ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer in Focus

Maintenance Therapy in Metastatic Colorectal Cancer

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H&O What are the advantages of maintenance therapy over other options for metastatic colorectal cancer, such as chemotherapy-free intervals?

JM We do not want to continue the initial dose of chemotherapy past 6 to 8 cycles because prolonged chemotherapy causes cumulative side effects, such as severe neuropathy and prolonged myelosuppression or liver toxicity. On the other hand, studies suggest that chemotherapy-free intervals allow the cancer to regrow quickly. If we keep just a little chemotherapy going, the results are better than if we had paused treatment—we have to keep a little gas on the pedal in order to get the best clinical outcomes. Maintenance therapy allows us to strike a balance between intensive chemotherapy and the need to back off.

H&O What factors should oncologists consider when deciding whether to administer maintenance therapy in metastatic colorectal cancer?

JM How the patient is doing is the primary factor. If the patient is responding well to the initial therapy, we are likely to use maintenance therapy. Patients who are not responding to induction chemotherapy may not be good candidates for maintenance therapy.

H&O What maintenance regimens are used to treat patients with colorectal cancer?

JM The current standard, which is based on the regimen used in CAIRO3 (Maintenance Treatment With Capecitabine and Bevacizumab Versus Observation After Induction Treatment With Chemotherapy and Bevacizumab in Metastatic Colorectal Cancer), is to use continuously dosed capecitabine plus bevacizumab (Avastin, Genentech) every 3 weeks. Studies are being conducted to determine what approaches might work even better.

H&O Could you talk more about the results of CAIRO3?

JM The CAIRO3 study, which was done in the Netherlands, has set the standard for maintenance therapy. This study is exciting for a couple of reasons.

The patients in the study received capecitabine and oxaliplatin (XELOX) plus bevacizumab for 6 cycles. A total of 558 patients were then randomized to either no treatment—a true chemotherapy holiday—or maintenance therapy using prolonged low-dose capecitabine plus bevacizumab. The study was positive for maintenance therapy, with a doubling of progression-free survival from 4.1 months to 8.5 months, according to results presented at the 2014 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancer Symposium. In addition, the results suggested an overall survival advantage among 2 specific subsets of patients on maintenance therapy: those with synchronous disease who underwent resection of the primary tumor, and those who attained a complete or partial response to induction therapy prior to randomization.

Another important lesson from the CAIRO3 study has been the value of using capecitabine at a lower, chronic dose vs a 2-weeks-on, 1-week-off schedule using a higher dose. This is certainly something we do routinely in our clinics, and more oncologists may wish to dose the medicine in this way.

H&O What studies besides CAIRO3 are important when it comes to looking at maintenance regimens?

JM The results of the OPTIMOX (Optimisation of Oxaliplatin) studies are what led to the CAIRO3 study. In OPTIMOX1, more than 600 patients were randomly assigned to receive either leucovorin, fluorouracil, and oxaliplatin (FOLFOX) until disease progression or FOLFOX for 6 cycles followed by fluorouracil alone; only when the disease progressed did patients begin receiving oxaliplatin again. The stop-and-start regimen was shown to be just as effective as continuing FOLFOX until disease progression, and it was less toxic because patients received less oxaliplatin. This was the first clinical trial to suggest that we did not need to keep all the drugs going continually.

OPTIMOX2 was a smaller study—with 200 patients—that was stopped early because of the approval of bevacizumab. In this study, patients who had completed 6 cycles of FOLFOX treatment were randomly assigned either to continue on leucovorin and fluorouracil or to receive no treatment until disease progression. The researchers found a significant benefit to continuing chemotherapy. This was the first study to show that halting all chemotherapy was harmful.

H&O What studies are ongoing?

JM Most of the ongoing studies are looking at different combinations of fluorouracil and bevacizumab. The DREAM (Double Inhibition, Reintroduction, Erlotinib, Avastin, Metastatic Colorectal Cancer) study is examining the use of erlotinib (Tarceva, Genentech/Astellas), which has not been approved for use in colorectal cancer. The results of this study, which were reported at the ASCO Genitourinary Cancer Symposium in 2012, suggested a benefit for the dual targeted therapy approach. Despite this, much needs to be understood before adopting this treatment. Other agents that are being investigated for maintenance therapy include immunotherapy and novel tyrosine kinase inhibitors.

H&O Are other maintenance regimens in widespread use for metastatic colorectal cancer?

JM Some oncologists will use bevacizumab alone, or fluorouracil pumps. I do not think that the evidence supports either of these options, however. Furthermore, regimens using a 46-hour infusion schedule do not provide much of a break for patients.

H&O Can epidermal growth factor receptor (EGFR) inhibitors be considered for maintenance therapy in metastatic colorectal cancer?

JM Yes, in patients who have the appropriate results on *RAS* testing. We have not seen many studies in which EGFR inhibitors have been continued long-term; I suspect we will see these types of studies over time. One problem is that these agents are not as well tolerated when taken chronically, so maintenance therapy is a little rougher than with other regimens. I think it would be reasonable to use single-agent cetuximab (Erbitux, Bristol-Myers Squibb and Lilly) or panitumumab (Vectibix, Amgen) for maintenance therapy, but no studies have looked specifically at EGFR inhibitors for maintenance.

H&O Do you use a stop-and-go approach only for patients started on oxaliplatin-based regimens, or do you also use it when you start with an irinotecan-based regimen?

JM The OPTIMOX stop-and-go approach was designed for oxaliplatin-containing regimens, such as FOLFOX and XELOX. I recommend applying the OPTIMOX approach to the combination of leucovorin, fluorouracil, and irinotecan (FOLFIRI)—an approach that has been dubbed "OPTIMIRI." Although stop-and-go is less essential with irinotecan-containing regimens than with oxaliplatin-containing regimens because the cumulative toxicities are not as severe, I still recommend backing off the irinotecan the same as we would if we were giving oxaliplatin.

H&O Could you discuss these trials in more detail?

JM The DREAM trial compared maintenance therapy with bevacizumab alone with bevacizumab plus erlotinib. The main problem with this study is that it was not enriched for *KRAS* or *RAS* status. Despite this shortcoming, it was a positive study that suggested that dual targeting of EGFR and vascular endothelial growth factor (VEGF) might be of benefit. At the time that this study was conducted, many believed that inhibiting EGFR and VEGF simultaneously was harmful. The DREAM trial actually suggested the contrary, and so I think that the results of this study warrant additional work looking at combinations of EGFR and VEGF inhibitors in the maintenance window.

MACRO (Maintenance in Colorectal Cancer) was a randomized trial that compared XELOX plus bevacizumab until disease progression—what I call "chemo until you can't tie your shoes"—vs 6 cycles of XELOX, followed by bevacizumab alone until disease progression. Although

the study did not meet its prespecified endpoints for noninferiority, the researchers were unable to detect a statistically significant difference in progression-free survival between the 2 groups. Some have interpreted this to mean that bevacizumab alone could be a decent maintenance approach. My interpretation is that bevacizumab alone may not be as good as bevacizumab plus capecitabine.

Prior to MACRO, most studies had a no-treatment control arm after induction therapy. The evidence suggests that continuing some chemotherapy—at least fluorouracil and perhaps bevacizumab—is a good idea. I think that going forward, we will see fewer studies with a no-treatment arm.

Suggested Readings

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