Target Practice: Lessons from Phase III Trials with Bevacizumab and Vatalanib in the Treatment of Advanced Colorectal Cancer

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Key Words. Colorectal cancer • Angiogenesis inhibitors • Bevacizumab • Vatalanib

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the safety of using bevacizumab in clinical practice.
2. Explain the benefit of adding bevacizumab to chemotherapy in colorectal cancer.
3. Discuss mechanisms of targeting the VEGF/VEGFR pathway.

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ABSTRACT

Vascular endothelial growth factor (VEGF) is one of the most important factors involved in tumor angiogenesis and has become an important target for anticancer treatment. In 2004, this approach was validated in a randomized, controlled phase III clinical trial. It was shown that the addition of bevacizumab, a humanized monoclonal antibody against VEGF-A, to conventional chemotherapy prolonged survival over chemotherapy alone in patients with metastatic colorectal cancer. In this review, we discuss the results of the clinical trials that have led to the incorporation of antiangiogenic agents into the treatment of patients with advanced colorectal cancer. We limit ourselves to the two agents that have been tested extensively in phase III trials: bevacizumab and vatalanib, a small molecule tyrosine kinase inhibitor against VEGF receptors. In addition, we discuss the adverse effects of bevacizumab and vatalanib and the clinical management of the side effects. The Oncologist 2007;12: 443–450

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Angiogenesis is an absolute requirement for tumors to become clinically relevant and detectable. The importance of angiogenesis for tumor growth is supported by several clinical studies that showed a positive correlation between tumor angiogenesis and tumor stage. Vascular endothelial growth factor (VEGF) has been recognized as one of the most important factors involved in tumor angiogenesis and has become an important target for anticancer treatment. In animal studies, inhibition of angiogenesis caused impressive suppression of tumor growth. At the American Society of Clinical Oncology (ASCO) 2003 Annual Meeting, the...
first phase III clinical trial was presented, which showed that the inhibition of angiogenesis is effective in the treatment of patients with advanced colorectal cancer. This study had a tremendous impact on the clinical management of patients with advanced colorectal cancer. In this review we discuss the results of the clinical trials that have led to the incorporation of antiangiogenic agents into the treatment of patients with advanced colorectal cancer.

**VEGF, a Key Player in Angiogenesis**

VEGF is the best studied member of a large family of dimeric glycoproteins acting as growth factors [1]. VEGF-A is the predominant member of the family that also contains VEGF-B, VEGF-C, VEGF-D, VEGF-E, platelet-derived growth factor (PDGF), and placenta growth factor. VEGF is essential for the normal development of blood vessel growth. In mice, the VEGF−/− and VEGF+/− phenotypes are lethal embryonically as a result of abnormal blood vessel development [2, 3]. VEGF is an important growth factor for vascular endothelium [4]. VEGF binds with high affinity to the transmembrane tyrosine kinase receptors VEGFR-1, -2, and -3 [5]. VEGFR-1 and VEGFR-2 are predominantly expressed on the cell surface of endothelial cells. VEGFR-2−/− mice die in utero between day 8.5 and 9.5 [6]. This phenotype is lethal in mice because of the lack of vasculogenesis and failure to develop blood islands and organized blood vessels. Binding of VEGF to VEGFR-2 results in dimerization of the receptor and subsequent tyrosine phosphorylation followed by induction of several proteins in endothelial cells. These VEGF-induced proteins include tissue factor, urokinase, tissue-type plasminogen activator, plasminogen activator inhibitor-1, matrix metalloproteinas, and antiapoptotic factors facilitating tumor growth and tumor metastases [5].

**Targeting the VEGF/VEGFR Pathway**

Because VEGF and its receptors play a critical role in angiogenesis and tumor progression, many approaches have been developed to inhibit this pathway. These include the development of (a) neutralizing antibodies and soluble receptors that inhibit the binding of VEGF to its receptors, (b) tyrosine kinase inhibitors that block downstream signaling from membrane-bound VEGFR receptors, (c) antisense constructs against VEGF mRNA, (d) mammalian target of rapamycin inhibitors, and (e) hypoxia inducible factor (HIF) antagonists. Most of these agents are in early clinical development. In this overview we limit ourselves to the two agents that have been tested extensively in phase III trials. Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a recombinant humanized monoclonal antibody to VEGF-A and vatalanib (PTK787/ZK 222584) is a small molecule tyrosine kinase inhibitor against VEGFR-1 to -3 [7, 8].

The original concept of antiangiogenesis is the inhibition of outgrowth of new blood vessels, thereby preventing further growth [9]. It is now clear that alternative mechanisms occur in patients. Bevacizumab may affect the vasculature through various mechanisms: it (a) causes regression of the tumor vasculature, (b) normalizes the tumor vasculature, (c) inhibits the formation of new blood vessels, and (d) prevents recruitment of progenitor cells from the bone marrow [7–10]. Different preclinical studies showed that, in addition to their direct antiangiogenic effects, anti-VEGF/VEGFR agents may improve the delivery of chemotherapy by altering tumor vasculature and decreasing the elevated interstitial pressure in tumors [11, 12]. Proof of concept was demonstrated by Willett et al. [11]. In a phase I clinical trial, six patients with primary and locally advanced adenocarcinoma of the rectum received a single dose of 5 mg/kg bevacizumab i.v. followed after 2 weeks by concurrent administration of bevacizumab with 5-fluorouracil (5-FU), external beam radiation therapy to the pelvis, and surgery. Twelve days after the administration of bevacizumab, the effect was analyzed by sigmoidoscopy, computed tomography scan, and positron emission tomography. A decrease in tumor perfusion, vascular volume, microvessel density, interstitial fluid pressure, and the number of viable, circulating endothelial and progenitor cells was observed. This confirmed the potential mechanisms of action found in preclinical studies.

Vatalanib is an orally administered molecule that blocks angiogenesis and lymphangiogenesis by inhibiting tyrosine kinase signaling. It also reduces interstitial fluid pressure as monitored by dynamic magnetic resonance imaging [13]. It has a higher selectivity for VEGFR-2 than for the tyrosine kinase receptors VEGFR-1, VEGFR-3, and PDGF receptor and c-Kit protein tyrosine kinase [8]. Vatalanib inhibited VEGF-induced autophosphorylation in Chinese hamster ovary cells and human umbilical vein endothelial cell proliferation and migration. Vatalanib also inhibited growth and angiogenesis in human tumor xenograft models in nude mice [14].

**Angiogenesis Inhibitors in Phase III Clinical Trials**

**Bevacizumab**

The first phase III clinical trial demonstrating the efficacy of inhibition of angiogenesis in colorectal cancer was published in 2004 by Hurwitz et al. [15]. They showed that the addition of bevacizumab to chemotherapy results in a sta-
tistically significant improvement in survival among patients with metastatic colorectal cancer. Eight hundred thirteen patients with previously untreated metastatic colorectal cancer were randomized to receive irinotecan, bolus 5-FU, and leucovorin (IFL) with either placebo or bevacizumab (5 mg/kg body weight every 2 weeks). The median duration of survival was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo \((p < .001)\). The median duration of progression-free survival (PFS) was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo \((p < .001)\); the corresponding response rates were 44.8\% and 34.8\% \((p = .004)\). This was the first randomized trial to show a clinically relevant effect of an angiogenesis inhibitor. The only criticism that one may have on this study was the choice of chemotherapeutic regimen. IFL is now, because of toxicity reasons, considered an obsolete regimen. However, several subsequent studies have demonstrated a consistent benefit of the addition of bevacizumab chemotherapy, regardless of the regimen [16–19].

The E3200 is a randomized phase III trial performed by the Eastern Cooperative Oncology Group [20]. This study evaluated the effect of bevacizumab (10 mg/kg biweekly), either as a single agent or in combination with 5-FU, leucovorin, and oxaliplatin (FOLFOX)-4, versus FOLFOX-4 alone in 829 previously treated patients with advanced colorectal cancer. Eligible patients were treated with a fluoropyrimidine- and/or an irinotecan-based regimen. The median overall survival (OS) time and median PFS time were significantly longer in patients receiving bevacizumab in combination with FOLFOX-4. The median OS duration in the bevacizumab plus FOLFOX-4, FOLFOX-4, and bevacizumab arms were 12.5, 10.7, and 10.2 months, respectively. The median PFS durations were 7.4, 5.5, and 3.5 months, respectively, for the different treatment arms. The addition of bevacizumab to FOLFOX-4 resulted in a significantly higher response rate (21.8\% versus 9.2\%; \(p < .0001\)). The response rate of monotherapy bevacizumab was not \(> 3.0\%\). Further analyses showed that OS and PFS in this study were not compromised for patients who underwent dose reductions of bevacizumab [21]. Dose reductions of bevacizumab to 5 mg/kg were allowed for hypertension, bleeding, thrombosis, proteinuria, and liver function abnormalities. Dose reductions were performed in 55\% of the patients treated with bevacizumab plus FOLFOX-4 and in 38\% of the patients treated with bevacizumab alone. There was slightly more neurotoxicity reported in the bevacizumab treatment arm, which may be a result of the higher number of courses of oxaliplatin chemotherapy in that arm.

The TREE studies evaluated the safety, tolerability, and efficacy of three oxaliplatin regimens with bolus fluoropyrimidine (bFOL), infusional fluoropyrimidine (FOLFOX), or oral fluoropyrimidine (capecitabine plus oxaliplatin [the CapeOx regimen]) without (TREE-1) or with (TREE-2) bevacizumab as first-line treatment of metastatic colorectal cancer [22]. The dose of bevacizumab was 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. The primary endpoint was toxicity (see below). Secondary endpoints were the overall response rate, time to progression (TTP), and OS duration. In TREE-1, 147 patients were treated, and in TREE-2, 213 patients were treated. The addition of bevacizumab resulted in a higher response rate for all chemotherapy regimens: FOLFOX (52\% versus 41\%), bFOL (39\% versus 20\%), and CapeOx (46\% versus 27\%). Similarly, the median TTP was longer: FOLFOX (9.9 versus 8.6 months), bFOL (8.3 versus 6.9 months), and CapeOx (10.9 versus 5.9 months). Taken together, all reported phase III trials with bevacizumab in metastatic colorectal cancer show a consistent pattern that the addition of bevacizumab leads to higher response rates and longer disease-free survival times.

Vatalanib

If equally active, agents that can be administered orally, such as vatalanib, generally have an advantage over i.v. drugs such as bevacizumab. A randomized, double-blind, placebo-controlled, phase III study was performed to assess the efficacy of vatalanib in combination with the FOLFOX-4 regimen in previously untreated patients with metastatic colorectal cancer (the Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases [CONFIRM]-1 trial). The results of that trial were presented at the ASCO 2005 Annual Meeting by Hecht et al. [23]. One thousand one hundred sixty-eight patients were randomized to receive FOLFOX-4 plus vatalanib (1,250 mg orally daily) or FOLFOX-4 plus placebo. Stratification factors were lactate dehydrogenase (LDH) \(\leq \) or \(> 1.5 \times \) the upper limit of normal (ULN) and performance status. The addition of vatalanib did not result in differences in the response rate (42\% for FOLFOX-4 plus vatalanib versus 46\% for FOLFOX-4 plus placebo) or PFS time (7.7 months for FOLFOX-4 plus vatalanib versus 7.6 months for FOLFOX-4 plus placebo). OS data are expected in the second half of 2006. The CONFIRM-2 trial is a double-blind, placebo-controlled, phase III study investigating the effect of FOLFOX-4 with or without vatalanib in second-line therapy of patients with metastatic colorectal cancer. The first results of this study were presented at the ASCO 2006 Annual Meeting [24]. Eight hundred fifty-five patients were randomized to FOLFOX-4 plus vatalanib (1,250 mg daily) or placebo. Patients were pretreated with
irinotecan- plus fluoropyrimidine-based chemotherapy for metastatic disease. The primary endpoint was OS. Secondary endpoints included OS and PFS in high LDH patients (stratified by baseline serum LDH level >1.5 × ULN). The OS time was 12.1 months in the vatalanib arm and 11.8 months in the placebo arm. The PFS time was significantly longer in the vatalanib arm (5.5 versus 4.1 months; \( p = .026 \)). Patients with high LDH levels had a longer PFS duration when treated with vatalanib (5.6 versus 3.8 months; \( p < .001 \)). A meta-analysis of the CONFIRM-1 and CONFIRM-2 trials showed that vatalanib significantly improved PFS in patients with high levels of LDH [25]. Because LDH is a nonspecific tumor marker, it is presently unclear how to interpret these data. The fact that both the CONFIRM-1 and -2 studies showed almost identical results strongly points to a potentially useful marker to select patients for future trials in advanced colorectal cancer. It is tempting to speculate that high levels of LDH reflect the growth rate and through this the dependency of tumors on angiogenesis. Bulky, rapidly growing tumors might boost HIF-1α expression and it has been suggested that LDH may serve as a surrogate marker for hypoxia. The dosing of vatalanib has been argued as a potential reason for the negative results of these trials. The current dogma is that angiogenesis inhibitors should preferably be given continuously. Because of the short half-life of vatalanib (4.7 hours), once-daily dosing may have caused intermittent inhibition [27]. A recent phase I study has provided support for twice-daily dosing [28]. It is widely believed that continuous suppression of the VEGF/VEGFR pathway is better than intermittent inhibition. Although this assumption has not been formally studied in clinical trials, there are several observations that support this notion. Blocking the VEGFR commonly leads to increased levels of circulating VEGF [29, 30]. In the case of intermittent inhibition, this increased level of circulating VEGF may induce a significant activation of the pathway in the absence of an inhibitor. This may be an explanation for the observation that long-acting inhibitors of the VEGF/VEGFR pathway appear to be more effective in clinical trials than agents with a shorter half-life. The pharmacokinetic data may explain why only a subgroup of patients, that is, patients with high LDH levels, respond better to vatalanib than those with normal levels. The group with high LDH levels may be more vulnerable (for reasons stated above) to VEGF/VEGFR inhibition, and partial inhibition may already be effective. It would be of interest to see if LDH has a predictive value in other studies in (colorectal) cancer incorporating VEGF/VEGFR inhibitors. This would support this hypothesis. Furthermore, it is important to realize that in the CONFIRM-1 trial there was a higher rate of early discontinuation because of toxicity in the vatalanib treatment arm. This may have contributed to the disappointing outcome of this study. Finally, it has become clear that tyrosine kinase inhibitors are not without side effects (see below). Management of side effects requires experienced oncologists to prevent early discontinuation of treatment. Investigators in future randomized trials should be aware of this phenomenon and ensure sufficient recruitment at experienced centers. Taken together, the studies with vatalanib have shown that VEGFR tyrosine kinase inhibitors have biological activity and paved the way for future studies with the various small molecule inhibitors that are currently in development in advanced colorectal cancer. Because bevacizumab is now considered a standard addition to first-line chemotherapy for patients with advanced colorectal cancer, this will likely influence the development of small molecule inhibitors of the VEGFR in first-line treatment.

**MANAGEMENT OF BEVACIZUMAB TOXICITY IN COLORECTAL CANCER**

The introduction of bevacizumab has brought along a spectrum of novel side effects (Table 1). Most side effects can be explained by the reduced availability of VEGF, but some are poorly understood. The addition of bevacizumab to the IFL regimen was well tolerated [15]. Grade 3 hypertension was more common during treatment with IFL and bevacizumab (11.0% versus 2.3%) but was easily managed using standard antihypertensive medication. There were no differences found in the incidence of bleeding, thrombosis, and proteinuria between the two groups. Gastrointestinal (GI) perforation was a striking adverse event in the IFL plus bevacizumab group. Six cases (1.5%) of GI perforation were observed in the group treated with IFL plus bevacizumab, versus none in the IFL plus placebo group. One patient died and two discontinued therapy permanently as a result of this complication.

The emerging toxicity profile was further supported by the First BEAT, BRI TE, and TREE trials. The First BEAT trial was initiated to evaluate the safety profile of bevacizumab in a broader patient population with metastatic colorectal cancer using bevacizumab in combination with a variety of chemotherapy regimens. Up to 2,000 patients from 41 different countries in Europe, Canada, and Australia were enrolled between June 2004 and February 2006. Eligible patients received first-line, 5-FU–based chemotherapy. Bevacizumab was administered in a dose of either 5 mg/kg every 2 weeks with 5-FU regimens or 7.5 mg/kg every 3 weeks with capecitabine-based regimens. In March 2006, data from 1,789 patients were evaluated, with a median follow-up of 8.7 months. Bevacizumab-related serious
adverse events (SAEs) were reported in 156 patients (9%) and included GI perforations (1.2%), bleeding events (1.3%), and arterial thromboembolic events (0.7%). No new safety signals were identified [31].

The BRiTE study is a large, observational registry in the U.S. of patients with metastatic colorectal cancer receiving bevacizumab. One thousand nine hundred sixty-eight patients receiving first-line chemotherapy with bevacizumab were followed for up to 3 years. SAEs were reported in 12% of the patients and were similar to those from the First BEAT trial. GI perforation (1.7%), bleeding and wound-healing complications (1.2%), and arterial thromboembolic events (2.1%) were reported [32, 33].

As mentioned earlier, the TREE study evaluates the safety, tolerability, and efficacy of three oxaliplatin plus fluoropyrimidine regimens without (TREE-1) or with (TREE-2) bevacizumab as first-line treatment of metastatic colorectal cancer patients. In line with the other studies, the addition of bevacizumab to each of the chemotherapy regimens caused more grade 3–4 hypertension, impaired wound healing, and bowel perforation [22]. Overall, bevacizumab is very well tolerated and does not increase the toxicity of chemotherapy. However, there are a number of side effects of bevacizumab that require specific attention.

**Bevacizumab and Surgery**

Surgeons are increasingly confronted with patients receiving antiangiogenic therapy. Scappaticci et al. [34] assessed wound-healing complications occurring ≤60 days after surgery in two randomized trials of metastatic colorectal cancer patients treated with 5 mg/kg bevacizumab once every 2 weeks in combination with 5-FU–based chemotherapy or with chemotherapy alone. Of the patients who underwent major surgery 28–60 days before study treatment, wound-healing complications occurred in 1.3% of the patients treated with bevacizumab and in 0.5% of the patients receiving chemotherapy alone. In 75 patients who underwent major surgery during treatment with bevacizumab, 10 patients (13%) had wound-healing problems, compared with 1 of 29 patients (3.4%) in the control group. While not statistically significant, this difference may be clinically important, and patients receiving bevacizumab who undergo surgery should be monitored carefully.

The half-life of bevacizumab is 20 days. In the pooled analysis of the two trials [15, 17], there appeared to be no definite relationship between the timing of surgery following the last bevacizumab dose and the development of a wound-healing complication. Within a 60-day time period, the risk for developing a wound-healing complication did not change, regardless of whether the surgery was performed within the first 30 days or during the second 30 days following the most recent bevacizumab dose. However, the number of cases was too small to make a definite conclusion regarding the window of risk for wound-healing complications. It was suggested that elective major surgery should preferably be delayed for at least 28 days following the last bevacizumab dose. The use of bevacizumab 28 days after primary surgery appears to be feasible and safe in colorectal cancer patients [34].

Although wound-healing complications are more frequent in patients who have major surgery during bevacizumab treatment, it is important to realize that the majority of the patients experience no complications. For minor surgery, for example, implantation of a venous access port, treatment with bevacizumab generally can be continued. These guidelines are important because, as a result of the high response rates, the use of bevacizumab in the neoadjuvant setting is very appealing. Gruenberger et al. [35] performed a pilot study in 22 patients with nonoptimal resectable metastatic colorectal cancer. Patients were treated with six cycles of neoadjuvant bevacizumab (5 mg/kg) and capecitabine plus oxaliplatin (XELOX) every 2 weeks. The sixth cycle did not include bevacizumab, resulting in a gap of 5 weeks between the last dose of bevacizumab and surgery. Surgery was performed in 21 patients, including liver resection in 11 patients. No adverse effects on surgical wound healing, bleeding, or liver regeneration were observed [35].

In the First BEAT study, the incidence and nature of postoperative wound-healing complications following me-

### Table 1. Summary of toxicity of bevacizumab and vatalanib

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<th>Adverse events attributable to bevacizumab</th>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Proteinuria</td>
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<td>Bleeding and wound-healing complications</td>
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<td>Gastrointestinal perforation</td>
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<td>Thromboembolic events</td>
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<td>Reversible posterior encephalopathy syndrome (RPLS)</td>
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<tr>
<th>Adverse events attributable to vatalanib</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Fatigue</td>
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<td>Nausea and vomiting</td>
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<td>Dizziness</td>
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<td>Thromboembolic events</td>
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<td>Reversible posterior encephalopathy syndrome (RPLS)</td>
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tastectomy were evaluated [36]. In that study 43 patients (2.4%) had undergone metastasectomy for residual disease after bevacizumab plus chemotherapy. Elective surgical procedures were scheduled at a minimum of 6–8 weeks after the last dose of bevacizumab. In cases of unplanned surgery, bevacizumab was stopped as soon as the indication for surgery was identified. When appropriate, bevacizumab was restarted 28 days after surgery when wound healing was complete. No postoperative bleeding or significant increase in postoperative complications related to bevacizumab was observed. There are currently several trials with neoadjuvant bevacizumab-based chemotherapy under way that will provide additional information on the safety of this treatment.

**Bevacizumab and GI Perforation**

GI perforation is the most puzzling adverse event of bevacizumab. Perforations occur along the GI tract without an apparent predilection site. Risk factors for a GI perforation are not well defined. No correlation was found between the presence of the primary tumor and the occurrence of bowel perforation during treatment with bevacizumab. A phase II study in patients with advanced platinum-resistant ovarian cancer that progressed after topotecan or liposomal doxorubicin and who were treated with bevacizumab monotherapy was prematurely stopped because of GI perforations. In that study, bevacizumab was dosed at 15 mg/kg every 3 weeks. The study enrolled 44 of the intended 53 patients and closed early because of a higher than expected rate of GI perforation. The presence of peritonitis carcinomatosa, the fact that these patients were heavily pretreated, and the relatively high dose of bevacizumab were suggested risk factors for GI perforation in ovarian cancer [37]. Inflammatory bowel disease and an obstructive primary tumor requiring surgery in the immediate future may be considered as contraindications for bevacizumab treatment.

The mechanism through which GI perforations occur is unclear. Recently it was suggested that platelets take up bevacizumab and release it at sites of active angiogenesis [38]. This uptake of bevacizumab leads to impaired platelet function and may contribute to impaired wound healing.

**Other Adverse Effects of Bevacizumab**

Hypertension is often seen in patients treated with bevacizumab. In the pivotal trial of Hurwitz et al. [15], 11% of the patients had grade 3 hypertension and 22% had some form of hypertension. All episodes of hypertension were manageable with standard oral antihypertensive agents. It is believed that VEGF acts as a homeostatic factor for blood pressure. Blocking VEGF or its receptors therefore results in increased vascular tension. Hypertension is now considered a class effect of anti-VEGF/VEGFR agents. A very rare side effect of bevacizumab is reversible posterior encephalopathy syndrome (RPLS) [39, 40]. RPLS is a brain-capillary leak syndrome related to hypertension, fluid retention, and the cytotoxic effects of immunosuppressive agents on vascular endothelium [41–43]. Clinicians should be aware of this potential complication.

**Management of Toxicity of VEGFR Tyrosine Kinase Inhibitors**

The most frequent grade 3–4 adverse events attributable to vatalanib in the CONFIRM-2 trial were similar to those in the CONFIRM-1 trial (Table 1). In the CONFIRM-2 trial, grade 3–4 adverse events were hypertension (21% for vatalanib versus 5% for placebo), diarrhea (16% versus 8%), fatigue (15% versus 7%), nausea (11% versus 5%), vomiting (9% versus 5%), and dizziness (9% versus 1%). Thrombotic and embolic events of all grades occurred in 6% of the vatalanib-treated patients, versus 1% of the placebo group [24]. Adverse events attributable to vatalanib were generally similar to those seen with other VEGF pathways inhibitors [44, 45]. However, RPLS was seen in 1% of the patients. This is much more frequent than that reported for bevacizumab. More adverse events associated with antiangiogenic therapy, such as bowel perforation and bleeding complications, were not observed in either trial [25].

**CONCLUSIONS AND PERSPECTIVES**

In conclusion, the addition of bevacizumab to fluoropyrimidine-based chemotherapy has significantly improved the response rate and PFS and OS durations in previously treated and untreated patients with metastatic colorectal cancer. “Target practice” with other VEGF/VEGFR pathway inhibitors has not (yet) demonstrated an effect on response rate or PFS in randomized clinical trials. However, several agents with different pharmacokinetic properties are currently under development. Clinical management of the side effects of these VEGF/VEGFR inhibitors to avoid dose reductions or delay in treatment provides a challenge to oncologists.

In light of the positive results with bevacizumab in patients with advanced colorectal cancer, it is expected that bevacizumab will be effective in adjuvant regimens in colorectal cancer. Various phase III trials assessing the efficacy and tolerability of bevacizumab in combination with oxaliplatin-based chemotherapy in the adjuvant setting are under way.

The AVANT trial is randomizing patients who have undergone surgery with high-risk stage II and stage III colon cancer to receive FOLFOX-4, FOLFOX-4 with bevacizumab, or XELOX with bevacizumab. The National Surgi-
clinical Adjuvant Breast and Bowel Project C-08 study is comparing FOLFOX-6 plus bevacizumab with FOLFOX-6 alone for the treatment of patients with resected stage II and III carcinoma of the colon. The aim of the U.S. Intergroup trial E5202 is to determine prospectively the prognostic value of molecular markers, for example, microsatellite instability and 18q loss of heterozygosity, in patients with stage II colon carcinoma at high risk for recurrence. The low-risk patients receive no further intervention postsurgery, whereas the high-risk patients, based on the molecular markers, are randomized to the FOLFOX regimen with or without bevacizumab. The U.S. Intergroup trial E5204 compares FOLFOX with FOLFOX plus bevacizumab in patients with stage II and III rectal cancer who received preoperative chemoradiation.

Some of these adjuvant trials are collecting tissue to identify biomarkers that might predict which patients are most likely to benefit from antiangiogenic therapy.

The results are eagerly awaited. However, it is important to realize that the mechanism of action of bevacizumab in a large tumor may be different from that in microscopic tumors. The mechanism of action of bevacizumab in the adjuvant setting might therefore differ from its mechanism of action in the metastatic setting. In the adjuvant setting, the inhibition of formation of new blood vessels and prevention of progenitor cells from the bone marrow facilitating the outgrowth of occult metastases may be more relevant. It may therefore be appropriate to continue antiangiogenic therapy for a prolonged period of time. It is tempting to speculate that, in the adjuvant setting, single-agent bevacizumab is as effective as chemotherapy. Adjuvant studies addressing these questions will bring the treatment of colorectal cancer patients another step forward.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
E.E.V. has acted as a consultant for Schering AG/Berlex, Pfizer, and AstraZeneca.

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