

Rational treatment planning for metastatic disease

Axel Grothey, MD

Mayo Clinic Rochester, Rochester, MN

In the majority of patients with metastatic colorectal cancer (mCRC), palliative chemotherapy is the only treatment option. In the past 10 years, the availability of new cytotoxic and targeted therapies has considerably prolonged survival and increased the time to disease progression in these patients. No single approach to mCRC management exists; treatment must be individualized for each patient. The National Comprehensive Cancer Network recommends at least four different first-line therapies, eight second-line therapies, and six third-line therapies for patients who can tolerate intensive therapy. With patients living longer, the current challenge in treating mCRC lies in long-term treatment planning—developing a strategy to allow patients to experience the maximum benefit of therapy by providing all available active agents over the course of therapy and, at the same time, minimizing toxicities. In an effort to reduce the toxicity associated with chemotherapy regimens, the concept of drug holidays in managing mCRC is being actively explored.

Approximately 30% of all patients with colorectal cancer (CRC) have metastatic disease at diagnosis, and 50% of patients with early-stage disease develop metastatic or advanced disease.¹ About half of all patients with metastatic disease will have metastases to the liver.² The primary goal of therapy is curative resection. However, only 5%–10% of patients with liver metastases are candidates for surgical resection.³

Palliative chemotherapy remains the only option for most patients with metastatic disease. The goal of therapy for these patients is to prolong survival and control disease progression while preserving function and maintaining quality of life. This objective has been made possible by the availability of both cytotoxic agents (irinotecan [Camptosar], oxaliplatin [Eloxatin], and capecitabine [Xeloda]) and targeted therapies (bevacizumab [Avastin], cetuximab [Erbix], and panitumumab [Vectibix]), which have considerably prolonged survival and increased the time to disease progression (TTP).⁴ With patients living longer, the current challenge in metastatic colorectal cancer (mCRC) is to develop a rational treatment plan that allows patients

to experience the maximum benefit of therapy from currently available active agents while minimizing their toxicities.

Key considerations in rational treatment planning

Treatment planning for patients with mCRC needs to be individualized and must take several factors into consideration, including disease status; overall health status; the nature, timing, and outcome of prior surgery and adjuvant treatment (chemotherapy, radiation therapy) and their effects on the tolerability and effectiveness of first-line therapy options; nonmedical factors, including lifestyle or daily living needs and expectations, psychosocial factors, economic factors, and logistical and support factors; overall goals of therapy; mode of administration of therapies; and patient preferences (Figure 1). In addition, the toxicity profiles of chemotherapy agents and regimens must be considered, as they are critical to the

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Correspondence to: Axel Grothey, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55902; telephone: 507-284-2779; fax: 507-202-0916; e-mail: grothey.axel@mayo.edu.

choice of first- and later-line therapies for mCRC.

First-line treatment considerations

Combination chemotherapy is the standard first-line treatment for mCRC. Based on data derived from randomized trials, the National Comprehensive Cancer Network (NCCN) has recommended four different treatment options—FOLFIRI: irinotecan/leucovorin (LV)/continuous-infusion 5-fluorouracil (5-FU) plus bevacizumab; FOLFOX: oxaliplatin/continuous-infusion 5-FU/LV plus bevacizumab; CapeOX: capecitabine/oxaliplatin plus bevacizumab; or 5-FU/LV plus bevacizumab—as first-line therapy in patients who can tolerate intensive therapy.⁵ During the past 5 years, the expanded armamentarium for mCRC has doubled overall survival (OS) from approximately 10 months to 20 months and nearly doubled response rates (RRs) from 25% to 46%.⁴ As no one combination regimen has been found to be superior over any other, the choice of which combination therapy to use up front should be based on consideration of the type and timing of prior therapy and the different toxicity profiles of the constituent drugs.⁵ Long-term planning also should be taken into consideration, as first-line combination therapy can impact the choice of later-line therapies.

Treating recurrent disease

The NCCN recommends various sequencing options for patients who can tolerate intensive therapy and whose disease has progressed on first-line therapy (Table 1).⁵ Irinotecan plus cetuximab is recommended as later-line therapy for patients whose disease is refractory to a previous irinotecan-containing regimen. This recommendation is based on data demonstrating that cetuximab may

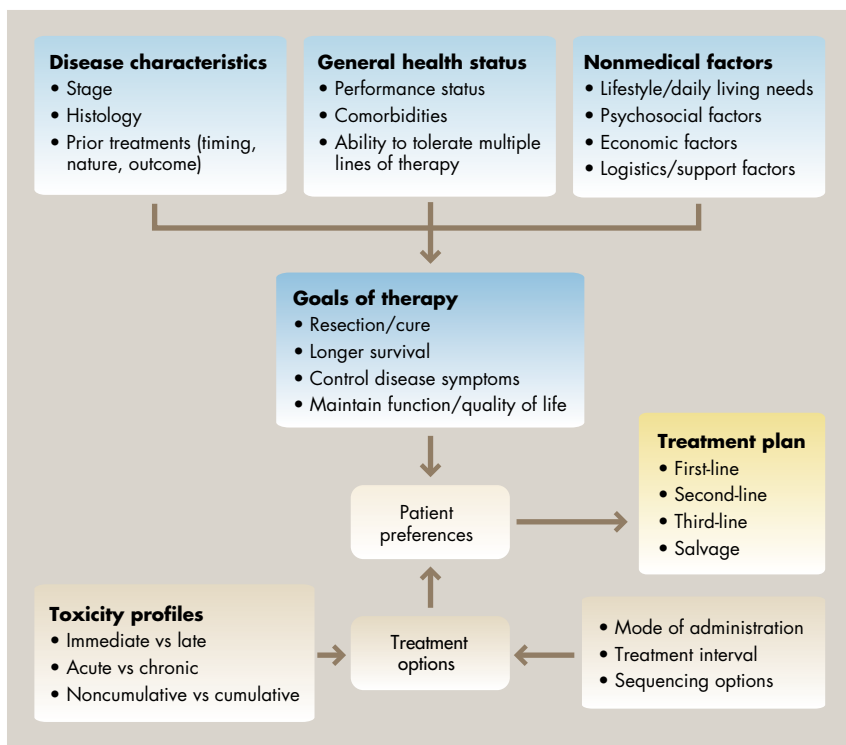


FIGURE 1 Parameters to consider when formulating a treatment plan for patients with metastatic colorectal cancer.

help overcome irinotecan resistance in some patients.⁶

For patients who cannot tolerate intensive therapy and whose disease progresses after first-line therapy with capecitabine, with or without bevacizumab, or 5-FU/LV, with or without bevacizumab, the NCCN guidelines recommend best supportive care if there is no improvement in functional status. If functional status has improved, however, the second-line treatment options recommended for patients who can tolerate intensive therapy may be considered.⁵

Toxicity profiles of therapeutic agents

Treatment-planning considerations to minimize toxicity include whether a particular toxicity usually occurs early or late in the course of treatment, whether it is acute or chronic, whether it is cumulative or noncumulative, and whether it is reversible or irreversible. Toxicities that are cumulative, such as the neurotoxic-

ity associated with oxaliplatin, can limit long-term therapy.

The most common side effects of the cytotoxic agents are gastrointestinal effects (nausea/vomiting and diarrhea) and myelosuppression (Table 2). Mucositis and hand-foot syndrome are characteristic side effects of fluoropyrimidines. Although hand-foot syndrome is often manageable and not life threatening, it can affect quality of life. Neurotoxicity is unique to oxaliplatin and is often the reason for stopping oxaliplatin therapy, even before disease progression has occurred. Fatigue, diarrhea, and myelosuppression are common side effects of irinotecan.

Side effects associated with biologic agents are distinctly different from the side effects of cytotoxic agents (Table 2). A low incidence of gastrointestinal perforation, wound-healing complications, hypertension, and congestive heart failure (seen mainly in breast can-

TABLE 1

Treatment sequencing options for patients with metastatic colorectal cancer who can tolerate intensive therapy⁵

Initial therapy	Therapy after first progression	Therapy after second progression
FOLFOX + bevacizumab or CapeOX + bevacizumab	FOLFIRI or irinotecan	Cetuximab or panitumumab or cetuximab + irinotecan
	FOLFIRI + cetuximab or cetuximab + irinotecan	Clinical trial or best supportive care
FOLFIRI + bevacizumab	FOLFOX or CapeOX	Cetuximab or panitumumab or cetuximab + irinotecan
	Cetuximab or panitumumab or cetuximab + irinotecan	FOLFOX or CapeOX
5-FU/LV + bevacizumab	FOLFOX or CapeOX	Irinotecan → cetuximab or irinotecan → panitumumab or irinotecan → cetuximab + irinotecan
	Irinotecan or FOLFIRI	Cetuximab or panitumumab or cetuximab + irinotecan

CapeOX = capecitabine + oxaliplatin; 5-FU/LV = 5-fluorouracil/leucovorin; FOLFOX = infusional 5-FU/LV; FOLFIRI = irinotecan + infusional 5-FU/LV

cer patients who had prior anthracycline therapy) is associated with bevacizumab therapy. In addition, a twofold higher incidence of thromboembolic events has been associated with the use of bevacizumab.⁷ Older patients and patients with a history of arteriothrombotic events are at greater increased risk. Cetuximab and panitumumab are associated mainly with infusion reactions and follicular rash, although infusion reactions appear to be less of a problem with panitumumab.

Treatment toxicities can lead to treatment changes (dose reductions or treatment-plan interruptions or discontinuations) and compromise outcomes. Thus, proactive patient and caregiver education, diligent application of prophylactic measures, close monitoring, and careful, prompt responses to emergent toxicities should be instituted to prevent or manage toxicities. Recently, the concept of “drug holidays” has been explored in mCRC in an effort to reduce the toxicity of chemotherapy regi-

mens, particularly those containing irinotecan or oxaliplatin.

Reducing toxicity with drug holidays

In the Italian Group for the Study of Digestive Tract Cancer (Gruppo Italiano per lo Studio del Carcinoma Apparato Digerente [GISCAD]) trial, the efficacy and safety of a FOLFIRI regimen administered every 2 weeks for 2 months and discontinued for 2 months until disease progression occurred (intermittent regimen, arm A) were compared with those of the FOLFIRI regimen administered continuously until disease progression occurred (continuous regimen, arm B) in patients with advanced CRC.⁸ Patients in arm A had an RR of 29%, compared with 35% among the patients in arm B. Median progression-free survival (PFS) was 8.8 months in arm A and 7.3 months in arm B (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.74–1.36). At a median follow-up of 27 months, median OS, the primary endpoint of

the trial, was 16.9 months in arm A and 17.6 months in arm B (HR, 1.11; 95% CI, 0.83–1.48). Grades 3 and 4 hematologic and nonhematologic toxicities in arm B were similar or only slightly higher than those in arm A (Table 3). The authors of the trial concluded that an alternating FOLFIRI regimen achieves the same survival benefit as a continuous regimen, with less patient discomfort and reduced expense.

In the stop-and-go trial of oxaliplatin in combination with 5-FU/LV (OPTIMOX1), patients were randomized to receive treatment with FOLFOX4 every 2 weeks until disease progression occurred or receive FOLFOX7 therapy for 6 cycles, followed by maintenance therapy with 5-FU/LV for 12 cycles and then reintroduced to FOLFOX7.⁹ The investigators found that oxaliplatin can be safely stopped after 6 cycles of FOLFOX7. Median PFS and OS were 9.0 and 19.3 months, respectively, in patients receiving FOLFOX4, compared with 8.7 and 21.12 months, respectively, in those receiving the FOLFOX7 reintroduction regimen.

OPTIMOX2 took the concept of chemotherapy reduction further and compared the FOLFOX7 maintenance therapy regimen of OPTIMOX1 with a chemotherapy-free interval regimen in which mFOLFOX7 was given for 6 cycles, but was not followed by any chemotherapy until disease progressed to baseline levels, at which point mFOLFOX7 was reintroduced.¹⁰ The mFOLFOX7 regimen used in OPTIMOX2 reduced the dose of oxaliplatin from 130 mg/m² to 100 mg/m² every 2 weeks. The study's primary endpoint was duration of disease control (DDC), defined as the sum of PFS associated with the first FOLFOX7 administration plus the PFS associated with the reintroduction of mFOLFOX7, if there was no disease progression at first evaluation. The maintenance chemotherapy regimen produced a

Clinical commentary

Clinicians should think about replacing the term “lines of therapy” with “treatment strategy.” To maximize survival and quality of life, we need to think in terms of strategy when caring for patients with CRC, instead of treating the disease with one line of therapy until disease progression or toxicity. A proposed new clinically relevant endpoint is “time to failure of a strategy.”

Drug holidays make sense, but the best way to intersperse chemotherapy and biologics with drug holidays is not yet known. We hope additional study and follow-up will define the best approach.

After adjuvant FOLFOX, I would always use irinotecan-based chemotherapy at recurrence because neurotoxicity is likely to be a problem.

Currently, the only time I use a biologic in any adjuvant setting is after complete resection of metastasis in a patient with stage IV disease.

—Alan P. Venook, MD

median PFS of 8.7 months compared with the chemotherapy-free interval regimen, with a median PFS of 6.9 months ($P = 0.009$). The researchers concluded that maintenance 5-FU/LV therapy prolongs PFS. However, although PFS was improved, DDC was comparable in the maintenance therapy (41 weeks) and chemotherapy-free interval (36 weeks) groups ($P = 0.17$).

The incidence of neuropathy seen in OPTIMOX2 during the initial cycles of therapy, at 2 months after FOLFOX discontinuation, and after the initial reintroduction of FOLFOX is summarized in Table 4. It appears that even when patients discontinue oxaliplatin, neurotoxic symptoms can continue to be manifested and become worse over time. Notably, mFOLFOX7—in contrast to mFOLFOX6 or FOLFOX4—completely omits the use of bolus 5-FU, which greatly reduces the myelotoxicity of the regimen without compromising efficacy.

Roundtable discussion

The roundtable discussion on key issues in rational treatment planning for metastatic disease was moderated by Dr. Axel Grothey. Participants included Drs. Al Benson III, Charles Blanke, and Charles Fuchs.

How has the approach to treatment planning evolved with the availability of multiple effective lines of therapy for mCRC?

Dr. Fuchs: There is no single standard treatment approach. An approach that is individualized to each patient’s needs makes sense. It is worth thinking ahead—realizing, of course, that you might change your mind over time. Where are you starting? Where might you want to go with additional therapies? The paradigm of lines of therapy does become blurred with colon cancer. Clinicians need to be a bit wary about thinking in terms of first- and second-line therapies.

When designing studies for treating refractory stages of colon cancer, I think about not how many lines of therapy are required before patients can be enrolled in the study but how many drugs they have been exposed to.

Dr. Grothey: I am no longer in favor of the phrase “lines of therapy.” We talk about treatment phases because we are adjusting the treatment regimens. We are looking at how many agents or which agent the patient has received and how long ago. We might reutilize agents in different combinations, even in situations where patients have shown tumor progression on prior, so-called lines of therapy.

A classic example is the way we

TABLE 2

Toxicity profiles of therapeutic agents for metastatic colorectal cancer

Agent	Toxicity
<i>Cytotoxic agents</i>	
Capecitabine	Dermatologic Hand-foot syndrome Hyperpigmentation Gastrointestinal Diarrhea Nausea/vomiting Stomatitis/mucositis Myelosuppression
5-FU/LV	Dermatologic Hand-foot syndrome Gastrointestinal Diarrhea Mucositis Myelosuppression
Irinotecan	Fatigue Gastrointestinal Diarrhea Myelosuppression
Oxaliplatin	Gastrointestinal Diarrhea Nausea/vomiting Hypersensitivity Myelosuppression Neurotoxicity Acute Chronic
<i>Biologic agents</i>	
Bevacizumab	Cardiovascular Arterial thromboembolic events Congestive heart failure Hemorrhage Hypertension Gastrointestinal perforation Proteinuria (nephrotic syndrome) Wound-healing complications
Cetuximab	Dermatologic Follicular rash Electrolyte depletion Infusion reactions Interstitial lung disease (rare)
Panitumumab	Dermatologic Erythema Follicular rash Pruritus Electrolyte depletion Gastrointestinal Diarrhea Infusion reactions Pulmonary fibrosis (rare)

5-FU/LV = 5-fluorouracil/leucovorin

use irinotecan. We know that to some extent we can resensitize patients to irinotecan when we combine irinotecan with an anti-EGFR (epider-

TABLE 3

GISCAD: toxicity profile of intermittent vs continuous administration of FOLFIRI*

Grades 3/4 toxicity	Intermittent (arm A), %	Continuous (arm B), %
<i>Nonhematologic</i>		
Diarrhea	3.6	3.2
Nausea/vomiting	4.2	6.4
Fever	12.8	14.7
<i>Hematologic</i>		
Neutropenia (no grade 4 seen)	1.8	2.6
Anemia	0.0	1.3
Thrombocytopenia	3.0	3.8

FOLFIRI = irinotecan/leucovorin/continuous-infusion 5-fluorouracil

* Patients in the intermittent-regimen arm received FOLFIRI every 2 weeks for 2 months, followed by a complete discontinuation of chemotherapy for 2 months until disease progression occurred. Patients in the continuous-regimen arm received FOLFIRI every 2 weeks until disease progression occurred, with no discontinuation in therapy.

Adapted from Labianca et al⁸

mal growth factor receptor) antibody, such as cetuximab, even though these patients have received prior irinotecan therapy. This finding blurs the concept of “lines of therapy.”

What is your approach to drug holidays?

Dr. Grothey: I define drug holidays in two ways: (1) a complete chemotherapy-free and biologic therapy-free interval or (2) maintenance therapy

using a biologic agent or fluoropyrimidine alone without a potentially toxic chemotherapeutic agent.

Dr. Fuchs: Drug holidays are valuable for patients, and data from OPTIMOX suggest that we should be considering this tactic more often. The idea of using bevacizumab alone after first-line therapy is intriguing, but this approach has not yet been proven an effective option.

Dr. Blanke: I do not use bevacizumab alone during a drug holiday, but I use it with 5-FU with increasing frequency.

Dr. Benson: I tend to drop oxaliplatin and continue the fluoropyrimidine and bevacizumab. However, some patients benefit from having a total break in therapy; it renews them so they can go on to the next regimen. What I typically offer patients is dropping oxaliplatin from first-line therapy, because it is important for them to understand that neurotoxicity can worsen even after discontinuing oxaliplatin.

Dr. Grothey: In the palliative setting, we should stop therapy before toxicity really hits the patient. The survival analysis of OPTIMOX2 due out this year will suggest whether it is worthwhile continuing therapy or whether patients should be given a

complete break. However, we need to keep in mind that OPTIMOX2 was conducted without biologics; thus, presumably, any impact on OS would be enhanced by whether or not biologic therapy is used. All currently available data concerning 5-FU/bevacizumab-containing regimens suggest that we should treat to disease progression outside a clinical trial setting.

Dr. Blanke: I give a complete drug-free holiday sometimes, usually later in the course of treatment. After patients have second- or third-line therapy, I give them a complete break. Giving maintenance therapy with any agent, except for a biologic-based, does not make sense to me.

Dr. Grothey: I have a patient with widespread mCRC. She responded well to FOLFOX/bevacizumab therapy but started to develop some neurotoxicity after 4 months of treatment. I stopped the oxaliplatin but have continued therapy with 5-FU/bevacizumab for 15 months. The patient is completely asymptomatic from her disease and from her treatment. She has stable disease, with calcified liver metastasis. At every visit, we discuss whether to continue therapy and whether to switch to capecitabine/bevacizumab. She always opts to continue 5-FU/bevacizumab.

What is your approach to managing disease that recurs after treatment with oxaliplatin in the adjuvant setting?

Dr. Fuchs: If the disease recurs less than 1 year from completion of adjuvant chemotherapy with FOLFOX, I would be reluctant to initiate FOLFOX again as first-line treatment for metastatic disease.

Dr. Blanke: I use FOLFIRI as first-line therapy. However, if other options have been exhausted during the course of treatment—and if evidence of treatment failure with oxaliplatin is absent—I would consider using it after a discussion with the patient. We don’t know for a fact that the disease

TABLE 4

OPTIMOX2: incidence of neuropathy associated with maintenance therapy vs a chemotherapy-free interval approach*

Time period	Grade	Maintenance therapy (arm), %	Chemotherapy-free interval, %
Cycle 1 through cycle 6	1	69.9	71.7
	2	17.2	17.3
	3	0.0	0.0
Two months after discontinuing FOLFOX	1	9.7	4.4
	2	32.2	19.1
	3	3.2	4.4
After first reintroduction	1	21.7	27.0
	2	30.4	16.2
	3	8.7	13.5

FOLFOX = infusional 5-FU/LV

* Patients in the maintenance-therapy arm received 6 cycles of FOLFOX7 followed by maintenance therapy with 5-FU/LV for 12 cycles and then were reintroduced to 6 cycles of FOLFOX7. Patients in the chemotherapy-free interval arm received 6 cycles of FOLFOX7 followed by no chemotherapy until disease progressed to baseline levels, at which point FOLFOX7 was reintroduced.

Adapted from Maindrault-Goebel et al¹⁰

is refractory to oxaliplatin.

Dr. Benson: That is the problem. We don't know whether the disease is refractory to oxaliplatin. We know only that adjuvant oxaliplatin-based therapy did not cure it. The adjuvant therapy may have delayed disease progression. Neurotoxicity may limit the treatment choice anyway. Whether the disease recurs by 6 months or 1 year, these patients should be considered as having metastatic disease and should receive an alternative regimen.

Dr. Grothey: Some data from follow-up of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial suggest that disease that recurs after oxaliplatin-based adjuvant therapy may not be as responsive to subsequent therapies.¹¹ Because we do not yet have long-term follow-up data from MOSAIC, these results would apply only to disease that recurs within a relatively short time. This is an area of CRC management where we need to look ahead at what may happen.

Would you ever use a biologic agent in the adjuvant setting?

Dr. Grothey: Patients should be randomized in an ongoing adjuvant trial with biologics.

Dr. Blanke: Outside of a trial, I would not use a biologic in the adjuvant setting.

Dr. Grothey: I would also caution against extrapolating data from the palliative setting. I agree that the biologics do not yet play a role in the adjuvant setting, outside a clinical trial.

Dr. Fuchs: I also agree that it is difficult to predict the outcome of on-

going adjuvant trials. One example is 5-FU and the immunostimulant levamisole (Ergamisol), which is essentially chemotherapy with 5-FU alone. With an agent like 5-FU that has as low an RR as it has in metastatic disease, we would not have expected the results of an adjuvant trial with 5-FU and levamisole¹² to be positive.

Dr. Benson: It is difficult to know whether cetuximab or bevacizumab will be helpful or whether one will be better than the other in the adjuvant setting without an understanding of how these agents work. Cetuximab may act directly on the tumor, whereas bevacizumab may act indirectly as an antiangiogenic agent, which may be why single-agent activity has not been seen with bevacizumab. However, we really do not know how these agents work and how they interact with chemotherapy. We know they do because responses are better, and cetuximab, at least transiently, can apparently overcome irinotecan resistance.

Perhaps one of the most valuable contributions of the ongoing trials is the superbly documented tumor banks that are being created. We cannot come up with the answers right now, but this is our best resource for understanding what really is going on.

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ABOUT THE AUTHOR

Dr. Grothey is Senior Associate Consultant, Division of Medical Oncology at the Mayo College of Medicine, Mayo Clinic, Director of Cancer Treatment North Central Cancer Treatment Group, Rochester, MN.