

The chemotherapy-naive patient with metastatic colorectal cancer

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Colorectal cancer (CRC) tends to manifest with clinical symptoms usually only after the underlying disease process is well advanced. The task for managing chemotherapy-naive patients with metastatic CRC is to develop a treatment strategy that is appropriate for their overall level of function, preexisting comorbidities, and treatment preferences. FOLFIRI and FOLFOX have become the two most common cytotoxic regimens used in practice today, with data strongly suggesting their essentially equal effectiveness in the front line. Patients should be advised, however, that certain toxicities are more likely with one regimen in comparison with the other.

This scenario, which reflects the insidious tendency of colorectal cancer (CRC) to manifest with clinical signs and symptoms only after the underlying disease process is (a) already metastatic, (b) beyond resectability, and (c) therefore almost always incurable, is familiar to oncologists. The task is to develop a treatment strategy that is appropriate to this chemotherapy-naive individual's overall level of function, preexisting comorbidities, and treatment preferences.

Chemotherapy based on an underlying foundation of 5-fluorouracil (5-FU) and folinic acid (leucovorin [LV]), to which other agents are added after consideration of relevant treatment factors, is the common method for treating nonresectable metastatic colorectal cancer (mCRC). Treatments employing first-line administration of 5-FU/LV in combination with either irinotecan (Camptosar) plus infusional 5-FU/LV (FOLFIRI) or oxaliplatin (Eloxatin) plus infusional 5-FU/LV (FOLFOX) have become the two most common cytotoxic regimens used in practice today.¹⁻⁵ Data strongly suggest that FOLFOX and FOLFIRI have essentially equal effectiveness in the front line,⁴ and either regimen is recognized as an appropriate initial selection. The combination of bevacizumab

Case history

A 68-year-old man comes to his primary care physician with a 6-month history of weight loss and intermittent, dull, lower-quadrant pain. Although the patient has hypertension that is well controlled (130/70 mm Hg) with beta-blocker therapy and type II diabetes (fasting blood glucose level, 150 mg/dL), he has no serious medical comorbidities. Colonoscopy reveals adenocarcinoma of the ascending colon; subsequent imaging and diagnostic laparoscopy confirm the presence of bulky retroperitoneal adenopathy and extensive bilobar hepatic lesions. Liver function tests remain within normal limits. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0.

(Avastin), the antivascular endothelial growth factor (VEGF) monoclonal antibody, with either FOLFOX or FOLFIRI (FOLFOX-BEV, FOLFIRI-BEV), is considered appropriate for

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standard practice in the absence of a particular contraindication. When administered with the bolus irinotecan plus 5-FU/LV (IFL) regimen, bevacizumab showed improved survival approaching 21 months, compared with IFL alone (almost 16 months), among patients with mCRC, with manageable toxicities and improved overall response rates⁶; however, bolus 5-FU-based regimens are no longer recommended for routine use, and FOLFIRI is the regimen of choice when using irinotecan. Recent data indicate that the addition of bevacizumab to front-line oxaliplatin-based chemotherapy (FOLFOX or oxaliplatin-capecitabine [Xeloda]) improved progression-free survival (PFS) but had no effect on response rate.⁷ Survival data from that trial are not yet mature.

Chemotherapy is associated with higher rates of hospitalization and complications in patients with a baseline ECOG PS of 2, compared with a PS of 0 or 1; this patient has an excellent PS (ECOG 0) and is a good candidate for standard palliative therapy. Both irinotecan and oxaliplatin are associated with a range of adverse events and cautions (Table 1),^{8,9} but no specific contraindications to either agent are apparent in this patient.

The selection of an irinotecan- or oxaliplatin-based regimen for a

particular patient requires careful consideration of the specific toxicity patterns and the acceptability of those patterns to the individual patient. It has been amply documented that FOLFOX and FOLFIRI offer equivalent activity against mCRC, suggesting that either regimen is appropriate for first-line therapy.¹⁰

Key studies

An important trial by Tournigand and colleagues evaluated sequential FOLFOX6 followed by FOLFIRI or the reverse sequence, with results suggesting no difference in efficacy.⁴ Patients with disease progression on one regimen were transferred to the alternative regimen. In this investigation, response rates for FOLFIRI and FOLFOX6 administered in the first line were 56% and 54%, respectively, and median PFS times were essentially identical (8.5 months and 8.0 months, respectively). No differences in the duration of second PFS (the primary endpoint) or overall survival (OS) were seen between the regimens or between the sequencing of regimens, and median survival times reached over 20 months with sequential combinations regardless of the order (FOLFIRI first: 21.5 months; FOLFOX6 first: 20.6 months).⁴

In a subsequent, confirmatory phase III study, 360 chemotherapy-naïve patients with advanced CRC were randomly assigned to receive either FOLFIRI or FOLFOX4. The overall response rates were similar for both treatment groups (FOLFIRI: 31%; FOLFOX4: 34%), with nearly identical times to disease progression (7 months) and median survival (14 and 15 months, respectively).⁵

It has been shown that exposure to all three active cytotoxic agents (fluoropyrimidine, oxaliplatin, and irinotecan) confers a survival benefit; a weighted analysis of seven phase III trials of advanced CRC concluded that the median OS was significantly correlated with the percentage of patients who received all three drugs during the course

of their disease ($P = 0.0008$) but not with the proportion of patients receiving second-line therapy ($P = 0.19$).¹¹ Patients who were exposed to only two of the three agents exhibited similarly nonsignificant improvement in OS ($P = 0.69$).¹² In this analysis, the use of combination protocols as first-line therapy was associated with a significant improvement in median survival of 3.5 months ($P = 0.0083$).¹¹

Toxicities

Although specific toxicity concerns underlie many treatment decisions, accumulating evidence suggests that toxicities associated with the FOLFOX and FOLFIRI regimens differ predominantly by type rather than severity. For instance, bolus 5-FU/LV has been supplanted by infusional therapy as a preferred administration method, an important practice modification reflecting the generally superior results documented for infusional therapies.¹³⁻¹⁶ In a revised protocol to the phase III BICC-C trial, FOLFIRI plus bevacizumab was superior to a combination of modified bolus IFL (mIFL) plus bevacizumab, achieving a superior response rate and significantly better OS at an initial early presentation. In addition, toxicity findings favored FOLFIRI.¹⁷ In terms of grade 3/4 toxicities, the study by Tournigand et al demonstrated that FOLFOX was associated with a significantly greater ($P < 0.05$) occurrence of neutropenia, thrombocytopenia, and neurotoxicity, whereas FOLFIRI was associated with significantly more ($P < 0.05$) instances of febrile neutropenia, nausea, vomiting, and mucositis. The incidence of diarrhea was comparable with both treatments.^{4,16}

Conclusions

It is likely that chemotherapy for CRC will continue to require combination therapies in the foreseeable future. This strategy targets multi-

TABLE 1

Prominent side effects and toxicities associated with oxaliplatin and irinotecan

Oxaliplatin	Irinotecan
Peripheral sensory neuropathies	Diarrhea
Allergic reactions	Febrile neutropenia
Hepatotoxicity	Nausea
Fatigue	Vomiting
Neutropenia	Alopecia
Nausea	Mucositis
Vomiting	Fatigue
Diarrhea	Hyperbilirubinemia

Source: official prescribing information for oxaliplatin (Eloxatin) and irinotecan (Camptosar)

ple pathways simultaneously, and its theoretic attractions have been amply confirmed in actual clinical practice. Unless there is a major contraindication or caution to the use of irinotecan or oxaliplatin, the choice of cytotoxic agents should be made on an individual basis, taking into account the patient's medical history and personal preferences. Patients should be advised that certain toxicities are more likely with one regimen in comparison with another; FOLFOX poses a higher risk for peripheral sensory neuropathy and neutropenia, whereas FOLFIRI carries a greater incidence of alopecia and possibly fatigue. Contrary to popular misconceptions, the incidence of diarrhea between the two regimens has been similar in head-to-head trials.

Therefore, a medically fit patient with resectable mCRC would benefit from first-line chemotherapy using either FOLFOX or FOLFIRI, with concurrent bevacizumab, in the absence of a specific contraindication (eg, active wound healing or a history of an arterial thrombotic event). For those patients treated with the FOLFOX regimen, a planned withdrawal of oxaliplatin after no more than 12 doses, with continuation of fluoropyrimidine and bevacizumab, is most appropriate to modify neurotoxicity. Oxaliplatin can then be reintroduced further into treatment, if needed. Current investigations are evaluating the use of epidermal growth factor receptor inhibitors (cetuximab [Erbix] or panitumumab [Vectibix]) in conjunction with front-line regimens. At present, no randomized data exist to support such an approach;

therefore, use of these agents in front-line management of mCRC should still be regarded as investigational. A preliminary report from March 22, 2007, on the company Web site (www.amgen.com) indicates *inferior* PFS and overall survival in a group of patients who received panitumumab in conjunction with either FOLFOX/bevacizumab or FOLFIRI/bevacizumab, as compared with those who received chemotherapy plus bevacizumab without panitumumab.

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Conflicts of interest: Dr. Saltz is a consultant for Pfizer Inc, sanofi-aventis, Amgen, Roche Oncology, and Genentech.