Review

A Decade of Advances in Cytotoxic Chemotherapy for Metastatic Colorectal Cancer

Amy S. Lucas, Bert H. O'Neil, Richard M. Goldberg

Abstract

Over the past decade treatment for metastatic colorectal cancer (mCRC) has advanced beyond single-agent fluoropyrimidine use to include various cytotoxic combination regimens and novel targeted therapies. Despite the targeted therapy era, traditional cytotoxic agents remain the mainstay of therapy. Improvements in survival in mCRC can be attributed mostly to combination therapy, with enhanced efficacy due to optimization of fluoropyrimidine dosing and the addition of irinotecan and/or oxaliplatin. Despite the enormous progress, few patients with metastatic disease are cured. To realize that ambitious goal we need a better understanding of predictive molecular markers of response, mechanisms of drug toxicity, innate and acquired drug resistance as well as how to optimize cytotoxic agents in combination with newer targeted therapies.

Clinical Colorectal Cancer, Vol. 10, No. 4, 238-44 © 2011 Elsevier Inc. All rights reserved.
Keywords: 5-Fluorouracil, Cytotoxic agents, Irinotecan, Oxaliplatin

Introduction

Approximately 142,570 new cases of colorectal cancer are diagnosed each year in the United States, of which 102,900 are colon cancer and the remainder rectal cancer. Annually, nearly 50,000 Americans die of colorectal cancer (CRC), accounting for 9% of all cancer deaths.[1] At diagnosis around 20% of individuals with colorectal cancer have overt metastatic disease, and up to 35% with disease that appears localized initially manifest recurrence despite resection and adjuvant therapy.[2, 3] Metastatic disease can be categorized as resectable, not initially resectable, or not likely ever to become resectable. When managed with best supportive care alone, patients with unresectable metastatic colorectal cancer (mCRC) have a very poor prognosis, with a median overall survival of 5 months.[4] Advances in chemotherapy for mCRC in the past decade have improved the median overall survival in patients treated in clinical trials to approximately 2 years.

This article focuses on the advances in traditional genotoxic/cytotoxic therapy in the past several decades, ranging from 5-fluorouracil (5-FU) and its many optimizations to the more recent additions of the alternative fluoropyrimidines irinotecan and oxaliplatin. Although targeted therapies have captured our attention in the last 6-7 years, it is reasonable to assert that the majority of the improvement in the cure rate for stage III disease and the extension in progression-free and overall survival for patients with mCRC have been due to optimization of administration of cytotoxic agents. Much of this work was completed in the decade since *Clinical Colorectal Cancer* began publication, and we predict that advances in understanding the mechanisms of drug toxicity and resistance through pharmacogenetics and related disciplines could lead to further optimization and improvements in outcome even with the current set of agents.

Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Submitted: June 14, 2011; Accepted: June 21, 2011

Address for correspondence: Richard M. Goldberg, MD, Division of Hematology/Oncology, 170 Manning Dr, CB 7305, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7305
Fax: 919-966-6735; e-mail contact: goldberg@med.unc.edu

The Players: Fluoropyrimidines, Irinotecan, and Oxaliplatin

Fluoropyrimidines

For > 40 years, the sole active class of agents against mCRC was the fluoropyrimidines. 5-FU was patented in 1957, and many consider this to be the first rationally targeted agent developed.[5] 5-FU may also be the most effective of all agents for CRC to this day. The primary mechanism of 5-FU cytotoxicity is thought to be impaired DNA synthesis through inhibition of thymidylate synthase (TS), but both DNA and RNA chain termination result from exposure to 5-FU.[5-7] Folinic acid (leucovorin [LV]) was found to stabilize the interaction between 5-FU and TS, resulting in both increased efficacy and increased toxicity but allowing for convenient rapid infusion of the drug. Compared with bolus 5-FU alone, LV plus 5-FU (5-FU/LV) is associated with a 2-fold higher response rate (21% vs. 11% in 2 meta-analyses), which also translated into a small but statistically significant 10% improvement in 1-year survival (47% vs. 37%) in 1 meta-analysis.[8,9]

1533-0028/$ - see frontmatter © 2011 Elsevier Inc. All rights reserved.
doi: 10.1016/j.clcc.2011.06.012

JHU 2111
Merck Sharp v. Johns Hopkins
IPR2024-00648

Table 1 Irinotecan Plus 5-FU Regimens

Regimen	Irinotecan	Leucovorin	5-FU	Schedule
FOLFIRI[34]	180 mg/m^2 day 1	400 mg/m^2 over 2 hours day 1	FU 400 mg/m^2 bolus day 1, followed by 2400-3000 mg/m^2 over 46 hours, continuous infusion	Every 2 weeks
Douillard et al Regimen[31]	180 mg/m^2 day 1	100 mg/m^{2a} over 2 hours day 1 + 2 before 5-FU	FU 400 mg/m^2 bolus then 600 mg/m^2 over 22 hours days 1 + 2	Every 2 weeks
IFL (Saltz et al)[32]	125 mg/m^2 weekly for 4 weeks	20 mg/m^2 IV bolus weekly for 4 weeks	500 mg/m^2 I.V. bolus weekly for 4 weeks	Every 6 weeks

[a] l-isomer of leucovorin (l-LV): When using the dl racemic mixture of leucovorin (the version commercially available in most countries), the dose is 200 mg/m^2.
Abbreviations: FOLFIRI = 5-FU/leucovorin/irinotecan; 5-FU = 5-fluorouracil; IFL = irinotecan + 5-FU/LV; I.V. = intravenous.

Infusional 5-FU may obviate the need for LV and produces a somewhat more tolerable side effect profile but at the cost of convenience and with the added expense of infusion pumps and maintenance of continuous intravenous access. In head-to-head studies, bolus 5-FU achieves an objective response in only 10% of treated patients, with slightly higher rates noted for infusional FU, but survival is similar between the 2 schedules. The toxicity profile differs between the 2 delivery approaches, with an increased frequency of grade 3/4 neutropenia with bolus dosing (31% vs. 4%) vs. hand-foot syndrome with infusional administration (34% vs. 13%). Gastrointestinal (GI) toxicity rates are similar, overall favoring infusional administration.[10,11]

Two principal bolus regimens have been established and widely used: the Mayo regimen and the Roswell Park Medical Institute (RPMI) regimen. The Mayo regimen consists of 5-FU (425 mg/m^2) plus low-dose LV (20 mg/m^2), both given on days 1 to 5, every 4 to 5 weeks.[12] The RPMI regimen is given as weekly 5-FU (500 mg/m^2) plus LV (500 mg/m^2) for 6 of every 8 weeks.[13] The monthly schedule of the Mayo regimen causes more neutropenia and stomatitis and is rarely used in clinical practice (but has frequently been the comparator arm for newer fluoropyrimidine treatment strategies), whereas the weekly RPMI schedule causes more diarrhea.[13-15] The weekly RPMI regimen has generally been favored because of the ability to stop or modify therapy if toxicity occurs, particularly important in patients who are deficient in the metabolizing enzyme of 5-FU, dihydropyridine dehydrogenase (DPD).

Response rates, tolerability, and convenience with 5-FU and LV have been further improved by the use of short-term hybrid bolus/infusion schedules. For example, de Gramont et al conducted a trial of 448 patients who were randomly assigned to a monthly regimen of 5-FU/LV (Mayo schedule) or a bimonthly regimen of LV (200 mg/m^2 over 2 hours) followed by bolus 5-FU (400 mg/m^2) and a 22-hour infusion of 5-FU (600 mg/m^2) given for 2 consecutive days every 2 weeks (LV5FU2).[16] The infusional regimen achieved higher response rates (33% vs. 14%) and improved progression-free survival (PFS) (28 vs. 22 weeks) without a statistical median survival advantage (62 vs. 57 weeks; $P = .067$). As will be discussed, this hybrid bolus/infusion regimen became the backbone for the modern combinations FOLFOX and FOLFIRI.

Capecitabine is a rationally designed orally administered fluoropyrimidine carbamate that was approved by the US Food and Drug Administration (FDA) in 2001 for mCRC when the drug was found to have response rates comparable to those of intravenous (I.V.) 5-FU/LV (Mayo schedule).[17,18] Capecitabine itself is not cytotoxic. The cytotoxic moiety is 5-FU, which is formed by 3 sequential enzymatic reactions. The final requisite enzyme, thymidine phosphorylase, is present at consistently higher levels in tumor tissue compared with normal tissue, thereby providing the theoretical basis for enhanced selectivity for tumor cells and better tolerability.[19] This drug has become an optional, more conveniently administered fluoropyrimidine backbone for the novel mCRC cytotoxic agents oxaliplatin and irinotecan. However in practice, tolerability is not necessarily significantly better than that observed with I.V. 5-FU. One finding of interest has been that capecitabine is less well tolerated in Western countries (particularly the United States) than in other parts of the world.[20] To date there has not been a satisfying mechanistic explanation for this observation, but differences in the intake of dietary folates have been implicated as a potential explanation.

Several other fluoropyrimidines are approved worldwide but not in the United States. Two of these formulations consist of a 5-FU prodrug (ftorafur) plus a DPD inhibitor: UFT and S-1.[21-24] These combination drug strategies have included intentional inhibition of DPD to lessen variability in absorption and metabolism or use of agents thought to minimize GI tract exposure to 5-FU.[25,26] In-depth discussion of these agents is not included in this article.

Irinotecan. Irinotecan is an inhibitor of topoisomerase I derived from the shrub *Camptotheca accuminata*.[27,28] The parent compound is converted by carboxylesterase localized primarily in the liver to the active metabolite known as SN-38. Irinotecan was first approved in the United States and Europe based on randomized studies in patients whose tumors had progressed on 5-FU.[29,30] Widespread use of irinotecan in combination with 5-FU began after 2 key phase III trials demonstrated a survival advantage of single-agent irinotecan in patients with mCRC whose disease was refractory to 5-FU. The combination regimens of 5-FU and irinotecan are discussed further on and represented in Table 1.

Douillard et al used a regimen that was the first of any combination to show a survival advantage over 5-FU/LV in mCRC. In their study, 387 previously untreated patients were randomly assigned to 5-FU/LV with or without irinotecan. Combination therapy could be administered either weekly (irinotecan 80 mg/m^2, 5-FU 2300 mg/m^2 over 24 hours, LV 500 mg/m^2) or every other week (irinotecan 180 mg/m^2 on day 1; 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 over 22 hours, both on days 1 and 2; and LV 200 mg/m^2 on days 1 and 2 [the Douillard regimen]). The control arm allowed

weekly (5-FU 2600 mg/m^2 over 24 hours plus LV 500 mg/m^2) or every-other-week regimens (5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 over 22 hours, both on days 1 and 2; and LV 200 mg/m^2 on days 1 and 2). A higher response rate (49% vs. 31%; $P < .001$) was achieved with combination therapy, along with longer time to progression (6.7 vs. 4.4 months; $P < .001$) and median survival (17.4 vs. 14.1 months; $P < .03$). Toxicities that were more common with irinotecan included grade 3/4 diarrhea (44% vs. 27%) and neutropenia (29% vs. 2%-4%), but these were manageable, reversible, and noncumulative.[31]

The second important early frontline irinotecan study was conducted by Saltz et al who developed the so-called (bolus) IFL (irinotecan + 5-FU/LV) regimen.[32] Their phase III trial compared combination therapy to the Mayo Clinic bolus regimen of 5-FU/LV as well as to single-agent irinotecan for first-line therapy in mCRC. Combination therapy consisted of irinotecan 125 mg/m^2 I.V. with LV 20 mg/m^2 I.V. bolus and 5-FU 500 mg/m^2 I.V. bolus given weekly for 4 weeks of every 6 weeks. The dosing for the single-agent irinotecan was the same as in the combination regimen. Again a higher response rate (39% vs. 21%; $P < .001$) was accomplished with the combination regimen compared with the 5-FU/LV, along with a longer median PFS (7 vs. 4.3 months; $P < .004$) and median overall survival (14.8 vs. 12.6 months; $P < .04$). Efficacy for single-agent irinotecan was comparable to the 5-FU/LV regimen.

Use of irinotecan with bolus 5-FU regimens, such as IFL, is now uncommon because of increased toxicity, especially ≥ grade 3 diarrhea (19% vs. 14%) and ≥ grade 3 febrile neutropenia (12% vs. 4%), occasionally resulting in death.[32,33] The randomized Bolus vs. Infusional Camptosar Colorectal plus Celecoxib (BICC-C) study compared modified IFL (2 weeks on and 1 week off) with the simplified modification of the Douillard regimen known as FOLFIRI (irinotecan 180 mg/m^2, 5-FU 400 mg/m^2 bolus, 5-FU 2400 mg/m^2 continuous infusion over 46 hours.[34,35] BICC-C demonstrated that PFS was significantly better for patients who received FOLFIRI (median 7.6 months) vs. a modified IFL regimen (median 5.9 months; $P = .004$). Intriguingly, overall survival was 23.1 months with FOLFIRI compared with 17.6 months for the modified IFL regimen, although this difference did not reach statistical significance ($P = .09$).[35]

The BICC-C study also included a capecitabine/irinotecan (CAPIRI) arm, which consisted of irinotecan 250 mg/m^2 I.V. over 90 minutes on day 1 and oral capecitabine 1000 mg/m^2 twice per day on days 1 through 14, repeated every 3 weeks. Although overall objective response rates did not differ significantly between FOLFIRI and CAPIRI (47.2% vs. 38.6%), median PFS was better for FOLFIRI than for CAPIRI (7.6 vs. 5.8 months; $P = .015$), as was overall survival (23.1 months for FOLFIRI vs. 18.9 months for CAPIRI). Additionally, CAPIRI was associated with high rates of ≥ grade 3 nausea, vomiting, diarrhea, dehydration, febrile neutropenia, and hand-foot syndrome. Discontinuation of study treatment for unacceptable toxicity was more common among patients treated with CAPIRI (25.5%) when compared with FOLFIRI (14.6%). As such it is difficult to recommend CAPIRI as a standard first-line choice, particularly in the United States.

Irinotecan: UGT1A1 Polymorphisms. One controversy that revolved around irinotecan in the past decade had to do with its metabolism and the potential for predicting severe toxicity in a subset of patients. SN-38 is inactivated and tagged for biliary elimination through glucuronidation, which occurs in the liver principally through the polymorphic enzyme UGT1A1 (Other UGT family members exist in the gut and may help detoxify irinotecan that has been deglucuronidated by intestinal bacteria).[36] Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (responsible for Gilbert syndrome) and an additional 40% are heterozygotes.[37] Several studies have documented increased risk of irinotecan-related neutropenia and more importantly febrile neutropenia in patients with the homozygous polymorphism in particular. Based on these findings, the FDA amended the product label for irinotecan, suggesting that patients with the homozygous *28 polymorphism be treated with lower initial doses of irinotecan. Unfortunately little prospective data have been generated to define safe dosing in this population. One finding of importance however has been that biweekly and weekly dosing schedules of irinotecan may not require modification because of a low risk of severe adverse events, whereas higher doses (≥ 300 mg/m^2), which are most often given on a every-3-week basis, may necessitate routine testing to prevent severe neutropenia with attendant risk of infection and death.[38]

Oxaliplatin. Oxaliplatin is a platinum derivative whose bulky oxalate side chain results in stearic hinderance thought to enhance its efficacy as a DNA repair inhibitor. It is the only approved platinum agent with known activity against colorectal cancer. The development of oxaliplatin and oxaliplatin-fluoropyrimidine combinations was the last and perhaps most significant undertaking of the past decade. Compared with irinotecan and 5-FU, oxaliplatin has relatively little single-agent activity.[39] Oxaliplatin has however been shown to synergize in both preclinical experiments and clinical studies when combined with fluoropyrimidines.[40]

The first trial to show a benefit from adding oxaliplatin to 5-FU/LV was a European study reported in 2000 in which the LV5FU2 regimen was administered with or without oxaliplatin (85 mg/m^2 on day 1 over 2 hours). The oxaliplatin regimen FOLFOX4 (5-FU/LV + oxaliplatin) produced a significantly higher objective response rate (51% vs. 22%; $P = .0001$) and longer PFS (9 vs. 6.2 months; $P = .0001$) but similar median overall survival (16.2 vs. 14.7 months; $P = .12$). Grade 3/4 neutropenia (42% vs. 5%), diarrhea (12% vs. 5%), and neurologic toxicity (18% vs. 0%) were more common with oxaliplatin. However only 1% of patients treated in the FOLFOX-4 arm experienced febrile neutropenia. Furthermore reversibility of grade 3/4 sensory neurotoxicity was observed in 74% of patients, with a median time to recovery of 13 weeks. Two additional trials showed significantly increased antitumor efficacy, with similar improved response rates and PFS but also without overall survival benefit. It can be speculated that this is due to crossover or receiving chemotherapy after leaving the study.[41,42] Unfortunately this effect resulted in delay of > 2 years in the approval of oxaliplatin in the United States.

Would You Like Irinotecan or Oxaliplatin With Your Fluoropyrimidine? At the time of the publication of the FOLFOX trial, IFL was the de facto standard of care in the United States. The US Intergroup study N9741 was designed to examine several potential irinotecan,

oxaliplatin, and 5-FU doublets simultaneously. After several arms containing bolus 5-FU regimens were closed because of excess toxicity (elucidated by a novel real-time toxicity monitoring system), the study showed a statistically significant survival benefit for FOLFOX-4 compared with IFL and IROX (irinotecan/oxaliplatin), with a median overall survival of 19.5 vs. 15 months for IFL and 17.4 months for IROX.[43] This comparison was criticized because of ready access to irinotecan for the oxaliplatin group but restricted access to second-line oxaliplatin in the United States and because of the "apples to oranges" comparison of an infusional to a bolus 5-FU combination. Despite that, the study was important in that it essentially changed the standard of care in the United States and helped to highlight the problems associated with bolus 5-FU and irinotecan administration that were mentioned previously. N9741 was notable in addition for being 1 of the first large multicooperative group studies to collect blood from patients at the time study enrollment. This has allowed for multiple analyses of this large group of patients that have provided insights into potential markers of response and toxicity, which are described in another article in this issue.

Subsequent to N9741, 2 small European randomized trials, neither of which were powered for a noninferiority comparison, failed to show a survival benefit when comparing FOLFOX variants with FOLFIRI variants.[34,44] One of these studies allowed patients to cross over to the alternative regimen at progression, essentially demonstrating that order of administration of the drugs was unimportant in the eventual outcome. Unfortunately this study also verified that response rates after first-line progression are very poor regardless of the second regimen.

Capecitabine has also been incorporated into oxaliplatin regimens in several randomized studies. The largest of these, the NO16966, was designed to demonstrate noninferiority between CAPOX and FOLFOX-4 as first-line therapy in mCRC.[45] The trial commenced as a randomized 2-arm phase III comparison of CAPOX vs. FOLFOX-4. After patient accrual had begun, the trial design was amended in 2003 after bevacizumab phase III data became available. The subsequent 2×2 factorial design randomly assigned patients to CAPOX vs. FOLFOX-4 and then to also receive either bevacizumab or placebo. The intent-to-treat analysis consisted of 2034 patients, with a median PFS of 8.0 vs. 8.5 months (hazard ratio [HR], 1.04; 97.5% confidence interval [CI], 0.93-1.16) and median overall survival of 19.8 vs. 19.6 months (HR, 0.99; 97.5% CI, 0.88-1.12) in the pooled CAPOX-containing arms and FOLFOX-4–containing arms respectively, confirming the study's hypothesis of statistical noninferiority. With respect to the toxicity evaluation, FOLFOX-4 was associated with more grade 3/4 neutropenia/granulocytopenia and febrile neutropenia than CAPOX, and CAPOX was associated with more grade 3 diarrhea and grade 3 hand-foot syndrome than FOLFOX-4.

FOLFIRINOX? One of the unresolved questions that has followed us into the second decade of the 21st century is whether triple-drug combinations might be better than the doublets that we have used for the past decade. Data have suggested that exposure to all the 3 main active cytotoxic agents obtains the best outcome in patients whose disease is unresctable,[34,46,47] but that only 50% to 80% of patients can be exposed to all 3 drugs when regimens are deployed as either sequential singlets or doublets. A theoretical way to further improve the outcome of mCRC could be to administer a first-line regimen containing the 3 active agents. An Italian group, the Gruppo Oncologico Nord Ovest (GONO), conducted a phase III study of 244 patients comparing FOLFOXIRI (irinotecan 165 mg/m^2 day 1, oxaliplatin 85 mg/m^2 day 1, LV 200 mg/m^2 day 1, fluorouracil 3200 mg/m^2 48-hour continuous infusion starting on day 1, every 2 weeks) with FOLFIRI. PFS and overall survival were both significantly improved in the FOLFOXIRI arm (6.9 vs. 9.8 months; $P = .0006$; 16.7 vs. 22.6 months; $P = .032$). This overall survival is better than most studies have shown with chemotherapy alone and rivals overall survival seen with combinations of chemotherapy and targeted agents. In addition, response rates were very high: 34% vs. 60% ($P < .0001$). An increase of grade 2/3 peripheral neurotoxicity (0% vs. 19%; $P < .001$) and grade 3/4 neutropenia (28% vs. 50%; $P < .001$) was observed in the FOLFOXIRI arm. The incidence of febrile neutropenia (3% vs. 5%) and grade 3/4 diarrhea (12% vs. 20%) was not significantly different.[48] This study suggested significantly better outcomes with FOLFOXIRI, with increased but manageable toxicity. Skepticism about the usability of this regimen has limited its study in the United States, but patients with borderline resectable disease might be a population in whom to consider FOLFOXIRI, given the high rate of conversion to resectability seen in the GONO study.

A cautionary note is necessary however, as a Greek group has also studied a FOLFOXIRI variant in 283 patients vs. FOLFIRI as first-line treatment in patients with mCRC. They noted a significantly higher incidence of alopecia, diarrhea, and neurosensory toxicity than did the Italian group. Also there were no differences in overall survival (median, 19.5 and 21.5 months, respectively), PFS (6.9 and 8.4 months, respectively), or response (33.6% and 43%, respectively) in their study.[49]

Sequential Singlets vs. Doublets: Does It Matter?

The previously mentioned trials with combination therapy provide good evidence that either irinotecan or oxaliplatin in addition to 5-FU improves survival for patients with metastatic colon cancer. However whether first-line multiagent therapy is essential to obtain this benefit vs. a sequential approach is uncertain from these studies. It has been demonstrated that overall survival is associated with the use of all 3 active chemotherapy drugs in the treatment course of mCRC.[34,46,47] For patients with extensive metastases who will not be cured, questions have been raised about how the active drugs and combinations should be sequenced to maximize duration of disease control while minimizing adverse effects.

The FOCUS (Fluorouracil, Oxaliplatin, and CPT11 [irinotecan]-Use and Sequencing) trial randomized 2135 patients with noncurative mCRC to first-line treatment using 3 strategies (creating a total of 5 arms) with a primary endpoint of overall survival. Strategy A was considered the control and consisted of treatment with infusional 5-FU/LV alone until progression followed by single-agent irinotecan. Strategy B also used infusional 5-FU/LV alone, but was followed by combination therapy at treatment failure (B-ir and B-ox). Strategy C consisted of combination therapy from the outset (C-ir and C-ox).

The median overall survival of patients allocated to the control group strategy A was 13.9 months. The median overall survival of each of the other groups was longer (B-ir 15.0, B-ox 15.2, C-ir 16.7, C-ox 15.4 months). The only group with a statistically significant difference in median overall survival to the control group was the C-ir (first-line combination therapy including irinotecan; $P = .01$). The comparison of deferred combination therapy (strategy B) to first-line combination therapy (strategy C) was not inferior. The choice of irinotecan vs. oxaliplatin also did not affect survival.[50]

In similar fashion, the Dutch CAIRO (capecitabine/irinotecan/oxaliplatin) trial investigated whether combination treatment is better than sequential administration of the same drugs in mCRC. This study randomly assigned 820 patients to first-line therapy with capecitabine, second-line irinotecan, and third-line capecitabine plus oxaliplatin (sequential treatment) or to first-line capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin (combination treatment). Although first-line PFS was significantly longer for the combination treatment group than it was for the sequential treatment group ($P = .0002$), overall survival was not statistically different (16.3 months for sequential treatment and 17.4 months for combination therapy; $P = .3281$).[51]

In the case of each of these studies, the investigators concluded based on this trial that a sequential strategy is a reasonable one compared with initial combination therapy for patients with disease that is not likely to be amenable to resection. Although there are some significant caveats to this argument, it would certainly argue that patients who do not require a response for resection or for symptomatic reasons might be offered sequential therapy. Study of sequential therapy with targeted agents is however significantly limited. Additionally, the median survival for all groups in both the FOCUS and CAIRO trials (which ranged from 13.9 to 17.4 months) was lower than expected from previous trials of combination chemotherapy. One explanation has been that patients with better prognosis and liver-only metastases were excluded from FOCUS and were underrepresented in CAIRO.

Can Unresectable mCRC Be Cured?

Historically, a small but real group of patients treated with fluoropyrimidines experienced 5-year survival after a diagnosis of unresectable mCRC.[52] An analysis of US Intergroup N9741 showed a 10% 5-year overall survival in patients with mCRC treated with first-line FOLFOX. Only 6 of 85 patients alive at 5 years had undergone resection. This suggests that a small fraction of patients with mCRC may be curable with cytotoxic therapy alone. An analysis of factors that were prognostic of patient outcome was completed and included treatment arm; age; sex; previous adjuvant therapy; body mass index; performance status; number of disease sites; neutrophil, hemoglobin, and platelet counts; and bilirubin, alkaline phosphatase, and aspartate aminotransferase levels. These were assessed for univariate association with overall survival and associated factors were included in multivariate Cox and logistic regression models. Pretreatment performance status, neutrophil count, and alkaline phosphatase level are prognostic for overall survival, although FOLFOX treatment was the strongest prognostic factor.[53]

Intermittent Strategies: Can Incurable Patients Safely Take Breaks?

In large part driven by the potentially permanent sensory neuropathy induced by continuous administration of oxaliplatin, several trials have addressed whether equivalent outcomes are provided by intermittent rather than continuous therapy.[54-56] Historically, 5-FU has been administered continuously until disease progression or unacceptable toxicity in the majority of patients with mCRC. In addition, current improved survival has resulted in a larger fraction of mCRC patients who potentially receive chemotherapy for several years, making treatment without breaks highly unsatisfying.

Support for intermittent therapy first came from a trial of 354 patients who were progression free after 12 weeks of first-line chemotherapy and were randomly assigned to stopping treatment (reinstituting the same regimen on disease progression) or to continuing treatment until progression. The treatment regimens consisted of 5-FU/LV with or without oxaliplatin, infusional 5-FU, or raltitrexed. Overall survival was similar in both groups, but significantly fewer grade 3 neuropathy events occurred with intermittent therapy. The median off-treatment duration with the intermittent-therapy group was 4.3 months. The objective response rate after retreatment in the intermittent-therapy group was about half of the initial response rate (21% vs. 41%).[56]

The OPTIMOX1 trial examined maintenance chemotherapy with 5-FU/LV. The study randomly assigned 620 previously untreated patients to FOLFOX-4 administered every 2 weeks until disease progression (arm A) or FOLFOX-7, a regimen that included a higher dose intensity of oxaliplatin (130 mg/m^2 every 2 weeks) for 6 cycles only, followed by reintroduction of oxaliplatin after 12 cycles of 5-FU/LV maintenance (arm B). Similar results for median PFS (9.0 vs. 8.7 months), overall survival (19.3 vs. 21.2 months), and response rate (58.5% vs. 59.2%) were seen with arms A and B at a median follow-up of 31 months. Toxicity was also comparable up to cycle 7, but fewer patients experienced grade 3/4 toxicity in arm B beyond 6 cycles. Grade 3 sensory neuropathy was observed in 17.9% of the patients in arm A vs. 13.3% of patients in arm B ($P = .12$). In arm B oxaliplatin was reintroduced in only 40.1% of the patients but achieved responses in 6.7% or stabilization in 42.7% of patients who restarted treatment because of progressive disease.[57]

A subsequent randomized phase II trial known as OPTIMOX2 tested the benefit of short-term maintenance 5-FU/LV compared with a chemotherapy-free interval (CFI) after an initial response to modified FOLFOX7 (oxaliplatin 100 mg/m^2 rather than 130 mg/m^2, and no 5-FU bolus) given for 6 cycles or 3 months in 200 patients with previously untreated mCRC. Patients in both arms were reintroduced to modified FOLFOX7 on tumor progression. The primary endpoint was the median duration of disease control, which was significantly longer in the maintenance arm than in the CFI arm (13.1 vs. 9.2 months; $P = 0.046$). Maintenance therapy was also associated with an increase in the median PFS (8.6 vs. 6.6 months; $P = .0017$). The median survival was not statistically different but exhibited a similar and clinically meaningful trend in favor of maintenance 5-FU/LV (23.8 vs. 19.5 months; $P = 0.42$).[58]

Lastly, a preliminary report of another multicenter trial in which patients were randomly assigned to continuous vs. intermittent ox-

aliplatin (alternating every 8 cycles with and without oxaliplatin) also appeared to confirm the benefit of intermittent rather than continuous oxaliplatin for increasing time on first-line therapy for oxaliplatin/bevacizumab–based combinations.[59]

Although irinotecan is not associated with known cumulative toxicities, treatment breaks might still be beneficial for amelioration of chronic fatigue and GI side effects that can be associated with irinotecan and fluoropyrimidine combinations. The only randomized trial addressing intermittent therapy with irinotecan and 5-FU was a multicenter trial of 336 patients with mCRC evaluating alternating vs. continuous FOLFIRI. Intermittent FOLFIRI was given every 2 weeks for 2 months followed by a 2-month break. Both intermittent and continuous FOLFIRI were given until disease progression. Median overall survival, the primary endpoint of the trial, was 16.9 months with intermittent therapy and 17.6 months with continuous treatment (HR, 1.11; 95% CI, 0.83-1.48).[54]

In summary, the evidence is good that maintenance can be carried out with 5-FU/LV without loss of efficacy, but for now complete breaks from chemotherapy should generally be reserved for patients who have had durable major responses to therapy, do not have bulky residual disease, are not at high risk for bowel obstruction from peritoneal carcinomatosis, or within the context of trials.

Conclusion

Traditional cytotoxic therapy remains the mainstay of therapy for patients with advanced colorectal cancer even in the targeted therapy era. Despite the advances of the past decade in cytotoxic therapy for mCRC and associated improvement in overall survival, questions remain and debates continue about how to further optimize these therapies in individual patients. We have come a long way toward understanding the role of drug combinations, sequencing, and the need for maintenance therapy. There is hope that further improvement in outcomes with traditional cytotoxic agents will come from elucidation of predictive molecular markers of response (discussed in more detail elsewhere in this issue) and better understanding of both innate and acquired drug resistance. Lastly, we still have much to learn about how to combine cytotoxic therapies with newer targeted therapies, an endeavor that should keep us all busy for the current decade and beyond.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; 60:277-300.
2. Midgley R, Kerr D. Colorectal cancer. *Lancet* 1999; 353:391-9.
3. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; 27:3109-16.
4. Scheithauer W, Rosen H, Kornek GV, et al. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993; 306:752-5.
5. Heidelberger C. Biochemical mechanisms of action of fluorinated pyrimidines. *Exp Cell Res* 1963; 24(suppl 9):462-71.
6. Klubes P, Cerna I, Meldon MA. Effect of concurrent calcium leucovorin infusion on 5-fluorouracil cytotoxicity against murine L1210 leukemia. *Cancer Chemother Pharmacol* 1981; 6:121-5.
7. Evans RM, Laskin JD, Hakala MT. Effect of excess folates and deoxyinosine on the activity and site of action of 5-fluorouracil. *Cancer Res* 1981; 41:3288-95.
8. Buyse M, Thirion P, Carlson RW, et al. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Meta-Analysis Group in Cancer. *Lancet* 2000; 356:373-8.
9. Thirion P, Michiels S, Pignon JP, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; 22:3766-75.
10. O'Dwyer PJ, Manola J, Valone FH, et al. Fluorouracil modulation in colorectal cancer: lack of improvement with N -phosphonoacetyl- l -aspartic acid or oral leucovorin or interferon, but enhanced therapeutic index with weekly 24-hour infusion schedule—an Eastern Cooperative Oncology Group/Cancer and Leukemia Group B Study. *J Clin Oncol* 2001; 19:2413-21.
11. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-analysis Group In Cancer. *J Clin Oncol* 1998; 16:301-8.
12. Poon MA, O'Connell MJ, Moertel CG, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989; 7:1407-18.
13. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol* 1996; 14:2274-9.
14. Buroker TR, O'Connell MJ, Wieand HS, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *J Clin Oncol* 1994; 12:14-20.
15. Wang WS, Lin JK, Chiou TJ, et al. Randomized trial comparing weekly bolus 5-fluorouracil plus leucovorin versus monthly 5-day 5-fluorouracil plus leucovorin in metastatic colorectal cancer. *Hepatogastroenterology* 2000; 47:1599-603.
16. de Gramont A, Bosset JF, Milan C, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997; 15:808-15.
17. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; 19:2282-92.
18. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; 19:4097-106.
19. Schuller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol* 2000; 45:291-7.
20. Haller DG, Cassidy J, Clarke SJ, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 2008; 26:2118-23.
21. Sulkes A, Benner SE, Canetta RM. Uracil-ftorafur: an oral fluoropyrimidine active in colorectal cancer. *J Clin Oncol* 1998; 16:3461-75.
22. Ohtsu A, Baba H, Sakata Y, et al. Phase II study of S-1, a novel oral fluorophyrimidine derivative, in patients with metastatic colorectal carcinoma. S-1 Cooperative Colorectal Carcinoma Study Group. *Br J Cancer* 2000; 83:141-5.
23. Van den Brande J, Schoffski P, Schellens JH, et al. EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. *Br J Cancer* 2003; 88:648-53.
24. Shirao K, Ohtsu A, Takada H, et al. Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. *Cancer* 2004; 100:2355-61.
25. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993; 53:4004-9.
26. Takechi T, Nakano K, Uchida J, et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother Pharmacol* 1997; 39:205-11.
27. Taguchi T, Wakui A, Hasegawa K, et al. Phase I clinical study of CPT-11. Research group of CPT-11 [in Japanese]. *Gan To Kagaku Ryoho* 1990; 17:115-20.
28. Oguro M, Seki Y, Okada K, et al. Collateral drug sensitivity induced in CPT-11 (a novel derivative of camptothecin)-resistant cell lines. *Biomed Pharmacother* 1990; 44:209-16.
29. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998; 352:1407-12.
30. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998; 352:1413-8.
31. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355:1041-7.
32. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343:905-14.
33. Rothenberg ML, Meropol NJ, Poplin EA, et al. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; 19:3801-7.
34. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22:229-37.
35. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007; 25:4779-86.
36. Carlini LE, Meropol NJ, Bever J, et al. UGT1A7 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. *Clin Cancer Res* 2005; 11:1226-36.
37. McLeod HL, Sargent DJ, Marsh S, et al. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from

North American Gastrointestinal Intergroup Trial N9741. *J Clin Oncol* 2010; 28:3227-33.
38. Hoskins JM, Rosner GL, Ratain MJ, et al. Pharmacodynamic genes do not influence risk of neutropenia in cancer patients treated with moderately high-dose irinotecan. *Pharmacogenomics* 2009; 10:1139-46.
39. Becouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. *J Clin Oncol* 1998; 16:2739-44.
40. Mathe G, Kidani Y, Segiguchi M, et al. Oxalato-platinum or 1-OHP, a third-generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatinum. *Biomed Pharmacother* 1989; 43:237-50.
41. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18:136-47.
42. Grothey A, Deschler, B, Kroening, H, et al.. Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/FA + oxaliplatin in advanced colorectal cancer (abstract). *Proc Am Soc Clin Oncol* 2002; 21:129a.
43. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22:23-30.
44. Delaunoit T, Goldberg RM, Sargent DJ, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. *Cancer* 2004; 101:2170-6.
45. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008; 26:2006-12.
46. Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. *J Clin Oncol* 2005; 23: 9441-2.
47. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004; 22:1209-14.
48. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; 25: 1670-6.
49. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006; 94:798-805.
50. Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; 370:143-52.
51. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; 370:135-42.
52. Sanoff HK, Sargent DJ, Campbell ME, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. *J Clin Oncol* 2008; 26:5721-7.
53. Sanoff HK, Sargent, DJ, Campbell ME, et al. N9741: survival update and prognostic factor analysis of oxaliplatin (Ox) and irinotecan (Iri) combinations for metastatic colorectal cancer (MCRC). *J Clin Oncol* 2007; 25(suppl):abstract 4067. Available at: http://www.asco.org. Accessed July 2, 2011.
54. Labianca R, Floriani I, Cortesi E; Italian Group for the Study of Digestive Tract, et al: Can alternating versus continuous "FOLFIRI" in advanced colorectal cancer (ACC): a randomized "GISCAD" trial. *J Clin Oncol* 2006; 24(suppl):abstract 3505. Available at: http://www.asco.org. Accessed July 2, 2011.
55. Lal R, Dickson J, Cunningham D, et al. A randomized trial comparing defined-duration with continuous irinotecan until disease progression in fluoropyrimidine and thymidylate synthase inhibitor–resistant advanced colorectal cancer. *J Clin Oncol* 2004; 22:3023-31.
56. Maughan TS, James RD, Kerr DJ, et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet* 2003; 361:457-64.
57. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer–a GERCOR study. *J Clin Oncol* 2006; 24:394-400.
58. Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009; 27:5727-33.
59. Grothey A, Hart, LL, Rowland, KM, et al. Intermittent oxaliplatin (oxali) administration and time to treatment failure (TTF) in metastatic colorectal cancer (mCRC): final results of the phase III CONcePT trial. *J Clin Oncol* 2008; 26(suppl):abstract 4010. Available at: http://www.asco.org. Accessed July 2, 2011.