Commentary (Grem)—Metastatic Colorectal Cancer: Is There One Standard Approach?

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In this issue, Dr. Saltz articulates his opinion on a variety of questions concerning therapy for patients with metastatic colorectal cancer. My commentary will reflect my opinions concerning these questions.

Bevacizumab Issues
The first issue is whether bevacizumab (Avastin) should be a component of most patient's first-line treatment. The pivotal trial reported by Hurwitz and colleagues compared IFL (weekly irinotecan [Camptosar] with bolus fluorouracil [5-FU] modulated by leucovorin), which was then considered to be standard front-line therapy for metastatic colorectal cancer, given either with placebo or bevacizumab, or 5-FU/leucovorin plus bevacizumab.[1] The results showed a significant improvement in response rate, time to progression, and overall survival with the addition of bevacizumab to IFL. Intermediate results were seen with 5-FU/leucovorin plus bevacizumab.[1] The approval by the US Food and Drug Administration (FDA) was broad: Bevacizumab was indicated as first-line therapy with a 5-FU-based regimen in patients with metastatic colorectal cancer. At that time, no information was available on the combination of bevacizumab with the more active FOLFOX regimen (oxaliplatin [Eloxatin] given with mixed bolus and infusional 5-FU modulated by leucovorin). Therefore, both the Southwest Oncology Group and the Cancer and Leukemia Group B launched phase III trials that addressed the value of adding bevacizumab to front-line chemotherapy regimens for advanced colorectal cancer. The slow accrual to these two phase III trials attests to the bias of medical oncologists that bevacizumab should be included in front-line therapy of medically fit patients with metastatic colorectal cancer. The release of data from an Eastern Cooperative Oncology Group trial in late 2004 showing that bevacizumab improved the outcome when added to FOLFOX as second-line therapy for patients with colorectal cancer effectively led to the closure of clinical trials that did not include bevacizumab in front-line therapy regimens for metastatic colorectal cancer.[2] Another question is whether there is a role for continuing bevacizumab with subsequent regimens after a patient's tumor has progressed on a first-line bevacizumab-containing regimen. Presumably, based on the premise that normal blood vasculature would not develop resistance to bevacizumab, the pharmaceutical-sponsored pivotal trial of bevacizumab allowed continuation of bevacizumab with the institution of second-line treatment. I agree with Dr. Saltz that the argument to continue bevacizumab is not evidence-based. Given the expense and potential adverse effects of bevacizumab, I do not believe there is justification for continuation of bevacizumab in the face of documented tumor progression.

Cetuximab Issues
Dr. Saltz questions whether there is a role for cetuximab (Erbitux) in off-protocol first-line regimens. I agree that the value of cetuximab should be evaluated in a clinical trial setting, but would not currently recommend combining cetuximab with bevacizumab-containing first-line regimens for advanced colorectal cancer. For patients whose tumors have progressed after first-line therapy, is immunohistochemical (IHC) testing of epidermal growth factor receptor (EGFR) needed before employing cetuximab as salvage therapy? The FDA-approved label for cetuximab is for colorectal cancer patients whose EGFR-positive tumors have progressed on prior irinotecan-based therapy. In the pivotal trial that led to the approval of cetuximab, there was no evidence that the degree of IHC staining for EGFR predicted for clinical benefit.[3] There are now additional reports that confirm the benefit of cetuximab in subjects whose tumors were negative for EGFR staining.[4,5] This finding is perhaps not unexpected, since IHC staining for EGFR does not provide information concerning the activity of that particular signaling pathway. The feasibility of using cetuximab in EGFR-negative colorectal cancer outside of the clinical trial setting may depend on third-party reimbursement issues.

Modified Regimens
An important question raised by Dr. Saltz concerns the acceptance of modified regimens by the
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oncology community that have not been directly compared to prior standard regimens for advanced colorectal cancer. As an example, he discusses the various permutations of FOLFOX. From a practical standpoint, a large number of patients would be required in a randomized clinical trial designed to show equivalence of two regimens that represent subtle variations in scheduling. Given the number of novel agents that are emerging as possible treatment options for metastatic colorectal cancer, many of which will likely be tested in combination with FOLFOX/bevacizumab, it is unlikely that the scarce subject resources will be allocated for trials designed to test equivalence. In addition, since systemic therapy for the majority of subjects with metastatic colorectal cancer is palliative in intent, it can be argued that adoption of regimens that increase patient convenience is reasonable, even in the absence of phase III data. Is either oxaliplatin- or irinotecan-based therapy optimal for first-line therapy, and what is appropriate second-line therapy? Tournigant addressed the former issue in a relatively small trial comparing sequential FOLFOX vs FOLFIRI (irinotecan plus leucovorin/5-FU) or the opposite sequence. The overall survival was similar among subjects randomized to the different sequences. It seems reasonable in medically fit subjects whose disease progresses on an oxaliplatin/5-FU regimen to switch to an irinotecan-based regimen, and vice versa. We do not have clinical evidence that clarifies whether the addition of 5-FU alone or with leucovorin adds to the efficacy of second-line irinotecan, and it is unlikely that clinical trial resources will be devoted to answering this question. Is cetuximab useful when added to non-irinotecan-based therapy? Since cetuximab has some modest evidence of therapeutic value when used as monotherapy in patients with refractory colorectal cancer, I believe that it would be reasonable to add it to a non-irinotecan-based salvage therapy outside of a clinical trial setting.

Disclosures:
The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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