Treating Metastatic Colorectal Cancer While Questions Remain Unanswered

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Over the past decade, new cytotoxic and biologic therapies beyond the old standard-of-care, biomodulated fluorouracil (5-FU), have become available for the treatment of metastatic colorectal cancer (mCRC). The introductions of irinotecan (Camptosar), oxaliplatin (Eloxatin), and bevacizumab (Avastin) have prolonged survival, but the optimal use of these new therapies remains to be determined. Issues remain regarding management of toxicities, treatment of elderly patients or those with poor performance status, and the duration of treatment with front-line therapy. This article reviews recent and ongoing studies of newer therapies in an effort to determine the best use of these drugs in the treatment of mCRC. Current data support the front-line use of bevacizumab added to either 5-FU/leucovorin alone or 5-FU/leucovorin in combination with oxaliplatin (FOLFOX/bevacizumab) or irinotecan (FOLFIRI/bevacizumab). If oxaliplatin is used in first-line therapy, oxaliplatin should be discontinued before the development of severe neurotoxicity and be reintroduced or replaced with irinotecan on disease progression. Definitive conclusions on the sequence and duration of front-line therapy and the most effective strategy to ameliorate toxicity await results of ongoing prospective clinical trials.

The noncurative treatment of metastatic colorectal cancer has become far more complicated over the past decade. The options are better than they were, although not nearly as good as they need to be. In their thorough review, Drs. Grothey and Marshall outline and discuss much of the progress that has been made as well as the limitations of the available data. As noted by the authors, many ongoing studies will hopefully shed further light on the many important questions that remain unsettled. It is important to note just how many questions do remain relatively unanswered. Often, the data are somewhat inconsistent. Why, for example, should the data be so overwhelmingly compelling that irinotecan (Camptosar) and oxaliplatin (Eloxatin) have comparable efficacy in the metastatic setting, when clearly oxaliplatin has shown benefit in the adjuvant setting and irinotecan has not? In other situations, the differences may be subtle enough to permit intelligent debate over the clinical or practical significance of modest findings that reach statistical significance in a large trial.

Implications of Terminology

Given the lack of definitive answers, I would be very cautious about using the term "standard of care," which has been used at times in this manuscript. It is perhaps a subtle point, but I would prefer to talk about "standard care" or "routine practice," which have far less of a medicolegal implication, and imply a general practice approach from which individualization of a patient's care can begin. I choose to think of a preferred treatment as a "default position"[3] an approach that I will start out considering for all patients. Then I will look for reasons to modify that position. For example, one such default position would be that front-line chemotherapy for a patient with metastatic colorectal cancer will be accompanied by the administration of bevacizumab (Avastin). I believe the current data support this approach for most patients. I then look for individual reasons that might warrant a deviation from that default position, based on the specific patient's profile. Does the patient have a relative contraindication? How strong is that contraindication? How transient is it? A patient with a recent history of a stroke would have, in my mind, an absolute contraindication to bevacizumab. A person with a history of a myocardial infarction 5 years ago, with surgical revascularization and no symptoms since, might have a somewhat less compelling contraindication, but a relative contraindication nonetheless. A person with an open abdominal wound healing by secondary intention may have a strong contraindication now, but may be a good candidate in a few months. The characterization of these relative contraindications, along with a discussion of this individual patient's preferences, expectations, and acceptance of risk, will inform this decision-making process.
Individualization of Therapy
Other situations are informed by sufficient data to tell us that there is no one right answer. The choice of FOLFOX (fluorouracil [5-FU], leucovorin [LV], oxaliplatin) vs FOLFIRI (5-FU, LV, irinotecan) in metastatic disease would seem to be one where individualization can play a role given the demonstrated similarity in terms of efficacy between these regimens. In the absence of meaningful predictive markers of efficacy which, sadly, we still do not have individual patient acceptance of one toxicity profile over another may dictate the appropriate decision. The current relative disproportionate use of one of these regimens over another (current surveys suggest FOLFOX is utilized in more than four out of five patients with first-line metastatic disease) does not appear to be justified by the data. In fact, it is reasonable to suggest that a doctor using dramatically more of one of these regimens than the other may be oversimplifying the decision process and may not be fully availing his or her patients of all possible options. Some situations do have definitive data, and a clear right/wrong can be discerned from the published literature. I concur, for example, with the sentiment expressed in the review that bolus 5-FU/LV, alone or in combination with irinotecan or oxaliplatin, should be regarded as inferior to infusional regimens. Such bolus 5-FU regimens should be regarded as anachronistic, and should not occupy a default position in routine treatment strategies.

Newer Treatment Options
Among the newer options that have achieved validity is the combination of capecitabine (Xeloda) and oxaliplatin (CAPOX) as an alternative to FOLFOX. As noted in the review, the NO16966 trial has established the CAPOX combination to be noninferior to FOLFOX. As noted by Grothey and Marshall, the issue of the appropriate dose of capecitabine for American patients remains unresolved. The Three Regimens of Eloxatin Evaluation (TREE) studies referred to in their manuscript do not, in fact, offer a randomized comparison of different dose levels of capecitabine. Rather the TREE-1 study, a small randomized phase II trial of three different oxaliplatin-based schedules, reported substantial toxicity with the CAPOX regimen. At a later time, the TREE 2 study used a lower dose of capecitabine and reported a lower level of toxicity. However, the usefulness of this nonrandomized comparison is limited. Given that the efficacy data from NO16966 are based on a starting dose of 1,000 mg/m² twice daily, it would seem most appropriate to begin at that dose in patients for whom the capecitabine/oxaliplatin combination is selected, and to pay close attention to toxicity, with early (weekly at least) toxicity assessment and adjustment of the capecitabine dose as warranted.

Note of Caution As noted by Grothey and Marshall, many questions remain unanswered, and many have not been, or are not yet being, directly addressed by clinical trials. I would caution that although we want answers, we must be careful to recognize the limitations of the data (and, in some cases, the limitations of the trial designs) and not think we know something based on suboptimal comparisons. Definitive data come only from adequately powered, randomized comparisons of well-balanced study populations. Non-randomized comparisons, either sequential or cross-study, are hypothesis-generating at best, and should not be regarded as compelling evidence for one course of action over another.

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