

Second-line treatment in a patient with refractory or recurrent disease

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For patients who failed to respond or transiently responded to an initial intervention for metastatic colorectal cancer but are sufficiently fit to advance to second-line treatment, a survival benefit may be obtained from additional chemotherapy with standard agents (irinotecan, oxaliplatin, and 5-fluorouracil). The use of combination therapy is a preferred strategy to maximize exposure to as many effective agents as possible, and failure of first-line therapy should not be seen as a negative predictor of subsequent response.

The treatment of mCRC with irinotecan (Camptosar) or oxaliplatin (Eloxatin) in combination with 5-fluorouracil (5-FU) and folinic acid (leucovorin [LV])—and now often in combination with the antivascular endothelial growth factor monoclonal antibody bevacizumab (Avastin)—represents a standard first-line approach that is consistently associated with improved survival among responders.¹ However, some patients will not respond satisfactorily to an initial regimen, whereas others will respond transiently and then manifest recurrent disease later. By the time the need for second-line therapy is apparent, perhaps only 50%–60% of patients will be well enough to undergo an additional intervention.¹ For medically appropriate patients—those who failed to respond to an initial intervention but are sufficiently fit to advance to second-line treatment—a survival benefit may be obtained with additional chemotherapy.

Current evidence strongly suggests that overall survival (OS) is significantly correlated to receipt of all three standard drugs (irinotecan, oxaliplatin, and 5-FU) during the course of therapy for mCRC rather than to exposure to a specific second-line therapy.^{2,3} Since in this scenario the patient's disease has progressed despite the FOLF-FOX regimen, her subsequent treatment should

Case history

A 58-year-old woman with metastatic colorectal cancer (mCRC), who initially responded satisfactorily to management with FOLFOX (folinic acid, 5-fluorouracil [5-FU], oxaliplatin) over an 18-month interval, now has disease progression, with unilobar hepatic involvement, a 2-cm metastasis to the anterior abdominal wall, and a 4-cm lesion in the mesentery. The patient has an excellent performance status (PS) and, apart from her malignancy, no new complicating medical conditions. She is employed, has a supportive family, and remains committed to additional therapy.

incorporate irinotecan, which is a key constituent of second-line treatment regimens for medically fit patients with CRC that has progressed or recurred following 5-FU treatment.

Historic approach

Historically, second-line monotherapy with irinotecan following 5-FU failure was the first

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salvage intervention to be validated in a randomized, controlled fashion.⁴ In a 1998 evaluation, 279 patients with proven mCRC progressing within 6 months of 5-FU therapy were randomly assigned in a 2:1 ratio to receive either best supportive care (BSC) plus irinotecan (300–350 mg/m² every 3 weeks) or BSC alone. Overall survival was significantly improved ($P = 0.0001$) in patients receiving irinotecan therapy. Slightly more than 36% of patients who received irinotecan were alive at 1 year, in comparison with only 14% of patients receiving BSC alone, indicating a 2.6-fold survival advantage for patients receiving irinotecan. The median survival was 9.2 months in the irinotecan + BSC arm versus 6.5 months in the BSC-alone arm ($P = 0.0001$). More than 80% of subjects in this study were rated at World Health Organization (WHO) PS of 0 or 1, and those who received irinotecan demonstrated significantly longer survival without deterioration of PS ($P = 0.0001$) as well as longer survival without substantial weight loss ($P = 0.018$) and longer duration of pain-free survival ($P = 0.003$).⁴

In a second study published at approximately the same time, 267 patients for whom 5-FU treatment failed were randomly assigned to receive irinotecan (300–350 mg/m² once every 3 weeks) or continue 5-FU. At 15 months, the primary endpoint of OS was significantly longer among patients receiving irinotecan ($P = 0.035$); and at 1 year, 45% of patients treated with irinotecan were alive versus 32% of those who continued to receive 5-FU. The median survival with irinotecan was 10.8 months versus 8.5 months for those treated with 5-FU. Irinotecan was associated with improvement in a range of secondary outcome measures, including median progression-free survival (PFS; 4.2 vs 2.9 months; $P = 0.030$)

and median pain-free survival (10.3 vs 8.5 months; $P = 0.06$).⁵

Current practice

Therapy for mCRC may be seen as a paradigm for the rapidity with which approaches to treatment change as we gain new knowledge through the results of clinical studies. In current oncology practice, administration of second-line irinotecan as monotherapy is uncommon, and simplified regimens of LV and 5-FU (5-FU/LV) combined with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX6) are now employed more often. Nevertheless, irinotecan monotherapy remains an acceptable alternative to FOLFIRI following first-line FOLFOX failure.

There is good evidence that second-line treatment with FOLFIRI is an appropriate strategy for achieving prolonged survival following combination chemotherapy with FOLFOX, as shown in a randomized crossover trial involving 226 patients. In this study,⁶ patients whose disease had progressed were assigned to receive either FOLFOX6 followed by FOLFIRI or the reverse sequence. Patients receiving either sequence achieved prolonged survival and experienced similar efficacy: 111 patients allocated to FOLFOX6 followed by FOLFIRI achieved a median survival of 20.6 months, and 109 patients initially treated with FOLFIRI and switched to FOLFOX6 at disease progression achieved a median survival of 21.5 months ($P = 0.99$). The median duration of PFS during second-line treatment with either FOLFOX6 (14.2 months) or FOLFIRI (10.9 months) was statistically indistinguishable ($P = 0.64$).⁶

The recent UK Fluorouracil, Oxaliplatin, and Irinotecan: Use and Sequencing (FOCUS) trial,⁷ which reported results in 2005, reaffirms the importance of ensuring exposure to many highly active agents in both initial and salvage treatments. This

5-arm phase III trial randomly assigned 2,135 patients in the United Kingdom and Cyprus to receive infusional 5-FU/LV followed by irinotecan monotherapy (arm A), infusional 5-FU/LV followed by FOLFIRI (arm B1) or FOLFOX (arm B2), or first-line FOLFIRI (arm C1) or FOLFOX (arm C2). Biologic agents such as bevacizumab and cetuximab (Erbix) were not components of any treatment.

Arm A demonstrated a trend toward inferiority in OS, whereas median OS in arms B and C was only 14.8–16.3 months. Recourse to second- and third-line therapies in the FOCUS trial was limited, and only approximately 20% of patients had access to all three active cytotoxic agents. As noted previously, exposure to multiple highly active agents predicts a higher rate of OS in advanced CRC^{2,3}; the relatively lower OS in this trial may be a reflection of this finding.

Today, most patients receive bevacizumab in combination with one of the accepted front-line chemotherapy regimens. However, compelling data attest to its efficacy in second-line regimens. In the randomized phase III Eastern Oncology Cooperative Group (ECOG) E3200 trial involving 829 patients,⁸ at a median follow-up of 18.7 months, the addition of bevacizumab to FOLFOX4 improved response rate, PFS (7.4 vs 5.5 months; $P = 0.0003$), and OS (12.5 vs 10.7 months; $P = 0.002$) over FOLFOX4 alone. Patients treated with FOLFOX4 alone as a first-line regimen conceivably could derive at least some benefit by having bevacizumab added to the irinotecan regimen used in second-line treatment, provided there is no contraindication to its use.

Novel option

Combining irinotecan with cetuximab, another monoclonal anti-

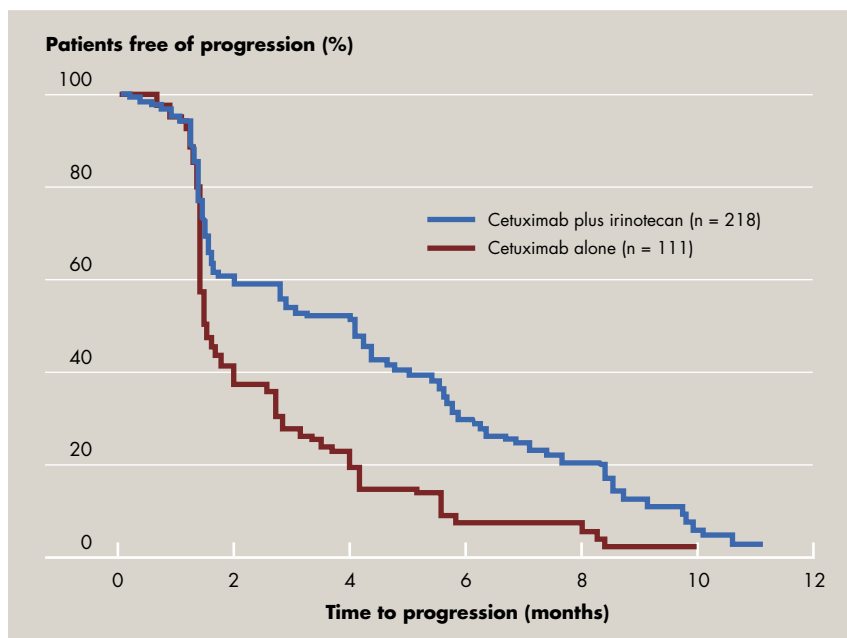


FIGURE 1 Median time to disease progression in 329 patients in the BOND-1 trial. Patients were treated with either cetuximab alone or in combination with irinotecan. Adapted, with permission, from Cunningham et al.⁹ Copyright © 2004, Massachusetts Medical Society. All rights reserved.

body directed against the epidermal growth factor receptor, is a relatively new approach, utilizing knowledge gained from recent trials. Cetuximab has synergistic activity with irinotecan against CRC, even in irinotecan-refractory tumors.

In the Bowel Oncology with Cetuximab Antibody (BOND)-1 trial, 329 patients with advanced, highly refractory CRC were randomly assigned to receive cetuximab or cetuximab plus irinotecan as salvage therapy. Nearly 80% of patients had received two or more previous regimens of chemotherapy; all had been treated previously with irinotecan, and more than 60% had also received oxaliplatin-based therapy.

Treatment with cetuximab plus irinotecan achieved a response rate of 22.9%, significantly higher than that achieved with cetuximab monotherapy (10.8%; $P = 0.007$). The median time to disease progression (TTP) in the two study groups is shown in Figure 1: 4.1 months with combination treatment versus

1.5 months with cetuximab alone ($P < 0.001$).⁹ The median survival was also significantly longer with combination therapy (8.6 vs 6.9 months in the monotherapy group; $P = 0.48$). Although toxic effects were more frequent in the combination-therapy group, their severity and incidence were similar to those associated with irinotecan alone. Cetuximab plus irinotecan was effective in patients who had been previously treated with oxaliplatin as well as irinotecan; cetuximab/irinotecan achieved a response rate of 22.2% in these multiply pretreated patients.⁹

BOND-2 compared cetuximab plus bevacizumab with cetuximab/bevacizumab/irinotecan (CBI). This was a relatively small trial, enrolling fewer than 80 patients. As in BOND-1, all enrolled patients had advanced CRC, all had failed to respond to prior irinotecan-based therapy, and most (approximately 60% in BOND-1 and nearly 85% in BOND-2) had failed to respond to

prior oxaliplatin treatment.

The addition of bevacizumab improved the efficacy of cetuximab and cetuximab/irinotecan in terms of response rate and TTP. In BOND-1, cetuximab/irinotecan therapy was associated with a median TTP of only 4.1 months, whereas 39 patients who received treatment with CBI exhibited a response rate of 38% and a median TTP of 8.5 months.¹⁰ An interim report suggests that toxicities in this study were not substantially different from those associated with the individual agents. Patients in the CBI arm had a higher rate of severe diarrhea, fatigue, and neutropenia than those treated with cetuximab plus bevacizumab.^{11,12}

For our patient in this scenario, despite failure of previous treatment with an oxaliplatin-containing regimen, a number of second-line therapies—many of which employ combinations of cytotoxic and biologic agents—are appropriate. The use of combination therapy is a preferred strategy to maximize exposure to as many effective agents as possible, and failure of first-line therapy should not be seen as a negative predictor of subsequent response. Irinotecan has a prominent role in many of the regimen possibilities available to the treating oncologist and can be considered a reference treatment for individuals who have responded unsatisfactorily to a previous regimen.

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Conflicts of interest: Dr. Hoff serves as a consultant for Roche Pharmaceuticals, Pfizer Inc, and sanofi-aventis Group, and has received honoraria from Roche Pharmaceuticals.