

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Colorectal Cancer In Focus

### Current Role of Bevacizumab in Colorectal Cancer

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#### **H&O** Can you discuss the history of colorectal cancer therapy?

**LS** If we go back to the mid 1990s, colorectal cancer (CRC) was treated primarily with fluorouracil, a pyrimidine analog also known as 5-FU. With minimal variations, this drug, which was patented in 1957, has been at the center of virtually all colorectal cancer treatment regimens. In 1996, irinotecan, a topoisomerase-1 inhibitor also known as CPT-11, became the second drug to be approved for the disease, and in the early part of this century, a platinum-based chemotherapeutic agent, oxaliplatin, was also approved. Then, in 2004, 2 monoclonal antibodies were registered: cetuximab (Erbix, Imclone) and bevacizumab (Avastin, Genentech). Bevacizumab is a monoclonal antibody that targets the vascular endothelial growth factor (VEGF). Whether bevacizumab is working as an antiangiogenic agent, as was originally thought, or whether it is working by increasing vascular permeability or some other mechanism, is not well established. If bevacizumab were truly an antiangiogenic agent, one would expect that it would work well by itself and would interfere with chemotherapy. But, it has been shown that bevacizumab does not work by itself for all practical purposes in CRC. However, a large study published by Dr. Hurwitz randomized patients to receive the IFL (irinotecan, 5-FU, and leucovorin) regimen, which was the standard chemotherapy regimen at the time, plus either placebo or bevacizumab. The group that received bevacizumab had a 4.7 month overall survival (OS) benefit and a 4.4 month progression-free survival (PFS) benefit. On the basis of those data, bevacizumab was approved by the US Food and Drug Administration and became part of standard treatment for metastatic CRC.

Several questions remain on the use of bevacizumab in CRC; firstly, there are questions of whether the drug has activity with more than 1 line of therapy. Currently, it is approved for either first *or* second line therapy for CRC; it is not approved for first *and* second line. The drug also has not been approved for use in the adjuvant setting after resection of earlier stage CRC (stage I, II, or III), and recent data from the 2,700 patient C-08 trial presented by Dr. Norman Wolmark at the recent meeting of the American Society of Clinical Oncology (ASCO) demonstrate that bevacizumab does not provide benefit in the adjuvant setting.

#### **H&O** How has the role of bevacizumab evolved, and what is the current use of bevacizumab in treating CRC patients?

**LS** We are still developing a sense of what this drug does and does not bring to the table. My colleague Jim Cassidy and I published a study in April 2008 in the *Journal of Clinical Oncology* that looked at the addition of bevacizumab to the most commonly used chemotherapy, which is the oxaliplatin-based regimen FOLFOX (5-FU, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin). In this study we found a much less robust 1.4-month improvement in PFS and a 1.4-month improvement in OS that did not reach significance and absolutely no benefit in terms of response rate for the addition of bevacizumab to oxaliplatin front-line chemotherapy. This was a very sobering and cautionary note. I think we are learning that bevacizumab is a drug with modest usefulness; it is not a home run. It has some benefits to offer and we have to think carefully about how to use it most appropriately to provide the most possible benefit.

### H&O What are some of the main adverse events associated with bevacizumab?

**LS** We recognize that all drugs have potential side effects, and as chemotherapy agents go, bevacizumab is subjectively rather benign. That being said, bevacizumab does interfere with wound healing, runs the risk of increased gastrointestinal perforation, and slightly increases the risk of arterial thrombotic events such as heart attack and stroke, especially in older patients or patients with cardiovascular disease.

### H&O What kind of patient is a good candidate for bevacizumab therapy?

**LS** Although we have not been able to molecularly define the subtype, I would say that bevacizumab use is most appropriate in first- or second-line therapy for a patient with medical conditions that are suitable for chemotherapy (ie, reasonable performance status) and for patients who do not have a history of gastrointestinal perforation or arterial thrombotic events. I would also think carefully about its use in patients who are older, based on their relative likelihood of cardiovascular disease and increased risk of a cardiovascular event.

### H&O What are the treatment options for patients with refractory CRC?

**LS** We give bevacizumab with frontline therapy. If a patient has progressed through a frontline-containing regimen with bevacizumab, I do not favor its use in subsequent lines of therapy because, in my opinion, we do not have adequate data to show that it is an active treatment.

If a patient gets initial frontline therapy, irinotecan is given. If the patient fails irinotecan, then oxaliplatin is used. If those therapies are exhausted, then we often go to a cetuximab or panitumumab (Vectibix, Amgen)-containing regimen for patients with KRAS and BRAF wild type tumors. Bevacizumab is not a treatment by itself and it is not appropriate as a salvage regimen. So if we do reach the point when oxaliplatin, irinotecan, and an EGFR agent in KRAS wild type, as well as fluoropyrimidine are exhausted, then we really do not have adequate treatments, and either supportive care or a clinical trial would be the option.

### H&O Can you discuss any recent study results that are of interest?

**LS** There have been some very important studies reported. One called the PACCE trial and one called CAIRO2. The PACCE trial evaluated standard chemo-

therapy with bevacizumab plus/minus panitumumab. In a very worrisome and totally unanticipated result, the addition of panitumumab in this study resulted in more rapid progression of metastatic CRC. Similarly, the CAIRO2 study was a combination of CAPOX and bevacizumab plus/minus cetuximab. Both studies determined that combining an EGFR inhibitor, such as panitumumab or cetuximab, with bevacizumab and chemotherapy in the first-line treatment of metastatic CRC results in worse outcome and worsened toxicity. This was an unexpected finding and one that we have to be very cautious of.

The C-08 study by Wolmark is another important study. Many doctors, believing that they were doing the right thing for their patients, have been giving bevacizumab plus FOLFOX as adjuvant therapy for stage III colon cancer. The C-08 trial showed that even with 2,700 patients and a full year of bevacizumab, an improvement was not seen in 3-year disease-free survival. The take home message is two-fold: firstly, bevacizumab should not be used in the adjuvant setting, and secondly, we need to wait for the results of trials before changing our practice. Until we do the trial, we do not know the answer.

Unfortunately, this was yet another lean year in terms of colorectal cancer, and there were very few, if any, practice-changing abstracts presented at ASCO. One interesting abstract from our group at Memorial Sloan-Kettering Cancer Center was presented by Poultsides and colleagues. We reviewed a large data set of patients who presented with stage IV disease without overt obstruction who were managed with initial chemotherapy, without up front surgery or up front radiation. Ninety-three percent of these patients never required surgery, and use of bevacizumab did not result in complications at the primary site. These data indicate that up front surgery is not appropriate for nonobstructed stage IV colorectal patients.

### Suggested Readings

Tol J, Koopman M, Rodenburg CJ, et al. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Ann Oncol*. 2008;19:734-738.

Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol (ASCO Annual Meeting Abstracts)*. 2009;27(18s):Abs CRA3040.

Saltz L, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol*. 2008;26:2013-2019.

Wolmark N, Yothers G, O'Connell MJ, et al. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08. *J Clin Oncol (ASCO Annual Meeting Abstracts)*. 2009;27(18s):Abs LBA4