Maintenance Therapy for Colorectal Cancer

April 15, 2014
By John L. Marshall, MD [1]

We have yet to establish a standard practice for maintenance therapy in metastatic colorectal cancer. Of course, ideally we could find a biomarker of benefit for patients who should be managed this way, but thus far we have had no such luck.

Maintenance therapy has become quite a hot topic for those of us working in the field of solid tumor malignancies. Our original concept of chemotherapy for solid tumors was to give a certain number of cycles and then stop treatment, or to continue treatment until an intolerable toxicity arose. Given that we now have more management tools at our disposal, and as treatments given chronically have become more tolerable, we have adapted our strategies to include an induction-like phase of more intensive chemotherapy followed by a maintenance approach of a dose-reduced, drug-changed, or modified schedule of treatment in the “maintenance” window. While maintenance treatment is now firmly established in diseases such as non–small-cell lung cancer, we have yet to establish a standard practice for maintenance therapy in metastatic colorectal cancer. Of course, ideally we could find a biomarker of benefit for patients who should be managed this way, but thus far we have had no such luck.

The primary pressure to adopt a maintenance approach has come from the cumulative neurotoxicity of oxaliplatin. For most patients, treatment with more than 8 cycles produces a significant and often long-lasting neurotoxicity, so patients are advised to stop their oxaliplatin treatment after several months of induction therapy (the so-called “OPTIMOX” protocol). Because of this, we have studied a variety of methods for maintenance approaches beyond the initial few months of oxaliplatin-containing combination chemotherapy. Studies have looked at bevacizumab alone, fluorouracil (5-FU) alone, combinations of bevacizumab and capecitabine, and combinations of bevacizumab and erlotinib. The most recently published of these studies is known as CAIRO3.[1] In this study, patients had initially been treated with oxaliplatin, fluoropyrimidine, and bevacizumab regimens. After an initial response, they were randomized to no further treatment vs capecitabine given as a chronically administered dose and every-3-weeks bevacizumab at 7.5 mg/kg. The progression-free survival (PFS) in the bevacizumab-capecitabine arm was 8 months, whereas that in the no-treatment arm was 4 months. I believe that this doubling of PFS is the most positive outcome to date in this setting and establishes a firm control arm in the maintenance window moving forward.

In my clinical practice, after roughly 6 cycles of oxaliplatin-containing chemotherapy, I change to capecitabine at a dosage of 1,000 mg orally twice daily, Monday through Friday every week, and bevacizumab at 7.5 mg/kg every 3 weeks. I do this in patients who have responded well to front-line therapy before neuropathy sets in. Patients with minimal to no tumor regression in the first-line setting are not great candidates for this approach. This is an incredibly well-tolerated regimen for patients, and the dose of capecitabine can be modified based on hand-foot syndrome—and interestingly, on mean corpuscular volume, an indirect measure of the folate inhibition in our patients. This does represent a true break for patients, and yet the capecitabine/bevacizumab combination is highly active in our patients with metastatic colorectal cancer. I then follow patients fairly routinely to assess toxicity, and follow with tumor markers and periodic CT scans to monitor for disease progression. Frankly, I employ the same scheme when I use irinotecan in front-line therapy (“OPTIMIRI”), to minimize cumulative bone marrow toxicity, as well as fatigue and other side effects of irinotecan.

Key Points Regarding Maintenance Therapy for Metastatic Colorectal Cancer

- Maintenance therapy is here to stay in the management of metastatic colorectal cancer (mCRC).
- The current standard is capecitabine and bevacizumab, based on the results of CAIRO3.
- Not all patients require therapy, but it is difficult to determine which ones do and which do not. There are no markers to go by.
- We use “OPTIMOX,” but can we also use “OPTIMIRI”? I do.
It is unclear how to handle maintenance therapy for mCRC if patients have received front-line treatment with an epidermal growth factor receptor antibody. There are no trials to guide us.

What we do when an epidermal growth factor receptor (EGFR) antibody is incorporated into front-line therapy is not clear, since no studies have been done that specifically address this issue. Nonetheless, I would likely adopt a maintenance approach in this setting as well. One word of caution: capecitabine and EGFR antibodies may not do well together, so I might either use just the EGFR antibody in maintenance, or switch to the capecitabine-bevacizumab regimen.

Having now established this maintenance approach as a very well-tolerated and clinically successful therapy, I think we need to begin to apply this kind of thinking to the management of other patients with colorectal cancer, as well as in the setting of pancreatic cancer. For example, how does one proceed after hepatic resection of liver metastases from colorectal cancer? There is no clear standard here, and it is not clear that more intensive chemotherapy is of benefit. Among patients with colorectal cancer at high risk for relapse, it might be very interesting to explore a maintenance-like approach, by giving these patients prolonged treatment to see whether it indeed prevents recurrence or delays it significantly, resulting in an overall survival advantage. We are also exploring this approach in pancreatic and gastric cancers. A recent publication[2] suggests that maintenance capecitabine following pancreas resections generated a very high 3-year disease-free interval for patients, serving as what may be an interesting experimental arm in future randomized clinical trials.

In summary, maintenance therapy is here to stay, and I believe that treatment with capecitabine and bevacizumab represents the current standard of care after initial induction therapy for patients with metastatic unresectable colorectal cancer. This regimen may one day have applicability to other settings in which, despite the availability of active well-tolerated agents that may result in an overall survival advantage, true adjuvant therapy has failed to yield a benefit.

**Financial Disclosure:** Dr. Marshall serves as a speaker for, and receives research funding from, Amgen, Bayer, and Genentech.

**References:**


**Source URL:**


**Links:**

[1] [http://www.physicianspractice.com/authors/john-l-marshall-md](http://www.physicianspractice.com/authors/john-l-marshall-md)