

# Chemotherapy for Metastatic Colorectal Cancer

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## Key Words

Colon cancer, oxaliplatin, irinotecan, bevacizumab, cetuximab, colorectal cancer, chemotherapy, metastases

## Abstract

The past decade has seen a significant survival improvement for patients with metastatic colorectal cancer, fueled in large part by the arrival of active novel chemotherapeutic drugs and their incorporation into combination regimens. Several randomized trials have successfully integrated oxaliplatin and irinotecan into previously existing 5-fluorouracil (5-FU)-based regimens for advanced colorectal cancer, resulting in median survivals that have risen from 9 months to almost 2 years. Even as the ideal combinations and sequences of these regimens are elucidated, targeted therapies such as recently approved bevacizumab and cetuximab have been added to treatment protocols, with favorable consequences. We review the evolution of primary chemotherapy for advanced colorectal cancer, focusing on the trials that have led to the new standard first-line treatments. We also review the data on newer targeted therapies, especially in combination with cytotoxic therapy. (*JNCCN* 2005;3;525–529)

Colorectal cancer (CRC) ranks as the second-most common cause of cancer-related death in the United States. Approximately 50% of patients have metastatic or locally advanced disease at presentation. Mortality from CRC will fall significantly only when physicians refer patients for appropriate CRC screening and the disease is diagnosed at earlier stages. This article reviews the major changes in active treatment options for colon cancer.

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For specific treatment algorithms, please see the NCCN Colon and Rectal Cancers Guidelines (in this issue).

## First-Line Therapy

The choice of first-line therapy for metastatic CRC has been in a stage of flux recently. The emergence of several new drugs for this indication has opened new avenues for the treatment of metastatic disease, improving both response rate and median survival. However, it has also clouded the issue of selecting the best front-line treatment. This dilemma represents an “embarrassment of riches” and bodes well for further therapeutic improvements in this area.

### 5-Fluorouracil (5-FU)/Leucovorin (LV)

Before 2000, bolus combinations of 5-FU/leucovorin were the North American standard of care in metastatic CRC. Studies showing its superiority to other 5-FU-based combinations (i.e., levamisole, methotrexate) emerged in the late 1980s and early 1990s. In a study of 457 patients with advanced CRC, Poon et al.<sup>1</sup> showed that bolus combinations of 5-FU and leucovorin given daily for 5 days at 4-week intervals (Mayo regimen) resulted in improved response rates and survival when compared with combinations of 5-FU with methotrexate.<sup>1</sup> Similarly, Petrelli et al.<sup>2</sup> showed a comparable response rate of 48% and time-to-progression of 10 months using a different weekly combination of 5-FU and leucovorin (Roswell Park regimen).<sup>2</sup> These two regimens would define the standard for the next decade.

Throughout this time, intense research was undertaken to find the most effective combinations and dosing regimens for 5-FU. Data accumulated that suggested that 5-FU cytotoxicity proceeded from at least 2 different mechanisms of action: RNA synthesis inhibition and DNA synthesis inhibition by blocking thymidylate

synthase (TS). The prolonged infusion schedule provides prolonged exposure of TS to 5-FU, with superior tumor pharmacokinetics. Consequently, regimens were developed, mostly in Europe, to deliver 5-FU as a continuous infusion. In a study of 448 patients with advanced CRC, de Gramont et al.<sup>3</sup> randomized patients to receive either the Mayo regimen of 5-FU/LV or a 2-day protracted infusion regimen. Results showed statistically significant improvements in favor of infusion therapy for response rate (32.6% vs. 14.4%) and median progression-free survival (27.6 vs. 22 weeks). In addition, a nonsignificant trend towards improved median overall survival (62 vs. 56.8 weeks,  $P = .61$ ) was seen, favoring the infusional regimen. Interestingly, the side effect profile also differed. The infusion regimen resulted in less granulocytopenia and more mucositis and hand-foot syndrome.

### Capecitabine

The development of oral pyrimidines such as capecitabine has opened new avenues in the treatment of metastatic CRC. Capecitabine is an oral fluoropyrimidine carbamate that is rapidly absorbed via gastrointestinal routes and converted into the active metabolite 5-FU by thymidine phosphorylase, an enzyme that is significantly more active in tumor cells. Therefore, capecitabine has the potential advantage of improved tumor-cell targeting as well as an administration schedule that mimics an infusional regimen. In a phase III study of 602 patients with metastatic CRC, Van Cutsem et al.<sup>4</sup> randomized patients to receive either the Mayo regimen of bolus 5-FU/LV or a daily oral regimen of capecitabine. The response rates (18.9% vs. 15%), median time-to-progression (4.2 vs. 4.0 months), and median overall survival (13.2 vs. 12.1 months) showed nonsignificant trends toward improvement with capecitabine. A follow-up study that randomized 1,207 patients with untreated metastatic CRC to capecitabine versus bolus 5-FU/LV via Mayo regimen resulted in a statistically significant difference in response rates (26% vs. 17%;  $P < .0002$ ) favoring capecitabine.<sup>5</sup> Toxicity profiles favored capecitabine. Only grade 3 hand-foot syndrome was seen more often with capecitabine.

### Irinotecan

Irinotecan is a camptothecin-derived topoisomerase inhibitor that was shown to have phase II single-agent response rates of 13% to 23% in CRC. Studies by Saltz et al.<sup>6</sup> comparing the combination of irinotecan with

bolus 5-FU/LV (IFL) to single-agent irinotecan or 5-FU/LV in 683 patients yielded a higher response rate (39% vs. 21%;  $P < .001$ ), longer progression-free-survival (7.0 vs. 4.3 months;  $P = .004$ ) and longer overall survival (14.8 vs. 12.6 months;  $P = .04$ ) for the three-drug combination IFL. Subsequently, however, two NCI-sponsored studies were found to have 60-day mortality rates that were three-fold higher for the IFL arm than the non-IFL comparators. The increased toxicity was caused by gastrointestinal or vascular toxicities.<sup>7</sup>

Given the superiority of infusion over bolus 5-FU, a combination regimen of irinotecan and infusional 5-FU was also tested. A GERCOR study using irinotecan in combination with infusion 5-FU/LV (FOLFIRI) as third-line treatment resulted in 6% partial response and 61% stable disease in heavily treated patients, with a median overall survival of 43 weeks.<sup>8</sup> These results were associated with grade 3 nausea, diarrhea, and neutropenia, but were considered acceptable for further study. Douillard et al.<sup>9</sup> randomized 387 untreated patients to receive a 5-FU/LV infusion regimen with or without irinotecan. They found statistically significant improvements in response rate (49% vs. 31%), time-to progression (6.7 vs. 4.4 months), and overall survival (17.4 vs. 14.1 months) for the irinotecan group.

### Oxaliplatin

Oxaliplatin is a non-nephrotoxic third-generation platinum compound with documented activity in CRC and single-agent response rates reported between 10% and 20%.<sup>10,11</sup> It is, however, inactive as a single agent in second-line colon cancer therapy. Its incorporation into 5-FU-containing regimens represents an important advance in the treatment of metastatic disease. Goldberg et al.<sup>12</sup> randomized 795 patients with metastatic CRC to receive either irinotecan with bolus 5-FU/LV (IFL), infusional 5-FU/LV with oxaliplatin (FOLFOX4), or irinotecan and oxaliplatin (IROX). Response rate, median time-to-progression, and median overall survival were all significantly superior for FOLFOX4 (45%, 8.7 months, 19.5 months) compared with IFL (31%, 6.9 months, 15.0 months) and IROX (35%, 6.5 months, 17.4 months). The FOLFOX4 regimen also resulted in decreased rates of gastrointestinal side effects and febrile neutropenia when compared with the other two regimens, although incidence of peripheral neuropathy was higher with oxaliplatin. Several other FOLFOX regimens are commonly used (Table 1).

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**Table 1 FOLFOX Regimens With Their Expected Clinical Results**

Regimen	Response Rate	Time-To-Progression, mo	Median Survival, mo	Toxicity
FOLFOX 4 <sup>12</sup>	45%	8.7	19.5	
FOLFOX 6 <sup>13</sup>	27% PR 45% SD	5.3	10.8	Neuropathy, 16% GI Toxicity, 14% Neutropenia, 24%
FOLFOX 7 <sup>14</sup>	42% PR 40% SD	6	16.1	Neuropathy, 15% Diarrhea, 11% Granulocytopenia, 20%

**Bevacizumab**

Bevacizumab is a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF) that has shown efficacy in colon cancer and several other solid tumors. A recent study by Hurwitz et al.<sup>15</sup> randomized 813 previously untreated patients with metastatic CRC to receive either IFL alone or IFL/bevacizumab. The bevacizumab arm yielded a statistically significant improvement in response rate (44.8% vs. 34.8%;  $P = .004$ ), progression-free survival (10.6 vs. 6.2 months;  $P < .001$ ), and median survival (20.3 vs. 15.6 months). Grade 3/4 adverse effects were overall increased by 10% in the bevacizumab group, largely because of hypertension, diarrhea, and leucopenia. Perforation of the gastrointestinal tract and arterial thrombosis were seen in the bevacizumab arm. A third arm of this study comprised 110 patients who received 5-FU/LV/bevacizumab, with a response rate of 40% and median survival of 18.3 months. Significant adverse effects were reported, including skin toxicity and hypertension. However, a decreased rate of neutropenia was seen, thereby providing another potential bevacizumab combination for first-line treatment of metastatic disease.

More recently, studies combining bevacizumab with newer regimens of chemotherapy have begun to mature. The ECOG E3200 trial randomized 828 patients with advanced CRC (who had already failed primary chemotherapy) to receive 1 of 3 regimens of a modified FOLFOX 4 (mFOLFOX 4): either mFOLFOX4 alone, mFOLFOX4/bevacizumab, or bevacizumab alone.<sup>16</sup> The trial was simplified into a two-regimen trial after interim analysis revealed the inferiority of single-agent bevacizumab. At preliminary analysis, results were in favor of the mFOLFOX4/bevacizumab arm with regards to overall survival (12.5 months vs. 10.7 months,  $P = .0024$ ). This improvement came at increased toxicity of Grade 3/4 hypertension and a 1% incidence of

bowel perforation, adverse effects that had previously been reported with bevacizumab. Interestingly, the combination arm also resulted in higher rates of neuropathy (15% vs. 9%), severe nausea (10% vs. 5%), and vomiting (9% vs. 4%), possibly because of increased survival and consequently both longer exposure time and higher cumulative dose of oxaliplatin.

A randomized phase II trial comparing FOLFOX versus bolus 5-FU/LV and Oxaliplatin (bFOL) versus capecitabine/oxaliplatin (CapeOX) was also positively affected by the FDA approval of bevacizumab. The original comparison trial evaluating these three regimens (TREE-1) had randomized 150 patients to receive one of these three study regimens. With the approval of bevacizumab, the trial was amended to include bevacizumab in all three arms (TREE-2).<sup>17</sup> Not only did this trial show improved response rates and toxicity profiles for both FOLFOX and CapeOX when compared with bFOL, but it also showed that the addition of bevacizumab resulted in improved response rates across the board (Table 2).

**Selection of First-and Second-Line Therapies**

Distillation of the results from recent trials has led to the establishment of infusional 5-FU-based regimens as first-line standards. Both FOLFOX and FOLFIRI

**Table 2 Overall Response Rates for the 3 Regimens in Tree-1 and Tree-2<sup>17</sup>**

	Without Bevacizumab	With Bevacizumab
FOLFOX	46.9%	62%
bFOL	32%	42.9%
CapeOx	37.5%	57%

have emerged as solid treatments in this setting, with the choice often being made based on the expected severity of the differing adverse effects. In an attempt to define the optimal sequencing of FOLFOX and FOLFIRI, Tournigand et al.<sup>18</sup> randomized previously untreated metastatic CRC patients to receive either FOLFOX6 or FOLFIRI as first-line treatment, with planned crossover to the opposite arm on progression. Initial response rates, progression-free survival, and overall survival were not statistically different with both regimens, nor were second-line parameters. There were, however, significant differences in toxicity profile, with higher rates of grade 3/4 mucositis and gastrointestinal side effects with FOLFIRI and greater grade 3/4 neutropenia and neurosensory toxicity with FOLFOX6. In effect, therefore, these two regimens are interchangeable in the first- and second-line metastatic setting.

### Cetuximab

Cetuximab is a monoclonal antibody that specifically blocks epidermal growth factor receptor (EGF-R) and has been shown to have efficacy in several types of cancer. The BOND-1 trial randomized 329 CRC patients with progressive disease during or within three months after treatment with an irinotecan-based regimen (IFL, FOLFIRI) to receive cetuximab either in combination with irinotecan or as monotherapy.<sup>19</sup> Response rates favored the cetuximab/irinotecan combination (22.9% vs. 10.1%;  $P = .007$ ), as did time-to-progression (4.1 vs. 1.5 months;  $P < .001$ ). However, no significant difference was found in overall survival (8.6 months vs. 6.9 months,  $P = .48$ ). The major take-home point of this study was the demonstration that cetuximab led to responses in this usually resistant population. Interestingly, responses did not correlate with EGFR positivity. With these findings, cetuximab has emerged as another potential weapon in the growing arsenal against CRC because its toxicities are mild and confined primarily to skin and nail changes.

A subsequent study to better delineate the role of cetuximab is the BOND-2 trial, which includes bevacizumab in its design.<sup>20</sup> In this study, patients with advanced CRC for whom first-line treatment failed are randomized to receive either cetuximab/bevacizumab (CB) or cetuximab/bevacizumab/irinotecan (CBI). Preliminary results have shown a dramatic increase in time-to-progression with the bevacizumab-containing arms, though the data remain immature.

### Liver-Directed Therapy

Of the 50% of CRC patients who develop liver metastases, approximately 25% will be candidates for surgical resection of liver-confined metastases. Although advances in liver surgery (non-anatomic resection, microwave ablation, and cryosurgery) remain the province of oncologic surgeons, the contribution of the medical oncologist after ablation is increasing as the role of hepatic artery chemotherapy is becoming better defined. In a population of CRC patients who underwent surgical resection of one to three liver metastases, an Intergroup phase III trial showed that the post-resection addition of hepatic artery floxuridine (FUdR) infusion to systemic chemotherapy was beneficial in prolonging time to recurrence and preventing hepatic recurrence compared with no further treatment.<sup>21</sup> Patients who received FUdR hepatic artery infusion and hepatic resection had an improved 4-year recurrence-free rate over those who received systemic chemotherapy alone (46% vs. 25%;  $P = .04$ ) and superior 4-year liver recurrence-free rate (67% vs. 43%;  $P = .03$ ). However, median survival was not significantly improved. Other single-institution studies have shown encouraging results for hepatic cancer-free survival and overall survival when hepatic artery infusion is added to systemic chemotherapy after resection of liver metastases from colorectal cancer.

The definitive trial to clarify the role of hepatic artery infusion of FUdR will be the phase III trial sponsored by the National Surgical Adjuvant Breast Program. In this upcoming trial, patients who have undergone ablation or resection of liver metastases will be randomized to receive systemic treatment with capecitabine and oxaliplatin alone or systemic therapy and hepatic artery infusion of FUdR. The unique anatomic properties of the liver and pharmacologic advantage of FUdR hepatic infusion will be explored in this study.

### Conclusions

The chemotherapeutic options for metastatic CRC have advanced tremendously over the past decade, progressing from 5-FU through the current standards, including several combinations of novel cytotoxins and molecular agents. Consequently, survival for these patients has increased from 6 months to the current average of approximately 20 months. The arrival of bevacizumab and cetuximab onto the stage heralds

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yet another leap forward in treatment. These approaches can hopefully reduce the toll that this disease takes on the lives and quality of life of our patients.

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