Individualizing Therapy for Metastatic Colorectal Cancer

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By Joleen Turja, MD [1] and Axel Grothey, MD [2]

Davies/Goldberg Article Reviewed. The past decade has seen exciting developments in the field of colorectal cancer, particularly in the setting of advanced disease.

This Review refers to the following Article: First-Line Therapeutic Strategies in Metastatic Colorectal Cancer

The past decade has seen exciting developments in the field of colorectal cancer, particularly in the setting of advanced disease. The developments of new treatment options have translated into impressive gains in response rates, progression-free survival, overall survival, and, in certain situations, potential cure. In this issue of ONCOLOGY, Drs. Davies and Goldberg have provided an excellent review of the history of the development of newer therapies for metastatic colorectal cancer (mCRC), presenting the data and rationale behind each new therapeutic approach. The article eloquently details how multiple studies have investigated the use of cytotoxic chemotherapeutic agents (fluorouracil [5-FU], oxaliplatin [Eloxatin], and irinotecan) in attempts to determine the best combination and the ideal order in which to administer them. Doublet chemotherapy regimens (FOLFOX [leucovorin (folinic acid), 5-FU, oxaliplatin] and FOLFIRI [leucovorin, 5-FU, irinotecan]) have improved efficacy over 5-FU/leucovorin alone.[1,2] It does not appear to change outcomes whether FOLFOX or FOLFIRI are used as first- or second-line therapy,[3] and ultimately it was shown that survival is improved with exposure to all three drugs.[4] Capecitabine (Xeloda) appears to be an acceptable alternative for 5-FU,[5,6] although this agent has not gained the popularity in the United States that it has in Europe.

Targeted therapies have provided an additional mechanism with which to attack advanced colorectal cancer. Bevacizumab (Avastin), a vascular endothelial growth factor (VEGF) inhibitor, and epidermal growth factor receptor (EGFR) inhibitors (cetuximab [Erbitux] and panitumumab [Vectibix]) can lead to increased response rates, progression-free survival, and—in the case of bevacizumab—overall survival, particularly when used in combination with cytotoxic chemotherapy.[7-11] Ongoing trials are aimed at determining the optimal combinations of cytotoxic and targeted therapies.

With the treatment options we have available, the challenge is the following: How do we best utilize these therapies to provide the greatest benefit to our patients with advanced colorectal cancer? The focus now should be to tailor each therapeutic option to the individual, minimizing toxicity while obtaining the maximum efficacy our treatments can provide.

Biomarker-Driven Treatment Decisions

The latest breakthrough in the individualization of therapy for mCRC involves determining whether the patient’s tumor has a mutation in K-ras. As outlined by Drs. Davies and Goldberg, a large body of evidence shows that only individuals with K-ras wild-type status stand to benefit from the use of EGFR inhibitors. These agents provide no survival advantage to patients with K-ras mutant tumors and, in fact, have the potential to harm this subset of patients.[12,13] To determine whether a given patient might benefit from the use of an EGFR inhibitor, tumors should be tested for K-ras mutation status. Ideally, this should be done at the time of diagnosis for all patients with colorectal cancer. Testing can also be performed on tissue from previously resected lesions or biopsies. Recurrent and metastatic lesions retain their K-ras status; therefore, knowledge of K-ras status initially, even in patients without advanced disease, will indicate whether EGFR inhibitors will be an option for treatment in the event of recurrence.

Beyond K-ras, further biomarkers such as B-raf (V600E) mutations, intact expression of PTEN,[14] and expression levels of EGFR ligands (amphiregulin, epiregulin) will conceivably allow us to more specifically identify patients who will benefit from EGFR-targeted therapies.[15-17] The ideal patient for cetuximab or panitumumab therapy would have a K-ras wild-type colorectal cancer without B-raf mutations, intact PTEN, and high expression levels of amphiregulin and/or epiregulin.

Curative vs Palliative Approach

Another question to ask when considering treatment for advanced colorectal cancer is: What is the
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goal of treatment? Is the hope to downsize metastatic lesions with chemotherapy to convert previously unresectable metastatic disease to resectable status with the intention of cure—so-called conversion therapy? Or, is the situation palliative, to help the patient live with the best quality of life for as long as possible? This decision can be made as part of a multidisciplinary approach, including surgical and medical oncology teams.

Surgical resection of metastatic disease can lead to significantly improved survival times and offers the patient potential for cure. Traditionally, based on prior criteria for resection, only 10% to 20% of patients with mCRC were eligible to have surgery at the time of presentation. Now, based on data showing that outcomes are not dependent on tumor size or number of lesions, surgeons focus on the amount of functioning organ that remains after resection to determine feasibility.[18,19]

Whether metastatic lesions are resected upfront or after downsizing with chemotherapy, patients gain a survival benefit.[20] Two prospective trials suggest improved resection rates with oxaliplatin-based regimens.[3,21] The addition of a biologic agent appears to improve resection rates as well. Data from two phase II trials support the use of bevacizumab in combination with an oxaliplatin-based regimen.[13,22] The CRYSTAL trial showed improved resection rates when cetuximab was added to FOLFIRI.[12] Due to concerns about postoperative complications, a 6- to 8-week interval is recommended between bevacizumab use and surgery. Cetuximab does not appear to increase the surgical complication risk.

The duration of neoadjuvant chemotherapy in this setting is dependent on the responsiveness of the disease. Treating until best response may make lesions undetectable, and the exact location of the tumor becomes difficult to detect. It is currently recommended that patients be treated until the point when their disease becomes resectable.

Minimizing Toxicity in the Palliative Setting
In the United States, first-line therapy for unresectable mCRC most commonly includes FOLFOX plus bevacizumab. The majority of patients discontinue oxaliplatin-based chemotherapy due to neurotoxicity, not because of disease progression. As mentioned in the review article, several trials provide guidance for extending duration of treatment and disease control while minimizing toxicity. The stop-and-go strategy used in an OPTIMOX1 fashion, does not compromise efficacy, and reduces the incidence of grade 3/4 neurotoxicity.[23] With disease stability, six cycles of FOLFOX plus bevacizumab can be followed by maintenance 5-FU and bevacizumab. Upon progression, FOLFOX can be reintroduced, and bevacizumab can be continued as well. Continuing bevacizumab beyond progression can potentially improve survival and does not add significant toxicity.[24] Giving patients a break from oxaliplatin during the maintenance phase, with reintroduction at a future point, allows us to gain the maximum benefit from oxaliplatin therapy while hopefully providing improved quality of life for patients. The use of targeted agents as maintenance therapy is currently being evaluated in phase III clinical trials. The DREAM-OPTIMOX3 study randomizes patients to receive bevacizumab with or without erlotinib (Tarceva) during a chemotherapy-free interval after six cycles of FOLFOX7 or XELOX4 (capecitabine, oxaliplatin) plus bevacizumab.[25]

Another study from the Spanish Cooperative Group for Gastrointestinal Tumour Therapy is comparing XELOX plus bevacizumab until disease progression or toxicity vs XELOX plus bevacizumab for six cycles followed by bevacizumab alone until disease progression.[26] These trials will hopefully provide more information regarding the incorporation of biologic agents as maintenance therapy.

Acceptable Regimens in the Elderly
A pooled analysis of adjuvant, first-line, and second-line trials showed that individuals over 70 years old benefit from oxaliplatin-based chemotherapy as much as younger patients.[27] Efficacy was comparable, and with the exception of more hematologic toxicity (including neutropenia and thrombocytopenia), the safety/toxicity profile did not differ by age. Similar findings of efficacy and safety in patients over 70 years have been reported in a pooled analysis of trials using irinotecan-based chemotherapy.[28] Keeping in mind that these trials include patients with good performance status, both irinotecan- and oxaliplatin-based therapy can be utilized in elderly patients.

However, caution must be used when considering the addition of antiangiogenesis agents to cytotoxic chemotherapy in the elderly. Patients over 65 years old have a 1.8-fold increased risk of arterial thrombotic events (ATE) with the use of bevacizumab.[29] This effect was substantially increased in patients with a prior history of ATEs. Analysis of the BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) registry confirmed this risk in patients older than age 75.[30] No increased risk of gastrointestinal bleeding/perforation or hypertension was seen in the

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elderly. When considering bevacizumab in the elderly, an increased risk of ATEs needs to be recognized, and for those who have experienced prior ATEs, bevacizumab is contraindicated.

**Conclusions**

Treatment options for mCRC have significantly expanded over the past 10 years, providing oncologists with the opportunity to choose therapies that are more closely tailored to the individual. The plethora of potential treatment sequences can be focused on the individual need of specific patients by using biomarkers, establishing treatment goals a priori, and employing treatment algorithms that prevent excess toxicity in order to administer optimal care while minimizing harm to patients. Ongoing research will continue to investigate how to appropriately utilize targeted therapies in the era of individualized medicine.

**References:**


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