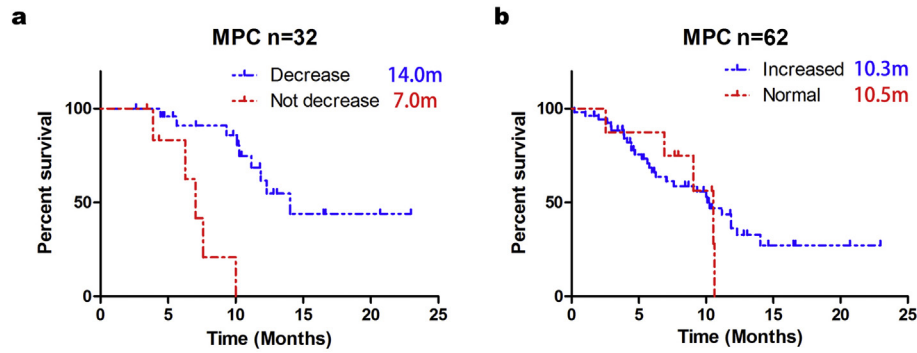


Fig. 1. The association between median OS and CA19-9 levels in MPC patients. a. Response was evaluated in 32 patients with elevated CA19-9 levels detected before chemotherapy. After four cycles of treatment, patients were divided into two groups according to the change of CA19-9 levels following chemotherapy. The median survival time of the decreased group ($n = 25$) was 14.0 months, and that of the others ($n = 7$) was 7.0 months ($P < 0.01$). b. The median OS of all patients was analyzed, according to the pre-chemotherapy CA19-9 level. No significant difference was observed between the normal ($n = 8$, 10.5 months) and elevated groups ($n = 54$, 10.3 months; $P = 0.78$).

Table 4
Adverse events.

Events	MPC	
	$n = 62$	
	Total	Grade 3/4
Hematologic-no.(%)		
Neutropenia	40 (64.5)	18 (29)
Febrile neutropenia	0	0
Thrombocytopenia	26 (41.9)	3 (4.8)
Anemia	35 (56.5)	5 (8.1)
Non-hematologic-no.(%)		
Infection	4 (6.5)	3 (4.8)
Fatigue	4 (6.5)	0
Vomiting	14 (22.6)	0
Diarrhea	2 (3.2)	0
Sensory neuropathy	0	0
Elevated level of ALT	28 (45.2)	9 (14.5)
Thromboembolism	0	0
Hematopoietin		
G-CSF	43 (69.4)	
IL-11	5 (8.1)	
TPO	2 (3.2)	
EPO	0	

Abbreviations: G-CSF, granulocyte-colony stimulating factor; IL-11, interleukin 11; TPO, thrombopoietin; EPO, erythropoietin.

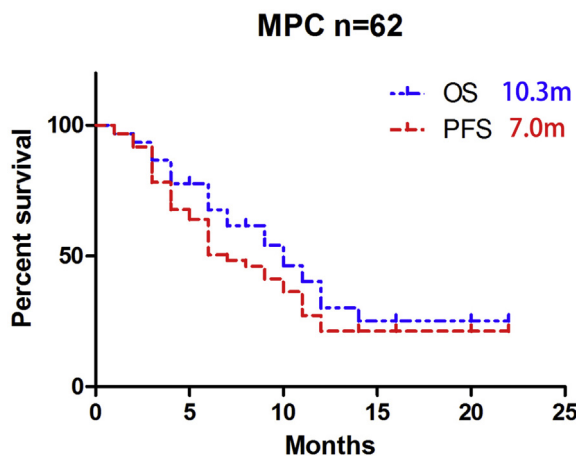


Fig. 2. Kaplan–Meier survival estimates of survival. A total of 62 patients were treated using modified-FOLFIRINOX. The median overall survival of all patients was 10.3 months, and the median progression-free survival was 7.0 months.

patients have tried FOLFIRINOX regimen in some Chinese institutions, and these studies were halted because of the poor tolerance.

To make FOLFIRINOX more practicable, many investigators have made their efforts to enhance patients' tolerance to this chemotherapy through various ways [13]. Mahaseth et al. significantly reduced the incidence of grade 3/4 neutropenia and diarrhea without compromising the efficiency of FOLFIRINOX simply by removing fluorouracil bolus and using hematopoietic growth factors at the same time [14]. Stein et al. reduced the doses of both irinotecan and fluorouracil bolus by 25%, and found that the incidences of neutropenia, vomiting and fatigue were significantly decreased [15]. Other modification strategy for advanced pancreatic cancer includes avoiding use of irinotecan [18] and it may be referential in MPC patients. However, all these attempts were made out of China. Due to the racial differences between Chinese and Western patients, the experience acquired from Western people may be not suitable for Chinese patients. Thus, appropriate modification of FOLFIRINOX is urgently needed in China. In the present study, we modified FOLFIRINOX by reducing oxaliplatin and irinotecan to 85% and 75% of the full dose, respectively, and abandoning fluorouracil intravenous bolus for the purpose of improving tolerability. Meanwhile, our modification maintained considerable efficacy of FOLFIRINOX, with an ORR of 32.5% and prolonged survival with acceptable toxicity.

Several studies have proven that modification of FOLFIRINOX did not compromise its efficacy. An American study recruiting 36 MPC patients treated with modified-FOLFIRINOX showed that median OS and PFS were 9.0 and 8.5 months, respectively [14]. Longer OS (median, 12.9 months) and PFS (median, 8.7 months) after modified-FOLFIRINOX treatment were also reported by another study with 66 MPC patients included [19]. In the current study, we enrolled 62 MPC patients and provided a novel modification strategy for FOLFIRINOX according to our experience. In our cohort, the median OS and PFS were 10.3 and 7.0 months, respectively, comparable to the previous studies. Furthermore, we found that the median OS of the patients with decreased CA19-9 levels was two-fold of that of the other patients after chemotherapy. Therefore, CA19-9 level after chemotherapy may be a prognostic indicator in MPC patients receiving modified-FOLFIRINOX. Since the pre-chemotherapy CA19-9 level did not influence OS in our study, the change of CA19-9 level more likely reflected tumor response to the treatment. Noticeably, a temporary increase of CA19-9 level was observed in some cases but it decreased after the following two cycles of treatment. Therefore, the elevation of CA19-9 level in the first two cycles may not suggest drug resistance.

Modified-FOLFIRINOX is also supposed to reduce adverse events. Conroy et al. reported that grade 3/4 adverse events with FOLFIRINOX treatment are neutropenia (45.7%), fatigue (17.8%), vomiting (14.5%), and diarrhea (12.7%) [9]. We showed that only 29% of patients receiving modified-FOLFIRINOX suffered grade 3/4 neutropenia, and no grade 3/4 fatigue, vomiting or diarrhea was observed at all. We believe that the removal of fluorouracil bolus from FOLFIRINOX and the use of hematopoietic growth factors contributed to the reduction of grade 3/4 neutropenia and diarrhea. The relatively low risk of hematological adverse events (thrombocytopenia and anemia) and none chemotherapy-related treatment cessation or death suggested a good tolerability of our modified-FOLFIRINOX regimen.

In summary, we showed that our modified-FOLFIRINOX was well tolerated in MPC patients, with an ORR of 32.5%, median OS of 10.3 month, and PFS of 7.0 months. Reduction of serum CA19-9 levels post-chemotherapy was associated with better prognosis. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire may be needed to obtain better evaluation of quality of life of patients receiving modified-FOLFIRINOX treatment. To our knowledge, this is the first prospective study aiming to evaluate the efficacy of FOLFIRINOX in Chinese MPC patients, and they did benefit from dose reduction with improved safety and similar tumor response. More studies in Chinese population are required to validate these results and provide better modification of FOLFIRINOX regimen.

Acknowledgments

The authors thank Mr. Jian-Feng Wang for his assistance with information collection. This work was financially supported by the National High Technology Research and Development Program of China (No. 2015AA020405), the Training Program of the Key Program of the National Natural Science Foundation of China (No. 91442115), the National Natural Science Foundation of China (No. 81672337), the Zhejiang Provincial Key Innovation Team of Pancreatic Cancer Diagnosis & Treatment (No. 2013TD06), the Key Program of the National Natural Science Foundation of China (No. 81530079), the Key Research and Development Project of Zhejiang Province (No. 2015C03044), and the Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents.

Conflict of interest

The authors declare no potential conflict of interest.

References

- [1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2015, *CA Cancer J. Clin.* 65 (2015) 5–29.
- [2] H. Haeno, M. Gonen, M.B. Davis, J.M. Herman, C.A. Iacobuzio-Donahue, F. Michor, Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies, *Cell* 148 (2012) 362–375.
- [3] D.P. Sohal, R.M. Walsh, R.K. Ramanathan, A.A. Khorana, Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy, *J. Natl. Cancer Inst.* 106 (2014) dju011.
- [4] W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, et al., Cancer statistics in China, 2015, *CA Cancer J. Clin.* 66 (2016) 115–132.
- [5] J. Luo, L. Xiao, C. Wu, Y. Zheng, N. Zhao, The incidence and survival rate of population-based pancreatic cancer patients: Shanghai Cancer Registry 2004–2009, *PLoS One* 8 (2013), e76052.
- [6] M. Bockhorn, F.G. Uzunoglu, M. Adham, C. Imrie, M. Milicevic, A.A. Sandberg, et al., Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS), *Surgery* 155 (2014) 977–988.
- [7] H.A. Burris, M.J. Moore, J. Andersen, M.R. Green, M.L. Rothenberg, M.R. Modiano, et al., Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial, *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 15 (1997) 2403–2413.
- [8] M. Di Marco, R. Di Cicilia, M. Macchini, E. Nobili, S. Vecchiarelli, G. Brandi, et al., Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? (Review), *Oncol. Rep.* 23 (2010) 1183–1192.
- [9] M. Suker, B.R. Beumer, E. Sadot, L. Marthey, J.E. Faris, E.A. Mellon, et al., FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis, *Lancet Oncol.* 17 (2016) 801–810.
- [10] T. Conroy, F. Desseigne, M. Ychou, O. Bouché, R. Guimbaud, Y. Bécouarn, et al., FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, *N. Engl. J. Med.* 364 (2011) 1817–1825.
- [11] G.F. Liu, G.J. Li, H. Zhao, Efficacy and toxicity of different chemotherapy regimens in the treatment of advanced or metastatic pancreatic cancer: a network meta-analysis, *J. Cell Biochem.* (2017 Jun 13), <http://dx.doi.org/10.1002/jcb.26210> [Epub ahead of print].
- [12] T. Conroy, C. Gavoille, E. Samalin, M. Ychou, M. Ducreux, The role of the FOLFIRINOX regimen for advanced pancreatic cancer, *Curr. Oncol. Rep.* 15 (2013) 182–189.
- [13] K.S. Gunturu, X. Yao, X. Cong, J.R. Thumar, H.S. Hochster, S.M. Stein, et al., FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity, *Med. Oncol.* 30 (2013) 361.
- [14] H. Mahaseeth, E. Brucher, J. Kauh, N. Hawk, S. Kim, Z. Chen, et al., Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma, *Pancreas* 42 (2013) 1311–1315.
- [15] S.M. Stein, E.S. James, Y. Deng, X. Cong, J.S. Kortmansky, J. Li, et al., Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer, *Br. J. Cancer* 114 (2016) 737–743.
- [16] S.J. Rombouts, T.H. Mungroop, M.N. Heilmann, H.W. van Laarhoven, O.R. Busch, I.Q. Molenaar, et al., FOLFIRINOX in locally advanced and metastatic pancreatic cancer: a single centre cohort study, *J. Cancer* 7 (2016) 1861–1866.
- [17] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45 (2009) 228–247.
- [18] H.A. El-Hadaad, H.A. Wahba, Oxaliplatin plus 5-fluorouracil and folinic acid (OFF) in gemcitabine-pretreated advanced pancreatic cancer: a phase II study, *J. Gastrointest. Cancer* 44 (2013) 313–317.
- [19] M.K. Chhanna, N. Cook, N.C. Dhani, K. Giby, A. Dodd, L. Wang, et al., FOLFIRINOX for advanced pancreatic cancer: the Princess Margaret Cancer Centre experience, *Br. J. Cancer* 115 (2016) 649–654.