

TREATMENT OF METASTATIC COLORECTAL CANCER

Review of recent advances

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Top-line summary

Colorectal cancer ranks second as a cause of cancer death in Canadian men and third in women.¹ Unfortunately, metastatic disease — either present at diagnosis or recurring following resection — occurs in a significant proportion of patients. The last few years have seen important advances in the treatment of metastatic colorectal cancer (MCRC), including introduction of regimens based on oxaliplatin, irinotecan, oral capecitabine, and the monoclonal antibodies cetuximab and bevacizumab. Here, *Oncology Exchange* reviews notable recent developments in the management of metastatic colorectal cancer, including chemotherapy as first-line, second-line and neoadjuvant treatment, and the integration of targeted therapies into existing regimens.

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An estimated 19,600 new cases of colorectal cancer (CRC) will be diagnosed in Canada in 2005,¹ and 25% of patients will exhibit metastatic disease at presentation. An additional 30% of those with localized resectable disease will subsequently develop metastatic recurrence.

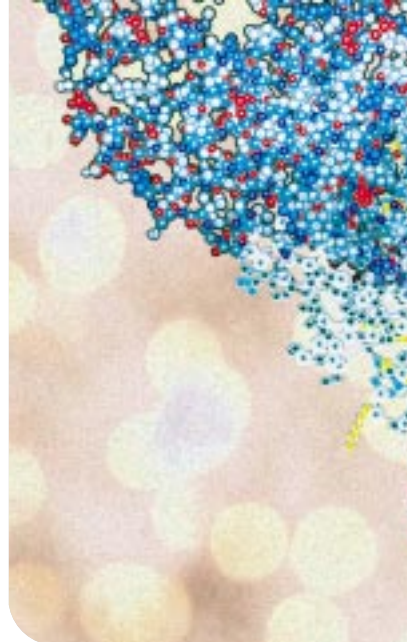
While a proportion of selected patients with liver and/or lung-limited oligometastases may be amenable to curative-intent metastatectomy, palliative systemic therapy remains the mainstay strategy for Stage IV (i.e. metastatic) CRC. The 3 most active agents currently available are 5-fluorouracil (5FU) (or capecitabine, an oral 5FU prodrug), irinotecan and oxaliplatin. These agents provide significant treatment-related improvement in median survival — approaching 2 years for treatment with all 3 agents² — compared to an estimated survival of 6 months with best supportive care alone.

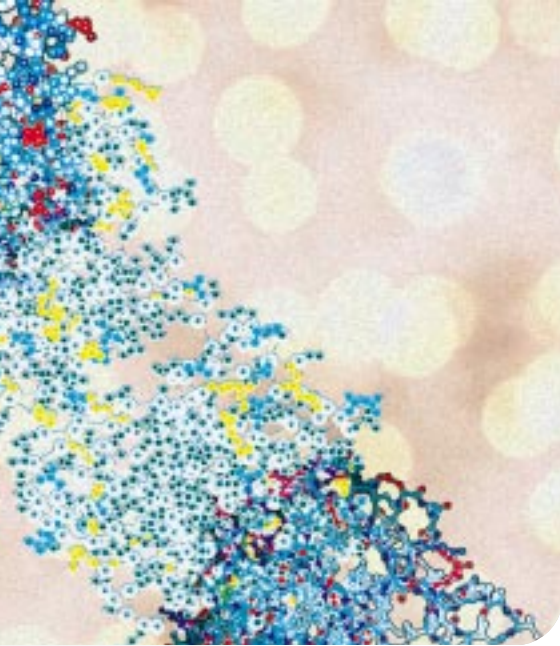
FIRST-LINE TREATMENT OF MCRC

N9741 was a randomized North American intergroup trial comparing FOLFOX4 and IROX to IFL — the standard first-line regimen for metastatic CRC at the time (see **Table 1**, page 8 for details of regimens).³ FOLFOX4 showed significantly superior efficacy compared to IFL in time to progression (TTP) (8.7 vs 6.9 months, $p = 0.0014$), response rate (RR) (45% vs 31%, $p = 0.002$) and median survival (19.5 vs 14.8 months, $p = 0.0001$). IFL was associated with more diarrhea, vomiting, nausea and febrile neutropenia, while patients

treated with FOLFOX4 experienced higher rates of paresthesias. Based upon these results, the US FDA approved oxaliplatin for first-line treatment in 2004; regulatory approval of oxaliplatin is still pending in Canada.

While IFL is no longer recommended for first-line therapy, 2 recent trials indicate that the combination of irinotecan with infusional 5FU and leucovorin (FOLFIRI) is a valid alternative. Tournigand et al of the French Groupe Coopérateur Mutidisciplinaire en Oncologie (GERCOR) designed a trial to determine the best strategy for sequential combination therapy, randomly assigning 220 patients with metastatic CRC to a sequence of FOLFIRI followed by FOLFOX6 or the reverse.⁴ Either sequence of FOLFOX6-FOLFIRI or FOLFIRI-FOLFOX6 achieved impressive equivalent first-line RRs (54% and 56% respectively) and median survivals (20.6 and 21.5 months) in this study. The randomized trial of first-line FOLFOX4 (36%) vs FOLFIRI (34%) reported by Colucci and colleagues, in 2003, also showed RR efficacy.⁵ Toxicity varied, with nausea, mucositis and alopecia more frequent in patients taking FOLFIRI and neutropenia and paresthesias more frequent in those on FOLFOX4.





Strategies to optimize these efficacious regimens are now being evaluated. To address whether an approach of first-line doublet therapy is superior to a single-drug, staged approach (drug A until it fails, then drug B until it fails) or a staged combination approach (drug A until it fails, then add drug B until both fail), the UK Medical Research Council (MRC) conducted the FOCUS randomized trial.⁶ While the staged combination approach was equivalent to first-line combination therapy, a trend towards inferiority was observed for the single-drug staged approach. Treatment toxicity was also a concern, with the major dose-limiting toxicity of oxaliplatin being cumulative neuropathy. The OPTIMOX1 trial⁷ randomly assigned patients to FOLFOX4 until progression or to OPTIMOX1: 6 cycles of modified FOLFOX7 followed by maintenance LV5FU2 for 12 cycles, and those with non-progressive disease then resumed treatment with FOLFOX7. Overall RR, progression-free survival (PFS) and survival were similar despite the decreased use of oxaliplatin in the OPTIMOX1 arm. Subsequent OPTIMOX trials are evaluating a stop and go strategy — no maintenance LV5FU2 (OPTIMOX2) — and integration of molecular targeted therapies (OPTIMOX3).

Biweekly infusional 5FU therapy is inconvenient, so the alternative use of the oral 5FU prodrug capecitabine appears promising. A randomized Phase II trial of capecitabine + irinotecan (CAPIRI) or oxaliplatin (CAPOX) demonstrated substantial first-line RRs

and TTP: 42.6%, 7.9 months, respectively in CAPIRI and 51.3%, 7.9 months in CAPOX.⁸ A Phase II trial of the XELOX regimen also reported similar tolerability and efficacy, with first-line RR of 55%, TTP of 7.7 months and median survival of 19.5 months.⁹ Phase III trials are ongoing, particularly comparing infusional 5FU/LV + oxaliplatin with capecitabine + oxaliplatin as first-line therapy. In one such trial, when compared to the weekly AIO regimen + oxaliplatin (FUFOX), CAPOX achieved comparable RRs (45% vs 41%) and PFS (35 weeks vs 30 weeks).¹⁰

At present, combination therapy with infusional 5FU plus oxaliplatin or irinotecan are appropriate choices for the first-line management of people with unresectable metastatic colorectal cancer and reasonable performance status. For less fit, poorer performance-status patients, first-line monotherapy with capecitabine remains a viable treatment option.

SECOND-LINE TREATMENT

Factors influencing selection of a second-line regimen include the first-line regimen, degree of response to first-line therapy, toxicity concerns and performance status. When IFL moved to first-line therapy in the late 1990s, the need for second-line options after IFL progression arose. Rothenberg and colleagues randomized 463 patients who progressed after IFL to LV5FU2, oxaliplatin alone or FOLFOX4.¹¹ FOLFOX4 achieved superior response rates (1%, 1% and 10% respectively) and TTP (8.1, 8.7 and 9.8 months). The previously-described Tournigand study highlighted the role of sequential therapy:⁴ 82% of patients on FOLFIRI received second line FOLFOX6 with a RR of 15% while 74% of those on FOLFOX6 went on to receive second-line FOLFIRI with a modest RR of 4%. Because exposure to all 3 active agents extends survival² and because a proportion of patients may not be suitable for second-line therapy, the strategy of combining oxaliplatin, irinotecan and 5FU in a single first-line regimen is also under investigation.¹²

NEOADJUVANT CHEMOTHERAPY

The liver is typically the initial and most common site of CRC metastases. Resection of liver-limited metastases is

curative in approximately 35% of selected patients.¹³ The likelihood of complete resection depends upon the extent of hepatic involvement, tumour location and hepatic reserve.¹⁴ Despite advances in surgery and the increasing use of ablative techniques including radiofrequency ablation and cryosurgery, most patients are not candidates for resection. With the availability of efficacious systemic chemotherapies, a neoadjuvant approach in those with unresectable metastatic CRC has the potential to downstage disease to resectability. Emerging evidence supports a greater prospect of resectability with an oxaliplatin-based regimen. In N9741, 24 of 795 (3.3%) randomized patients subsequently underwent curative metastectomy, and 92% of these had received an oxaliplatin-based regimen.¹⁵ Similarly, the rate of metastectomy was higher with first-line FOLFOX6 vs FOLFIRI (13% vs 7%, $p = \text{NS}$) in the Tournigand trial.⁴

A trial of neoadjuvant chemotherapy can also be undertaken as an in vivo test of chemosensitivity to guide post-resection therapy, as it may identify patients for whom surgery would not be appropriate. A review of clinical trial patients with liver-limited, initially unresectable metastases found the efficacy of neoadjuvant chemotherapy to be a strong predictor for resectability of liver metastases.¹⁶ Consideration of neoadjuvant therapy can also be extended to those with resectable disease, as it may facilitate more complete resections and limited hepatectomies.

BIOLOGIC THERAPIES Targeting EGFR

Cetuximab is a chimeric monoclonal antibody (MAb) against the extracellular domain of the epidermal growth factor receptor (EGFR). Earlier studies suggested efficacy in patients with irinotecan-refractory metastatic CRC.^{17,18} The BOND trial was a UK MRC randomized (2:1 assignment) Phase II trial of irinotecan + cetuximab (400 mg/mg² loading dose, then weekly 250 mg/m²) or cetuximab alone in irinotecan-refractory metastatic CRC.¹⁹ Over 60% of enrolled patients had previously progressed on oxaliplatin. Response rate (the primary

TABLE 1. Chemotherapy regimens discussed in this review

LV5FU2	leucovorin 400 mg/m ² on day 1 with bolus 5FU 400 mg/m ² followed by a 46-hour infusion of 5FU 2400–3000 mg/m ² every 2 weeks	FOLFOX7	oxaliplatin 130 mg/m ² , leucovorin 400 mg/m ² and a 46-hour infusion of 5FU 2400 mg/m ² every 2 weeks
IFL	irinotecan 125 mg/m ² with bolus 5FU 500 mg/m ² and leucovorin 20 mg/m ² on days 1, 8, 15 and 22 every 6 weeks	FOLFIRI	irinotecan 180 mg/m ² with bolus 5FU 400 mg/m ² and leucovorin 400 mg/m ² followed by a 46-hour infusion of 5FU 2400 mg/m ² every 2 weeks
IROX	oxaliplatin 85 mg/m ² on day 1 with bolus 5FU 400 mg/m ² and leucovorin 200 mg/m ² followed by a 22-hour infusion of 5FU 600 mg/m ² on days 1 and 2 every 2 weeks	FUFOX	oxaliplatin 50 mg/m ² with leucovorin 500 mg/m ² and a 24-hour infusion of 5FU 2000 mg/m ² on days 1, 8, 15 and 22 every 5 weeks
FOLFOX4	oxaliplatin 85 mg/m ² on day 1 with bolus 5FU 400 mg/m ² and leucovorin 200 mg/m ² followed by a 22-hour infusion of 5FU 600 mg/m ² on days 1 and 2 every 2 weeks	CAPIRI	capecitabine 1000 mg/m ² po BID on days 1 to 14 plus irinotecan 80 mg/m ² on days 1 and 8
FOLFOX6	oxaliplatin 100 mg/m ² with bolus 5FU 400 mg/m ² and leucovorin 400 mg/m ² followed by a 46 hour infusion of 5FU 2400 mg/m ² every 2 weeks	CAPOX	capecitabine 1000 mg/m ² po BID on days 1 to 14 oxaliplatin 70 mg/m ² on days 1 and 8 every 21 days
		XELIRI	capecitabine 1000 mg/m ² po BID on days 1 to 14 plus irinotecan 250 mg/m ² per day
		XELOX	capecitabine 1000 mg/m ² po BID days 1 to 14 plus oxaliplatin 130 mg/m ² on day 1 every 21 days

endpoint), TTP and survival were respectively 23%, 4.1 months and 8.6 months for irinotecan + cetuximab and 11%, 1.5 months and 6.9 months for cetuximab alone. Cetuximab use was associated with an acneiform rash. Response did not correlate with expression of EGFR as measured by immunohistochemistry did but may correlate with the severity of rash.^{19,20} Cetuximab has been approved in the US, the European Union and Canada for second or subsequent-line therapy in patients with EGFR-positive, irinotecan-refractory metastatic CRC. Active trials of interest include the National Cancer Institute of Canada Clinical Trials Group Study CO-17, which randomizes patients with chemotherapy-refractory disease between cetuximab and best supportive care. EPIC (CA225-006) is a randomized trial of irinotecan + cetuximab vs irinotecan alone in oxaliplatin-refractory advanced disease while the EXPLORE trial (CA225-014) randomly assigns patients with irinotecan-refractory disease to second-line FOLFOX4 or FOLFOX4 + cetuximab.

Recent Phase II trials also suggest promising efficacy for cetuximab in patients with chemotherapy-naïve metastatic CRC. When used in combination with first-line FOLFOX4, an

overall RR of 72% was achieved with acceptable safety.²¹ Phase III randomized trials are examining cetuximab in combination with chemotherapy as first-line therapy.

Targeting VEGF

Bevacizumab is a humanized MAb to vascular endothelial growth factor A (VEGF-A) that halts the VEGF signaling pathway. The pivotal trial was a randomized comparison of first-line IFL + placebo with IFL + bevacizumab 5 mg/kg every 2 weeks.²² As reported last year by Hurwitz et al, the addition of bevacizumab increased median survival from 15.6 to 20.3 months ($p < 0.001$), TTP from 6.2 to 10.6 months ($p < 0.001$) and RR from 35% to 45% ($p = 0.004$). Significant toxicity with bevacizumab was limited to grade 3 hypertension (10.3% vs 2.3%) and rare reports of gastrointestinal perforation and wound dehiscence.

Bevacizumab in combination with first-line 5FU/LV chemotherapy has been evaluated in two Phase II trials^{23,24} and as a third treatment arm of the Hurwitz trial (which was discontinued after a planned interim analysis established acceptable safety for the IFL + bevacizumab arm).²⁵ In a combined efficacy analysis of these 3 studies, the addition of bevacizumab to 5FU +


LV was associated with a significant improvement in survival (17.9 vs 14.6 months, $p = 0.008$), TTP (8.8 vs 5.6 months, $p < 0.0001$) and RR (34% vs 24%, $p = 0.019$).²⁶ Based upon these data, the US FDA approved bevacizumab in February 2004 for use with any 5FU-based first-line regimen. Approval in Canada (September 2005) was received for a similar indication. European Union approval (January 2005) was limited to use with a first-line irinotecan-based regimen. A randomized Phase III 2 X 2 factorial intergroup trial of first-line FOLFOX6 vs XELOX with or without bevacizumab (SWOG 0303) was initiated in April 2004 but has been prematurely closed due to poor accrual.

Giantonio and colleagues recently reported the results of ECOG 3200, a randomized second-line trial of FOLFOX4 + placebo vs FOLFOX4 + bevacizumab vs bevacizumab alone in patients with IFL-refractory metastatic CRC.²⁷ Survival, TTP and RR with FOLFOX4 + bevacizumab (10 mg/kg every 2 weeks) was superior to FOLFOX4 alone: respectively 12.9 vs 10.8 months ($p = 0.0018$), 7.2 vs 4.8 months ($p \leq 0.001$) and 22% vs 9% ($p < 0.001$). No meaningful activity was seen with single-agent bevacizumab (RR 3%). Hypertension and rare reports

of bowel perforation were again associated with bevacizumab use. In summary, enhanced efficacy and acceptable toxicity have been demonstrated with the addition of bevacizumab to first-line irinotecan-based therapy and 5FU/LV, and to second-line oxaliplatin-based therapy. Emerging evidence suggests that the additive efficacy of bevacizumab in combination with cytotoxic chemotherapy is mediated by anti-VEGF-induced vascular normalization that may alleviate hypoxia and improve drug delivery.²⁸

The VEGF signaling pathway can also be targeted by inhibiting the tyrosine kinase receptor. Valatanib (PTK787) is an oral small-molecule tyrosine kinase inhibitor with pan-VEGF receptor activity. CONFIRM1 was a randomized trial of first-line FOLFOX4 with or without valatanib.²⁹ As reported at this year's American Society of Clinical Oncology (ASCO) Annual Meeting, this study failed to meet its primary endpoint of improved TTP (7.7 vs 7.6 months, $p = 0.118$). Results from the second-line CONFIRM2 trial are expected in 2006.

OPTIMAL THERAPY SELECTION

New effective chemotherapies and biologic therapies have introduced several potential treatment options for the management of metastatic CRC. The optimal strategy to implement available therapies and achieve maximal clinical benefit continues to be defined. Planned trials include a first-line Inter-group trial of FOLFOX or FOLFIRI in combination with bevacizumab, cetuximab or both. At present, it is difficult to endorse a single standard regimen for first- and subsequent-line therapy. The selection of a particular therapy needs to be judicious and deliberate, based upon an appraisal of the best available clinical evidence. One must also reflect on the consequent potential toxicities of such therapies and on their financial costs. Ultimately, studies pursuing rational treatment selection based upon individualized molecular and pharmacogenomic profiles will be required to prospectively identify patients most likely to benefit from a given therapy. 

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