Is there a Benefit from Addiction to Anti-VEGF Therapy in Patients with Colorectal Cancer?

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Abstract. *Studies carried out through the past two decades have evidenced that addition of bevacizumab to chemotherapy improves the efficacy both in first-line and second-line treatment in patients with metastatic colorectal cancer. Benefit of adding bevacizumab to second-line regimen after failing a bevacizumab-containing regimen, or aflibercept plus FOLFIRI) (irinotecan, 5-FU and leucovorin) after failing first-line oxaliplatin regimen with or without bevacizumab or regorafenib as a salvage therapy, do indicate the addiction to anti-vascular endothelial growth factor (VEGF) agents in these patients. This concept also lends some support from the NSABP C-08 adjuvant trial of colon cancer which showed very substantial improvement in time-to-recurrence for the one year of bevacizumab administration, but this benefit was quickly lost once the drug was stopped. The author reviews the data on anti-VEGF therapy in metastatic colorectal cancer.*

The American Cancer Society estimates 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer in the United States for 2013. These diseases are expected to cause about 50,830 deaths during 2013 (1). Colorectal cancer is the third leading cause of cancer-related death in the United States when men and women are considered separately, and the second leading cause when both sexes are combined. The mortality rate has slightly decreased in recent decades. In addition to public awareness and early detection, effective adjuvant and palliative therapies are significant players in improving the outcome.

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Vascular Endothelial Growth Factor and Anti-vascular Endothelial Growth Factor Therapy

Vascular endothelial growth factor (VEGF) plays a central role in human growth and development, and vascular maintenance (2). VEGF-mediated angiogenesis is essential for tumor growth, which is characterized by abnormal neovascularization. VEGF is a potent activator of angiogenesis throughout the lifecycle of a tumor and is thought to be critical to a tumor's ability to grow and metastasize. Bevacizumab (Avastin) is a monoclonal antibody designed to specifically inhibit the VEGF protein. Bevacizumab has been approved for the treatment of the advanced stages of four common cancer types: colorectal, breast, lung and kidney (3).

Bevacizumab in First-line Therapy

Bevacizumab in combination with intravenous fluorouracil-based chemotherapy has been proven to extend overall survival by 52% compared to chemotherapy alone in patients with advanced colorectal cancer. This is one of the largest improvements in survival ever reported in a randomized phase III study of advanced colorectal cancer (HR=0.66) (4).

Bevacizumab in Second-line Therapy

In a phase III study in second-line advanced colon cancer, bevacizumab in combination with FOLFOX4 (oxaliplatin, 5-FU, leucovorin)-chemotherapy improved overall survival by 33% compared to chemotherapy alone (HR=0.75) (5). Of note, prior to the publication of this trial, the study of FOLFOX4 as first-line therapy for metastatic colorectal cancer (mCRC) had just been accepted as the standard-of-care for initial treatment in the United States (6). The E3200 trial also proved the antitumor effect of FOLFOX4 with or without bevacizumab in second-line setting after irinotecan failure. Bevacizumab-related toxicities were thrombosis, hypertension, proteinuria and epistaxis.

Bevacizumab Beyond Progression

However, many clinical questions have remained unanswered, such as the role of bevacizumab maintenance, or continuation of bevacizumab in second- or third-line settings in patients who had prior exposure to bevacizumab-containing regimens. Recent data from TML study (bevacizumab plus chemotherapy continued beyond first progression in patients with mCRC previously treated with bevacizumab plus chemotherapy, randomized phase III intergroup study) showed that the continuous use of bevacizumab improved the odds of overall survival by 19%, for a median 1.4 month advantage over a strategy of chemotherapy alone after progression (p=0.0062) (7). This phase III trial included 820 patients whose mCRC progressed while on a regimen of bevacizumab and standard first-line oxaliplatin (Eloxatin) or irinotecan (Camptosar)-based chemotherapy. For second-line therapy, patients were switched to the other of the two chemotherapy regimens with randomization to take the second therapy or with continued bevacizumab. These findings indicate a potential new model for treatment approaches through multiple lines for mCRC and across other tumor types. Overall survival after progression improved with bevacizumab to a median of 11.2 months compared with 9.8 months usually on chemotherapy alone. While a small difference, the hazard ratio (HR) of 0.81 for death was statistically significant at p=0.0062. The same was true for progression-free survival (PFS). The combination of bevacizumab and chemotherapy in second-line was associated with an HR of 0.68 for progression or death (p<0.0001). The median PFS was 5.7 and 4.1 months, respectively. Continuing bevacizumab after the first progression of metastatic cancer did not appear to add significantly to toxicity. The same strategy is commonly used to treat breast cancer, despite little clinical trial data.

Bevacizumab in Adjuvant Therapy

The results of the National Surgical Adjuvant Breast and Bowel Project C-08 trial (NSABP C-08) did not show survival benefit with the use of bevacizumab in this and the adjuvant setting (8). This randomized phase III trial enrolled 2,710 patients to compare modified FOLFOX6 (every 2 weeks for 12 cycles) with bevacizumab *vs*. without bevacizumab. For the non-bevacizumab arm, patients received standard modified FOLFOX6 for a total of 12 cycles; while patients in the bevacizumab arm were offered bevacizumab maintenance after completion of 12 cycles of modified FOLFOX6 plus bevacizumab. At one year, there was a 40% reduction in the event rate (p=0.0004) with bevacizumab. However, after one-year this effect disappeared. This observation suggested that there was statistically significant transient benefit in disease-free survival (DFS) during the one year that bevacizumab was given. Clearly, the early trend toward improved DFS does not argue for treating all patients with bevacizumab to salvage some early failures. When there may be no survival difference, this is not justifiable.

Aflibercept in Colon Cancer

Aflibercept, also known as VEGF-Trap, is a recombinant, decoy receptor fusion protein, rationally designed to block angiogenesis by targeting not only all forms of VEGF-A, but also VEGF-B and placental growth factor (9). It inhibits VEGF-induced angiogenesis in pre-clinical models. In tumor models, aflibercept is associated with the reduction of tumor vasculature and size, and the inhibition of ascites formation. Phase I and II studies have provided proof-of-principle, and support the continuing clinical investigation of aflibercept. The phase III VELOUR study of aflibercept plus FOLFIRI compared with placebo plus FOLFIRI in patients with mCRC following failure of an oxaliplatin regimen showed that the addition of aflibercept to FOLFIRI improved PFS and overall survival (OS) both statistically significant and clinically meaningful (10). The VELOUR study randomized 1,226 patients with previously treated metastatic disease to one-hour intravenous aflibercept (4 mg/kg) or placebo, plus FOLFIRI with the primary endpoint of OS, that was reached, with a [HR] of 0.82 (p=0.0032). The median OS in the intention-to-treat population was 12.1 months with FOLFIRI alone, and 12.5 months with FOLFIRI plus aflibercept. Positive results were also observed for PFS, with an HR of 0.76 (p=0.00007). The median PFS was 4.7 months with chemotherapy alone *versus* 6.9 months with the addition of aflibercept. Response rates were 11.1% *versus* 19.8%, respectively (p=0.0001).

Investigators assessed the impact by stratification factors (performance status, prior bevacizumab treatment), and patient characteristics (age, gender, geographic region, prior hypertension, number of metastatic sites, disease confined to the liver, location of primary tumor) and the pre-planned subgroup analyses supported the consistency and robustness of the efficacy results across all domains, including prior treatment with bevacizumab.

A significant interaction was observed between treatment arm and the presence of liver metastases only, indicating a greater treatment effect in this group of patients as compared with patients with disease not confined to the liver or no liver disease. Among patients with liver metastases only, mortality was reduced by 35%, compared with an 11% risk reduction among other groups. PFS followed a similar pattern. For patients with prior bevacizumab treatment who received aflibercept, the median PFS was 6.7 months, and OS was 12.5 months, which did not differ from the overall study results.

The incidence of grade 3-4 adverse events were as expected with the anti-VEGF class of agents, and were similar among patients with and without prior bevacizumab exposure. Grade 3-4 hypertension occurred in 16.6% and 20.5% of these groups, respectively. Prior treatment with bevacizumab does not appear to significantly impact the safety profile of aflibercept.

This was a well-designed and well-conducted study, which included a pre-planned subgroup analysis with *a priori* biological rationale to look for associations. However, the findings of subgroup analyses should always be considered hypothesis generating rather than practice changing. In my opinion, the data from VELOUR study do change the landscape of the second-line treatment of advanced disease by offering a new agent for those patients whose disease progresses following front-line treatment with FOLFOX with or without bevacizumab. In August, the FDA approved aflibercept (Zaltrap) for use in combination with a FOLFIRI regimen for patients with mCRC.

Regorafenib in Colon Cancer

Regorafenib (Stivarga) is the latest drug approved by the FDA for patients with mCRC. The trial that led to the approval of regorafenib, the CORRECT trial included 760 patients with mCRC whose disease had progressed following earlier treatment (10). Patients received best supportive care and were randomized two to one to either regorafenib or placebo. The results showed that patients treated with regorafenib had a median of 6.4 months *versus* 5 months for patients treated with placebo (p=0.005). The median PFS was 1.9 months for patients on regorafenib (95%=1.88-2.17) *versus* 1.7 months for those taking placebo (95%=1.68-1.74). The disease control rate for patients on regorafenib was 44.8% *versus* 15.3% for placebo (p 0.0001).

Adverse events in the regorafenib arm, of grade 3 or higher, were fatigue (15%), hyperbilirubinemia (8%), diarrhea (8%), hand-foot skin reaction (17%), and hypertension (7%). Other common adverse events included loss of appetite and weight loss, infection, oral mucositis, and dysphonia.

Discussion

The clinical studies conducted during the last two decades have confirmed that the addition of an anti-VEGF agent ± chemotherapy improves the efficacy in patients with mCRC. This benefit from addiction is evidenced when bevacizumab was added to either first-line or to second-line regimen, or adding bevacizumab to second-line chemotherapy after failing a bevacizumab-containing regimen, or aflibercept plus FOLFIRI after failing the first-line oxaliplatin regimen with or without bevacizumab, or regorafenib as a single agent when used as a salvage therapy in patients with mCRC who have failed both first-line and second-line therapies. This concept of anti-VEGF addiction is further supported by the fact that the NSABP C-08 adjuvant trial of colon cancer showed very substantial improvement in time-to-recurrence for the 1 year of bevacizumab administration. However, this benefit was quickly lost once bevacizumab was stopped.

Distinctions between Bevacizumab and Aflibercept. Distinctions between bevacizumab and aflibercept and small-molecule TKIs include: • Bevacizumab seems to lack any significant single-agent activity outside of glioblastomas and renal cell carcinoma (11, 12); Utility of bevacizumab mainly resides in its combination with chemotherapy; Early phase II trials of single-agent aflibercept have shown single-agent responses in a number of settings including temozolomide-resistant glioblastoma, platinum- and erlotinib-resistant adenocarcinoma of the lung, platinum-resistant epithelial ovarian cancer, and metastatic melanoma (13-17); and Studies in experimental xenograft models suggest that aflibercept is more potent than bevacizumab (18). The suggested difference in efficacy has been explained by the fact that bevacizumab causes only partial VEGF inhibition, which allows for initial recruitment of blood vessels despite inhibition of later vessel remodeling. This results in long-term persistence of the recruited vascular structures. However, VEGF Trap results in more complete blockade, which eventually leads to regression of recruited vasculature. Another potential explanation is that VEGF-Trap binds to placental growth factor, whereas bevacizumab does not.

As a caveat to these findings, it must be noted that pre-clinical studies are not predictive of clinical efficacy in the treatment of cancer or other pathological conditions. One could also presume that aflibercept will act like bevacizumab in regard to chemotherapy in the clinical setting; however, this remains to be determined. Bevacizumab was used at 5 mg/kg dose in first-line and 10mg/kg dose in second-line. However, no data exist at present to show any benefit in escalating the dose to a higher level if a patient's disease has progressed on the lower dose. We can only speculate that higher dose may have cause more antiangiogenic effect, but again, there is lack of benefit at present.

At present, we have the choice of combining intravenous bevacizumab in the first or second lines of therapy, or switching to aflibercept in second line therapy when wishing to deploy and antiangiogenic agent in combination with chemotherapy for the treatment of mCRC. Regorafenib is an option for third-line treatment for patients with mCRC whose disease had progressed following earlier treatment. As the field of anti-VEGF agents expands, we must think about the number of patients and resources needed to examine all these agents in phase III trials. Although some of these agents may find niche indications, the majority will be competing for the

same patient population and respective indication. It would be wise to consider comparing some of these agents early in drug development. Randomized phase II trials may provide with an optimal decision point for the go or no-go decision in drug development, especially when these agents are combined with chemotherapy. In addition, we are desperately in need of markers to predict benefit from these agents.

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