

# Clinician challenges in the community setting: treatment selection for metastatic colorectal cancer

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**D**r. Lee Schwartzberg, Editor-in-Chief of *Community Oncology* and a member of National Peer Reviews in Colorectal Cancer, provides his clinical perspective on some of the major advances in the treatment of metastatic colorectal cancer reviewed in this supplement. Dr. Schwartzberg addresses some of the outstanding questions on the application of recent study results into daily clinical practice.

## What are the clinical practice implications of the Grothey data?

The meta-analyses by Grothey and colleagues continue to show the survival benefits of exposing patients to all active chemotherapy agents over the course of their disease. (See Figure 2 in "Metastatic colorectal cancer: treatment strategies with current cytotoxic regimens" by Charles D. Blanke, MD, page 5.) It must be noted that the data showed increased survival benefits, even though the additional benefits we are seeing from the inclusion of targeted agents were not considered.

The treatment of metastatic colorectal cancer (mCRC) is at an optimistic crossroad. Only 10 years ago, there was a single active drug, 5-fluorouracil (5-FU), which we used in a variety of different schedules to little avail. We have progressed from single-agent therapy to numerous combination treatment options, still using 5-FU as the foundation. When a patient newly diagnosed with mCRC first presents, community oncologists should develop management plans that look be-

yond first-line therapy. We should consider all potential agents that could be used immediately and along the course of the disease to maximize survival and quality of life.

## What is the optimal first-line combination therapy for mCRC?

There is no definitive answer to this question. The Tournigand study showed essentially equal activity for FOLFIRI and FOLFOX when given as first-line regimens. (See Table 2 in "Metastatic colorectal cancer: treatment strategies with current cytotoxic regimens" by Charles D. Blanke, MD, page 5.) However, the choice of chemotherapy in the first-line setting is clearly influenced by prior events, such as what treatment (if any) was given in the adjuvant setting. Patients who received irinotecan (Camptosar)-containing adjuvant therapy should logically receive oxaliplatin (Eloxatin) as first-line therapy for metastatic disease; conversely, those who previously received oxaliplatin should then receive an irinotecan-containing regimen in this setting.

There are not much data regarding the use of bevacizumab (Avastin) with oxaliplatin administered in combination with infusional 5-FU/LV (FOLFOX) or with irinotecan and infusional 5-FU/LV (FOLFIRI) in the first-line setting. The data show superiority of irinotecan with bolus 5-

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FU/LV (IFL) plus bevacizumab over IFL alone. However, we infer that either FOLFOX or FOLFIRI with bevacizumab will be superior because these regimens have been shown to be more efficacious than IFL. Clearly, FOLFOX or FOLFIRI plus bevacizumab is widely used as first-line therapy, and we look forward to more clinical trials to confirm these findings.

Ultimately, the order of drugs probably does not matter. Some patients are unable to tolerate second-line therapy. This is not as much a problem in colorectal cancer (CRC) as in some other tumors, such as lung cancer, which are more likely to progress quickly and cause a faster decline in a patient's performance status. We now have more effective therapies, and people are living longer with mCRC. Therefore, it is important to consider the entire scope of therapy at the start of treatment.

#### **Are there patients for whom intensive first-line therapy with all three cytotoxic agents (FOLFOXIRI) is appropriate?**

At this point, no group for whom 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFOXIRI) is appropriate has been definitively identified, nor has triple-cytotoxic therapy been compared with two cytotoxic agents and one biologic agent. The data on intensive first-line therapy are intriguing, but this approach remains investigational.

#### **When choosing a first-line regimen for the treatment of mCRC, what are some of the primary considerations in the community setting?**

It is important to consider the impact of potential toxicities when selecting a first-line regimen. In clinical practice, physicians should ask patients about their treatment preferences and assess their tolerance for potential adverse side effects.

Logistics may come into play as well. There can be issues about how often a patient can realistically get to the office, clinic, or hospital for a treatment or visit. Clearly, there will be patients who cannot or do not want to receive infusional therapy. Patients need to know their options and be able to meet the requirements mandated by a regimen's schedule. Capecitabine (Xeloda) alone or in combination is an option in the first-line setting.

Another consideration is the potential of a treatment to exacerbate existing cancer- and noncancer-related side effects and comorbidities or increase their risk. Therefore, in a patient with preexisting neuropathy—as from prior adjuvant chemotherapy or from diabetes—FOLFIRI is usually the first-line choice. The impact of cancer treatment on other aspects of quality of life must also be considered. For example, patients who work or engage in activities that require being outdoors in a cold climate or involve fine-motor skills may not be appropriate candidates for an agent that may cause neuropathy.

Some evidence exists that older patients, those with intrinsic diseases of the gastrointestinal tract (eg, inflammatory bowel disease), and patients with short-gut syndrome may be at higher risk for diarrhea and adverse outcomes. The anatomic deficit from surgery on the bowel is another factor that may influence a patient's risk for cancer treatment-induced diarrhea and, therefore, should be considered when selecting an agent or regimen.

Biologic agents do increase myelotoxicity a small amount, and because patients are getting more lines of chemotherapy, neutropenia is likely to become more common. Patients should be monitored closely and appropriate growth factors begun.

When choosing among the somewhat complicated combination cytotoxic and biologic agent regimens

now available, the more education the oncologist can impart to the patient, the better. In my practice, I have a formal patient education policy. Patients meet with a nurse who explains the potential side effects. They also receive written information regarding their disease and its treatment and instruction regarding potential side effects and what scenarios require them to contact the clinic.

#### **What are some of the strategies for managing treatment side effects?**

There are several common cancer-related and cancer treatment-related toxicities, particularly in patients with CRC. Diarrhea can be distressing to patients and, in rare cases, life threatening. It is, however, a fully reversible adverse effect. With the increasing use of infusional regimens, the incidence of diarrhea from both irinotecan- and oxaliplatin-containing regimens is 10%–14%, as pointed out in the article by Dr. Blanke on page 5. If a patient experiences early-onset diarrhea, he or she will receive atropine as a premedication with the next cycle for secondary prevention. For late-onset diarrhea (occurring more than 24 hours after infusion), loperamide (4 mg) is given immediately after the first diarrhea episode and continued at 2 mg every 2 hours until the patient is diarrhea free for more than 12 hours.

Maintenance of adequate hydration is critical. Patients should be instructed to drink a volume of liquid sufficient to compensate for the volume lost due to diarrhea, in addition to their normal daily intake. Large quantities (more than 3–4 L) of water and electrolyte- and sugar-containing drinks may be required, but patients should be cautioned that ingestion of large volumes of water alone can cause adverse effects (eg, hyponatremia and hypokalemia) due to lack of electrolyte replacement.

Preprinted forms outlining the

diarrhea protocol should be given to patients. To avoid confusion, they should be told that the protocol differs from the recommended dosage on the loperamide package.

Diarrhea does not occur in every patient. It would be helpful to have a predictive algorithm that could identify patients at greatest risk. Some evidence exists that older patients and those with gastrointestinal tract diseases, such as inflammatory bowel disease or short-gut syndrome, may be at higher risk.

In clinical trials, the most important, and dose-limiting, toxicity of oxaliplatin is neuropathy; it occurs later in treatment, may not be fully reversible, is chronic, and may adversely affect a patient's quality of life. Chronic neuropathy—not disease progression—is the primary reason for discontinuation of oxaliplatin therapy. The oxaliplatin dose can be decreased when neuropathy occurs, but this has not been studied formally. There are anecdotal reports that dose modification does not substantially reduce the progression of neuropathy. The OPTIMOX data show that disease response can be sustained by discontinuing oxaliplatin and continuing 5-FU, with reintroduction of oxaliplatin when there is improvement in neurotoxicity. This is a viable approach.

Acute neurotoxicity may be alleviated by extending the infusion time and adding a calcium and magnesium infusion. A calcium/magnesium infusion may also reduce the incidence and severity of chronic neurotoxicity. Investigators for the CONCEPT trial are evaluating whether the infusion of calcium and magnesium reduces the incidence of acute and chronic neurotoxicity. The trial results that evaluated xaliproden for prophylaxis of oxaliplatin neurotoxicity were disappointing, and its usefulness is unclear. Xaliproden did decrease grade 3 neuropathy, but not grade 2, nor did it increase the

amount of oxaliplatin that could be administered.

The most common toxicity associated with capecitabine is palmar-plantar erythrodysesthesia, commonly called hand-foot syndrome, which occurs in more than half of patients receiving it. Symptoms range from tingling to erythema and, in more severe cases, edema, pain, blistering and fissuring, and desquamation and scarring. Heat and repetitive pressure on the hands or feet can exacerbate the condition. Although capecitabine is an appropriate choice for many patients, it might not be suitable for those whose livelihoods or leisure activities require being in hot or heated environments or performing tasks such as carpentry or pottery making.

Patients taking capecitabine should be instructed to call if they experience side effects. Because we usually do not see these patients as often as we see those on other regimens, they need to understand that they should notify us so that dose or schedule adjustments can be made as needed and in a timely fashion to avoid excessive toxicity.

#### **Before bevacizumab is started, what are some clinical considerations?**

The toxicities associated with the targeted agent bevacizumab are related largely to its effects on the vascular system. The most common toxicities associated with bevacizumab—hypertension, delayed wound healing, arterial thromboembolic events, and proteinuria—have implications for the clinical decision-making process.

Bevacizumab is initiated at least 4 weeks post surgery because of the risk of delayed wound healing. In the preoperative setting, for example, in patients who are receiving chemotherapy and bevacizumab and who may undergo resection of liver metastases, bevacizumab usually is discontinued 6–8 weeks before surgery. Blood pressure, the presence of proteinuria,

and the risk of bleeding or thrombosis must be evaluated at baseline and followed throughout therapy. In my practice, I have used bevacizumab safely in some patients on anticoagulant or antiplatelet agents; a well-conducted study in such patients would be welcome. Some current cooperative group clinical trials involving bevacizumab allow patients to participate who are on a stable anticoagulant dosage.

Hypertension is a common side effect of bevacizumab, particularly when it is used at higher doses. In most studies, modest blood-pressure elevations were managed easily with standard antihypertensive agents. Blood pressure, particularly in patients with preexisting hypertension, should be monitored and elevations managed aggressively. In my practice, I prefer angiotensin-converting enzyme inhibitors because of their positive effects on blood pressure as well as proteinuria. We strive to bring preexisting hypertension under control before starting bevacizumab. If it is not controlled, preexisting hypertension is a relative contraindication to bevacizumab.

#### **How important is a patient's epidermal growth factor receptor (EGFR) status when considering initiating therapy with cetuximab?**

Cetuximab (Erbix) is approved for use in patients with EGFR-positive tumors; however, this has little substantial clinical relevance. As noted in Dr. Ilson's article, EGFR status does not predict response to cetuximab. EGFR status must be checked, but it is more a barrier to treatment than a source of clinically useful information. It should be mentioned that the US Food and Drug Administration's approval of cetuximab does include a requirement for a positive EGFR test result. The data indicate, however, that this is not a relevant test to predict response.

### What are your treatment strategies for cetuximab side effects?

Rash is the predominant side effect associated with cetuximab. Although rarely severe or life threatening, it can be distressing to patients. Unfortunately, topical agents and oral antibiotics often are not helpful; in general, cetuximab-associated rash improves over time and may respond to dose reduction.

Uncommon, severe, life-threatening anaphylactic infusion reactions do occur, usually during the first cycle. Of course, it is imperative that all offices have emergency medications available to treat anaphylaxis. Cetuximab-treated patients must be closely monitored, and nurses must be well trained for a rapid response to these reactions. Also, electrolyte imbalances with decreased phosphorus and magnesium can occur with cetuximab. These levels need to be checked at appropriate intervals and replaced accordingly.

### Is there any role for combining cetuximab and bevacizumab or continuing bevacizumab after progression while on it?

Although the Bowel Oncology with Cetuximab Antibody-2 (BOND-2) study was a phase II trial, it did show that using cetuximab and bevacizumab together resulted in an improved response rate and prolonged time to treatment failure. Again, more results are needed before we will know whether using the two agents together instead of sequentially is superior. At present, bevacizumab with chemotherapy remains a first-line therapy. More data on cetuximab alone or with bevacizumab in the first-line setting are needed. Cooperative group trials are now investigating the combination of cetuximab and bevacizumab as first-line therapy and are of intense interest. The issue of continuing bevacizumab at progression and chang-

ing the chemotherapy remains a research question.

### What is the role of hepatic metastasectomies in the contemporary treatment of mCRC?

There are multiple ways to integrate chemotherapy and liver resection.

It's important to underscore that metastasectomies for liver lesions are being performed with increasing frequency in the community. This is a trend that should be continued. Of course, surgical expertise is essential. Even in the most experienced surgeon's hands, significant morbidity and mortality can occur. Community oncologists should develop relationships with surgeons—preferably local surgeons but, if not, those at nearby centers—who are experienced and comfortable with resection procedures for liver metastases.

I do believe that patients with resectable liver metastasis should receive chemotherapy. The current issue is whether chemotherapy should be administered in the neoadjuvant setting, the adjuvant setting, or both. There are no data on the use of both neoadjuvant and adjuvant chemotherapy. Dr. Kemeny's article does show that neoadjuvant therapy can downstage tumors. In my practice, I use neoadjuvant chemotherapy for patients with resectable or borderline resectable liver metastasis. These patients usually are better able to tolerate therapy, and we can judge whether or not their tumors are chemosensitive. Moreover, surgery tends to be easier because the lesions are smaller as the result of chemotherapy.

### If neoadjuvant therapy is given, do you have any preference for the number of cycles and the type of chemotherapy?

Although data on the use of neoadjuvant chemotherapy plus cetuximab or bevacizumab are not avail-

able yet, we can extrapolate that these targeted agents will add to the effectiveness of chemotherapy in the setting of potentially resectable liver metastasis as they do in other scenarios with mCRC. My standard approach is to use chemotherapy with bevacizumab up front.

As an example, I recently had a patient who presented with stage 4 disease. He had three liver lesions, one of which was 6 cm. He had surgery to remove the primary tumor, and the pathology showed three positive lymph nodes and two microscopic nodules in the omentum. The patient then received a full, 6-month course of chemotherapy. Bevacizumab was started on cycle 3 and stopped 8 weeks prior to surgery. The patient's oxaliplatin was discontinued before the last 2 cycles because of neuropathy, but 5-FU/LV was continued. The patient had a 60% response of the liver lesions, and all three were removed. He now is disease free. One could argue that he should now receive adjuvant therapy, but no supportive data exist for this approach. I favor watchful waiting at this point.

### What do you do if patients are not responding to neoadjuvant therapy?

Patients who do not respond to neoadjuvant therapy, not surprisingly, do worse. If a patient with resectable liver disease does not have a response after 2 months, I operate immediately. If patients have borderline resectable lesions and are not responding to chemotherapy, I do not operate.

### What are the indications for hepatic arterial infusion (HAI) or chemoembolization, as opposed to standard intravenous chemotherapy preoperatively?

The data on HAI are good, but it is being superseded by the availability of better systemic therapy. As shown in randomized studies, Dr. Kemeny's

work is important and effective, but its place with rapidly changing effective chemotherapy is unclear. This approach can be influenced by the interest and availability of experienced physicians at your institution as well. For example, we used to perform HAI because we had a very skilled surgeon on staff. Because he has relocated out of the area, we no longer perform the procedure. The same is true for chemoembolization. Because of the availability of effective systemic chemotherapy, the role for chemoembolization is unclear as well. Again, this approach requires oncologists who are interested in and experienced with the procedure.

#### **What is your approach to unresectable liver lesions?**

I prefer systemic treatment in the patients with unresectable disease, as

I do with those who have resectable disease. However, patients with unresectable liver metastasis should be approached carefully. The fraction of patients presenting with unresectable disease who eventually are treated to an R0 resection is small. If I have a patient who has a very good performance status and whose liver metastases respond well enough to systemic treatment to become resectable, I may attempt this approach. But, the data here must be interpreted cautiously. This is a difficult approach. We should remember that patients in clinical trials tend to be better selected than the general population in the community setting. It is hoped that with better systemic therapy, this will become easier to perform. I may consider FOLFOXIRI in a patient with unresectable disease, and we can just

extrapolate that the addition of a biologic agent will be superior to cytotoxic therapy alone.

#### **Is there value to radiofrequency ablation (RFA) combined with resection?**

I do think there can be a value to RFA combined with surgery. When it is used, I think it is best used in conjunction with surgery. However, I am uncertain that RFA has value in treating unresectable lesions. A very small fraction of patients achieve long-term survival with this approach.

#### **ABOUT THE AUTHOR**

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