A biomarker may help to maximize the clinical benefit of the VEGF inhibitor bevacizumab for several tumor types.

Lessons Learned From the Bevacizumab Experience

Joanne Mortimer, MD, FACP, Helene B. Zonder, MN, AOCNP, NP-C, and Sumanta K. Pal, MD

Background: Bevacizumab is an important agent in the oncologic armamentarium, with activity in a broad spectrum of solid tumors. It has been approved in the management of metastatic colorectal cancer, non–small cell lung cancer, renal cancers, and recurrent glioblastoma multiforme.

Methods: We reviewed the published literature and briefing documents of the US Food and Drug Administration that provided the data leading to approval or change in approval status.

Results: Bevacizumab initially received accelerated approval for the treatment of advanced breast cancer. However, lack of confirmatory data from additional clinical trials resulted in the loss of that indication. Both the expected and unexpected toxicities reported from clinical trials using bevacizumab have helped us to understand the drug’s mechanism of action and to identify who are most likely to benefit from this important agent.

Conclusions: The side effects of treatment may provide important information about drug mechanism and efficacy. Bevacizumab is clearly an important agent in oncology and is likely to become more significant once a clinical or pathological marker to predict its efficacy has been identified.

Introduction

Bevacizumab is an important agent in the oncologic armamentarium and is currently approved by the US Food and Drug Administration (FDA) for the treatment of a number of solid tumors. Despite its acknowledged benefits in patients with a variety of solid tumors, the oncologic community has focused on the recent decision by the FDA to remove treatment of advanced breast cancer from its labeling. We have learned a great deal from the drug development of bevacizumab in oncology: the approval process, its impact on underserved diseases, and the identification and management of unusual and unexpected toxicities.

Because the growth and spread of cancers are dependent on the development of a neovasculature, angiogenesis is an important therapeutic target in oncology. Bevacizumab is a humanized antibody that targets vascular endothelial growth factor (VEGF)-A, which stimulates blood vessel formation. Bevacizumab is not a cytotoxic agent and has no meaningful single-agent efficacy. When VEGF-A is blocked, the aberrant tumor vasculature is altered or destroyed, and interstitial pressure is reduced. The alteration in pressures is credited with an increase in tumor hypoxia and improved delivery of chemotherapy.1,2
**Summary of Phase III Clinical Data on Bevacizumab**

Bevacizumab has been studied in a number of solid tumors and has been approved by the FDA for the treatment of advanced colorectal cancer, non–small cell lung cancer (NSCLC), advanced renal cell cancer, and recurrent glioblastoma multiforme. Data from the phase III trials that led to FDA approval are provided in Table 1.3-7

**Colorectal Cancer**

In 2004, the FDA approved bevacizumab in combination with irinotecan, 5-fluorouracil (5-FU), and leucovorin (IFL) as first-line therapy for metastatic colorectal cancer. Hurwitz et al3 reported that progression-free survival (PFS) improved from 6.2 months for those given IFL plus placebo to 10.6 months for those receiving IFL plus bevacizumab ($P < .001$) and overall survival (OS) increased from 15.6 months to 20.3 months ($P < .001$). Grades 3–4 adverse events were 10% higher in the experimental arm. Six patients receiving bevacizumab experienced gastrointestinal perforation, which was fatal in 1 patient.

Two years later, bevacizumab was approved for second-line therapy in combination with 5-FU, leucovorin, and oxaliplatin (FOLFOX4).4 Even as second-line therapy, the response rate, PFS, and OS rates were improved with the addition of bevacizumab. The median PFS increased from 4.7 months to 7.3 months ($P < .0001$), and OS increased from 10.8 months to 12.9 months ($P = .0011$). The difference in grade 3–4 toxicities was 14% higher in the bevacizumab arm and an increased risk for bleeding became apparent.4 The benefits of bevacizumab in metastatic colorectal cancer clearly outweighed the reported side effects of hypertension, proteinuria, and bleeding.

**Lung Cancer**

Results from a phase II randomized trial of carboplatin and paclitaxel with and without bevacizumab in patients with locally advanced or metastatic NSCLC identified bleeding as a potential toxicity associated with bevacizumab in this disease. Six patients whose tumors were located near major blood vessels, with squamous cell histology, tumor necrosis, and caviation, experienced severe hemoptysis, which was fatal in 4 patients.8 Therefore, in designing the confirmatory phase III trial, these patients were excluded from study participation, as were patients with brain metastasis.

The addition of bevacizumab to paclitaxel and carboplatin improved the response rate, PFS, and OS compared with carboplatin/paclitaxel alone.5 PFS was significantly improved from 4.5 months to 6.2 months ($P < .001$), with a corresponding OS from 10.3 months to 12.3 months ($P = .005$). Even with the exclusion of patients identified to be at increased risk for bleeding, life-threatening pulmonary hemorrhage was reported.

---

**Table 1. — Timeline for US Food and Drug Administration (FDA) Approval of Bevacizumab by Disease Site**

<table>
<thead>
<tr>
<th>Date of FDA Approval</th>
<th>June 2006</th>
<th>October 2006</th>
<th>May 2009</th>
<th>July 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>E3200</td>
<td>E1505</td>
<td>Friedman et al6</td>
<td>AVOREN Escudier et al7</td>
</tr>
<tr>
<td>Disease Site</td>
<td>First-line metastatic colorectal cancer</td>
<td>Second-line metastatic colorectal cancer</td>
<td>First-line unresectable, locally advanced, recurrent and metastatic non–squamous cell carcinoma, non–small cell lung cancer</td>
<td>Second-line glioblastoma</td>
</tr>
<tr>
<td>Regimen</td>
<td>Irinotecan, 5-fluorouracil, and leucovorin ± bevacizum</td>
<td>FOLFOX4 ± bevacizum</td>
<td>Carboplatin/paclitaxel ± bevacizum</td>
<td>Bevacizumab ± irinotecan</td>
</tr>
<tr>
<td>Response Rate</td>
<td>34.8% vs 44.8% ($P = .004$)</td>
<td>8.6% vs 22.7% ($P &lt; .0001$)</td>
<td>15% vs 35% ($P &lt; .001$)</td>
<td>28.2% vs 37.8%</td>
</tr>
<tr>
<td>PFS</td>
<td>6.2 mos vs 10.6 mos ($P &lt; .001$)</td>
<td>4.7 mos vs 7.3 mos ($P &lt; .0001$)</td>
<td>4.5 mos vs 6.2 mos ($P &lt; .001$)</td>
<td>4.2 mos vs 5.6 mos</td>
</tr>
<tr>
<td>OS</td>
<td>↑OS 15.6 mos vs 20.3 mos ($P &lt; .001$)</td>
<td>↑OS 10.8 mos vs 12.9 mos ($P = .0011$)</td>
<td>↑OS 10.3 mos vs 12.3 mos ($P = .003$)</td>
<td>Bevacizumab vs bevacizumab + irinotecan</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Grade 3 hypertension 2.3% vs 11%</td>
<td>–</td>
<td>Clinical bleeding 0.7% vs 4.4%</td>
<td>2 cranial wound dehiscence; 2 gastrointestinal perforations; 5 intracranial hemorrhages (2 with bevacizumab and 3 with bevacizumab and irinotecan)</td>
</tr>
</tbody>
</table>

*FOLFOX4 = 5-fluorouracil, leucovorin, oxaliplatin, PFS = progression-free survival, OS = overall survival.*

---
in 1.9% of patients and was fatal in 1.2%. In clinical practice, bevacizumab continues to be contraindicated in patients with squamous cell tumors.

Breast Cancer

Given the success of bevacizumab in 2 of the most common solid tumors, it seemed likely that the drug would be beneficial in women with breast cancer. The first combination trial in advanced disease enrolled 462 pretreated patients to receive capecitabine alone or capecitabine in combination with bevacizumab. Although response rates were significantly higher with the combination (19.8% vs 9.1%; \( P = .001 \)), the primary endpoint of improved PFS was not achieved (4.86 months vs 4.17 months; hazard ratio [HR] = .98). The higher response rate suggested a potential benefit with bevacizumab, and any improvements in survival may have been masked by the fact that the patients enrolled had been heavily pretreated.

The next major randomized trial, E2100, enrolled women with newly metastatic non-HER2-positive cancers to receive either paclitaxel on days 1, 8, and 15 or paclitaxel in combination with bevacizumab on days 1 and 15. Each cycle consisted of 28 days. No improvement in OS was seen, a target established by the FDA for approval of first-line therapy in this setting. A significantly higher response rate (36.9% vs 21.2%) and improvement in PFS (11.8 months vs 5.9 months) led to the accelerated approval of bevacizumab in this setting.

Data from ongoing trials were expected to confirm these optimistic results and lead to full approval status. However, subsequent clinical trials of bevacizumab in metastatic breast cancer have failed to support the encouraging data from E2100. Two additional FDA reviews by the Oncology Drug Advisory Committee ultimately led to the removal of the breast cancer indication for bevacizumab. The phase III randomized trials of bevacizumab in the first-line treatment of advanced breast cancer are summarized in Table 2.

The AVADO trial was a three-arm trial comparing docetaxel as a single agent with docetaxel and bevacizumab at two dose levels: 7.5 mg/kg and 15 mg/kg. All drugs were administered at 21-day intervals. Results for the two bevacizumab arms were virtually superimposable. A 1-month improvement was observed in PFS favoring the bevacizumab arms, but no difference was observed in OS. The median OS in the control arm was 31.9 months compared with 30.8 months with low-dose bevacizumab and 30.2 months with high-dose bevacizumab. Patients receiving bevacizumab experienced more treatment disruptions. In the bevacizumab arm, gastrointestinal perforation was reported in 3% of patients, with 0.8% of deaths attributed to toxicity.

The third trial, RIBBON-1, randomized patients to receive or not receive bevacizumab with whatever first-line chemotherapy regimen was favored by the treating medical oncologist. The data were analyzed in two distinct chemotherapy groups: “anthracycline-based” or “taxane-based” chemotherapy with or without bevacizumab. A significant improvement in both response rate and PFS was reported when bevacizumab was added to each chemotherapy regimen. However, OS was not improved. As in the AVADO trial, treatment disruptions were more common with bevacizumab in the RIBBON-1. One in 4 patients discontinued bevacizumab due to side effects, and death was attributed to drug toxicity in 1.2%.

In the AVADO and RIBBON-1 trials, the taxane was administered every 21 days, whereas in the E2100 trial, weekly paclitaxel was utilized for 3 of 4 consecutive weeks. Genentech Inc is conducting a confirmatory trial using the weekly schedule of paclitaxel and serum VEGF-A as a biomarker.

Bevacizumab was studied in the second-line setting in RIBBON-2. Women with HER2-negative disease that progressed after first-line therapy were randomly assigned to receive chemotherapy according to the choice of the treating oncologist with or without bevacizumab. With subsequent disease progression, bevacizumab could be added to the third-line regimen. A 2:1 randomization was used to assign 225 women to the control arm and 459 to chemotherapy with bevacizumab. PFS favored the bevacizumab-treated patients (5.1 months vs 7.2 months; \( P = .0072 \)). No improvement in OS was observed, and no unique toxicity profile was identified.

The results of two large neoadjuvant trials have recently been published. The GeparQuinto trial randomized 1,948 women with HER2-negative disease who were considered candidates for neoadjuvant therapy to receive 4 cycles of epirubicin and cyclophosphamide with or without bevacizumab. The primary endpoint was pathological complete response (PCR) in both the primary tumor and regional nodes. The PCR rates were higher for those assigned to bevacizumab: 18.4% vs 14.9% for those receiving chemotherapy alone (\( P = .04 \)). Two thirds of patients in each arm were candidates for breast-conserving therapy. In a subset analysis of 663 women with triple-negative breast cancers, the PCR rate favored those receiving bevacizumab (39.3% vs 27.9%; \( P = .003 \)). The toxicities associated with bevacizumab included hand-foot syndrome, mucositis, fever and neutropenia, and hypertension. No increase in surgical complications was observed.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B40 trial assigned 1,528 women with palpable tumors \( \geq 2 \) cm (T1c-T3, N0-N2a, M0, HER2-negative disease) to 1 of 3 chemotherapy regimens: docetaxel, docetaxel with capecitabine, or docetaxel with gemcitabine. In a second randomization, patients were assigned to receive bevacizumab or not. The primary endpoint of PCR was defined as complete disappearance of the tumor in the breast only. A significant increase in PCR was observed for those
women assigned to bevacizumab (34.5% vs 28.2%; \(P = .02\)). However, when the data were analyzed using the GeparQuinto definition of PCR in the primary and lymph nodes, no significant benefit for bevacizumab was observed. In a subset analysis, the addition of bevacizumab significantly improved the clinical complete response rate for patients with hormone receptor-positive disease (62.2% vs 50.7%; \(P = .003\)), but not hormone receptor-negative disease. The toxicities were comparable to those reported in GeparQuinto.

In addition, significantly more women experienced sensory neuropathy with bevacizumab. Left ventricular dysfunction was also significantly higher in women receiving bevacizumab (1.3% vs 0.2%).

Consistently higher response rates with bevacizumab added to chemotherapy are reported in all stages of breast cancer. However, clinically meaningful endpoints of improved OS in advanced disease and an increased use of breast-conserving therapy have not been seen. It does not appear that hor-

### Table 2. — Summary of Bevacizumab Trials in Patients With Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>E2100 Miller et al10,11</th>
<th>AVADO Miles et al12</th>
<th>RIBON-1 Robert et al13,14</th>
<th>GeparQuinto von Minckwitz et al14</th>
<th>NSABP Bear et al15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>First-line metastatic</td>
<td>First-line metastatic</td>
<td>First-line metastatic</td>
<td>Any stage deemed appropriate for neoadjuvant therapy by 1 stage of clinical lymph nodes +</td>
<td>Palpable tumor ≥ 2 cm; T1c-T3, N0-N2a, M0, and HER2–</td>
</tr>
<tr>
<td><strong>No. of Patients</strong></td>
<td>722</td>
<td>726</td>
<td>1,237</td>
<td>1,948</td>
<td>1,528</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized open-label phase III</td>
<td>Randomized double-blind phase III</td>
<td>Randomized, placebo-controlled phase III</td>
<td>Randomized open-label phase III</td>
<td>Randomized open-label phase III</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Paclitaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum</td>
<td>Cepetitabine or anthracycline ± bevacizum</td>
<td>Epirubicin + docetaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum, docetaxel/capecitabine ± bevacizum, docetaxel/gemcitabine ± bevacizum</td>
</tr>
<tr>
<td><strong>Response Rate</strong></td>
<td>Paclitaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum</td>
<td>Cepetitabine or anthracycline ± bevacizum</td>
<td>Epirubicin + docetaxel ± bevacizum</td>
</tr>
<tr>
<td><strong>Chemotherapy + Bevacizum vs Chemotherapy</strong></td>
<td>Paclitaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum</td>
<td>Cepetitabine or anthracycline ± bevacizum</td>
<td>Epirubicin + docetaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum, docetaxel/capecitabine ± bevacizum, docetaxel/gemcitabine ± bevacizum</td>
</tr>
<tr>
<td>Response Rate</td>
<td>Paclitaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum</td>
<td>Cepetitabine or anthracycline ± bevacizum</td>
<td>Epirubicin + docetaxel ± bevacizum</td>
<td>Docetaxel ± bevacizum, docetaxel/capecitabine ± bevacizum, docetaxel/gemcitabine ± bevacizum</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>11.8 mos vs 5.9 mos (P &lt; .001)</td>
<td>7.89 mos vs 8.71 mos (P = .0054)</td>
<td>7.89 mos vs 8.77 mos (P = .0003)</td>
<td>8.6 mos vs 5.7 mos (P &lt; .001)</td>
<td>9.2 mos vs 8.0 mos (P &lt; .001)</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>26.7 mos vs 25.2 mos (P = .16)</td>
<td>31.9 mos vs 30.8 mos (P = .482)</td>
<td>31.9 mos vs 30.2 mos (P = .983)</td>
<td>25.7 mos vs 22.8 mos (P = .33)</td>
<td>27.5 mos vs not reached</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>34% of patients not followed until independent review committee, PFS event or end of study; grades 1/2 not collected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>20.2% increase in grades 3–5 toxicity; 1.7% therapy-related deaths</td>
<td>More dose disruptions with bevacizumab; 0.8% toxic deaths; 3% gastrointestinal perforation</td>
<td>25% discontinued bevacizumab due to toxicity; 1.2% toxic deaths</td>
<td>Bevacizumab was associated with significant increased incidence of febrile neutropenia, grades 3/4 mucositis, hand-foot syndrome, infection, hypertension</td>
<td>Patients assigned bevacizumab had significantly more neutropenia, mucositis, hand-foot syndrome, and sensory neuropathy; left ventricular dysfunction in 9 patients, 8 receiving bevacizumab</td>
</tr>
</tbody>
</table>

PFS = progression-free survival, OS = overall survival, PCR = pathological complete response.
mone receptor status will be helpful in identifying a population of women who are likely to benefit from bevacizumab. Despite a clear signal of increased efficacy, we have yet to identify a population of women who clearly benefit from bevacizumab. A pathological marker to predict bevacizumab efficacy is needed.

**Renal Cell Cancer**

Two phase III studies evaluated the efficacy of bevacizumab in metastatic renal cell carcinoma. In the AVOREN study, 649 patients were randomized to receive either bevacizumab with interferon alpha (IFN-α) or placebo with IFN-α. The study satisfied its secondary endpoint, demonstrating an improvement in PFS with bevacizumab therapy (10.2 months vs 5.4 months; HR = .63; \( P = .0001 \)). A more recent update of OS in this study suggested a nonstatistically significant advantage with bevacizumab as well (23.3 months vs 21.3 months; HR = .86; \( P = .13 \)).

A second study, conducted by the Cancer and Leukemia Group B (CALGB 90206), employed a similar randomization and yielded a similar result. In this study, 732 patients were randomized to receive either bevacizumab with IFN-α or IFN-α alone. In this open-label study, bevacizumab was again associated with a significant benefit in PFS (8.4 months vs 4.9 months; \( P < .0001 \)) and a nonsignificant improvement in OS (18.3 months vs 17.4 months; \( P = .097 \)). Consistent with other trials, hypertension and proteinuria were more common with bevacizumab. Fatigue and anorexia were also more common. Of the 369 patients assigned to bevacizumab with IFN-α, 2 patients developed gastrointestinal perforation.

**Glioblastoma Multiforme**

Vascular proliferation and tumor necrosis have been hallmarks of glioblastoma multiforme, and VEGF is highly expressed in these tumors. A phase II trial of bevacizumab in combination with irinotecan conducted in 35 patients with recurrent glioblastoma multiforme resulted in a 6-month PFS rate of 46% and an OS rate of 77%.

To confirm these optimistic results, a randomized trial was performed in 167 patients comparing the combination of bevacizumab and irinotecan to bevacizumab alone. The study assumed that a 6-month PFS rate of 15% would be expected with single-agent irinotecan. The 6-month PFS rate with single-agent bevacizumab was 42.6% compared with 50.3% for the combination arm (\( P = NS \)). Objective tumor response was observed in 28.2% of patients treated with bevacizumab and 37.8% of those treated with combination therapy. Fatigue, headaches, and hypertension were the most commonly reported toxicities. Intracranial hemorrhage occurred in 5 patients (3%) — 2 who received bevacizumab alone and 3 who also received irinotecan. Two patients experienced wound dehiscence at the craniotomy site, and 2 patients developed gastrointestinal perforation.

Based on these data, bevacizumab was approved for use in the United States as a single agent in patients with recurrent glioblastoma multiforme. This is the only malignancy for which bevacizumab is recommended without the coadministration of another agent. Given the unmet need, bevacizumab is an important addition to the treatment of these patients.

**Ovarian Cancer**

The results from 2 randomized controlled trials of bevacizumab in ovarian cancer have been published recently, one by the Gynecologic Oncology Group (GOG)23 and the other by the European International Collaborative Ovarian Neoplasm study 7 (ICON7). As summarized in Table 3. Each trial enrolled over 1,500 women with newly diagnosed ovarian cancer to receive 6 cycles of paclitaxel and carboplatin (AUC 5–6) with or without bevacizumab. When bevacizumab was assigned, the drug was initiated on cycle 2 to minimize postoperative complications. The GOG trial was a three-arm study. In two of the study arms, bevacizumab was administered every 3 weeks with the chemotherapy during cycles 2–6 or for a longer duration with cycles 2–6 and continuing every 3 weeks up to 22 cycles. In the ICON7 trial,

Table 3 — Summary of Bevacizumab Trials in Patients With Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>GOG Burger et al23</th>
<th>ICON7 Perren et al24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>3-arm double-blind, placebo-controlled phase III</td>
<td>Open-labeled phase III</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Stage III (incompletely resected) and stage IV epithelial cancers, primary peritoneal, or fallopian tube cancers</td>
<td>High-risk stages I–IIA and clear-cell or grade 3, stages IIIB–IV epithelial cancers, primary peritoneal, or fallopian tube cancers</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>1,873</td>
<td>1,528</td>
</tr>
<tr>
<td>Paclitaxel + carboplatin (AUC 6) × 6 cycles 2–6</td>
<td>Paclitaxel + carboplatin (AUC 6) × 6 + bevacizumab cycles 2–6</td>
<td>Paclitaxel + carboplatin (AUC 5–6) × 6 + bevacizumab cycles 2–12</td>
</tr>
<tr>
<td>PFS</td>
<td>10.3 mos</td>
<td>11.2 mos</td>
</tr>
<tr>
<td>Hypertension Requiring Treatment</td>
<td>7.2%</td>
<td>16.5%</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>1.2%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
bevacizumab was administered with chemotherapy for cycles 2–6 and subsequently as a single agent for up to 12 cycles.

For both studies, PFS favored the addition of bevacizumab. In the GOG study, gastrointestinal perforation was reported in all three treatment arms, and the incidence was more than doubled in patients receiving bevacizumab. In an early phase II study of bevacizumab added to paclitaxel and carboplatin, 5 of 44 women with ovarian cancer developed bowel perforation. The GOG and ICON7 studies suggest that the increased incidence of gastrointestinal perforation is comparable to what has been reported with bevacizumab in other primary cancers. The pathophysiology for development of this complication remains unclear.

Bevacizumab may be safely administered in patients with ovarian cancer. A subset analysis of women with high-risk disease who were enrolled in the ICON7 study identified an OS advantage to bevacizumab. Results from this unplanned analysis are encouraging, and with additional follow-up, an improvement in median OS may be seen for all patients enrolled.

**Adjuvant Therapy Trial for Colorectal Cancer**

To date, the only published adjuvant trial was conducted by the NSABP in colorectal cancer. In NSABP C08, 2,672 patients with stages II and III colorectal cancer were randomized to receive FOLFOX6 for 26 weeks with or without 52 weeks of bevacizumab. With 3 years of median follow-up, no advantage in disease-free survival or OS has been observed. Cytotoxic agents with demonstrated activity in advanced disease have generally resulted in an improvement in OS when used in the adjuvant setting in patients with a high risk of disease recurrence who have undergone definitive treatment of the primary tumor. The lack of efficacy of bevacizumab in this adjuvant trial raises the possibility that micrometastatic disease has not yet established the aberrant vasculature targeted by bevacizumab. A number of adjuvant trials are ongoing in a variety of solid tumors, and we await these results with interest.

**Safety Data**

The most commonly recognized toxicities observed with bevacizumab, such as proteinuria, hemorrhage, and thrombosis, have been attributed to its vascular targeting activity. Hypertension requiring treatment develops in nearly one-quarter of patients treated with bevacizumab. Thromboembolic complications are frequently seen in patients with cancer for a variety of reasons, including advanced age, the hypercoagulable state associated with cancer and inflammation, and indwelling devices that affect the vessel wall and predispose to clot formation. An increase in arterial thromboembolic complications such as myocardial and cerebrovascular events has been observed with bevacizumab. However, venous thromboembolic complications are not increased. In a review of 10 randomized trials of bevacizumab in over 6,000 patients with different primary tumor types, venous thromboembolic events were not increased. It is postulated that the increase in hemorrhage observed with bevacizumab is due to the inability of endothelial cells to renew. Although the highest rates of bleeding were reported in NSCLC, hemorrhage is a consistent toxicity observed with every primary cancer site.

Cardiac complications associated with bevacizumab have been described in patients with colorectal and breast cancers. In a literature review of 3,784 women enrolled in randomized controlled trials, congestive heart failure was reported in 1.6% of bevacizumab-treated patients compared with 0.4% of control patients. This represents a 4.74 relative risk for developing left ventricular dysfunction with bevacizumab compared with chemotherapy alone. In the NSABP B40 neoadjuvant trial, an increased risk of left ventricular dysfunction was reported.

In an adjuvant colorectal trial of FOLFOX6 with and without bevacizumab, ovarian failure was identified in 32 of 95 women (34%) in the bevacizumab arm compared with 2 of 83 women (2%) in the chemotherapy-alone arm. With cessation of therapy, 22% have had recovery of ovarian function, suggesting a causal relationship. This is the only trial to report this side effect, which may be attributed to the fact that these women had potentially curable disease, whereas the majority of the clinical trials were conducted in patients with metastatic disease. This same trial also identified osteonecrosis of the jaw (ONJ) as a side effect. Because ONJ has also been reported with sunitinib use, it raises the possibility that antiangiogenic agents alter the normal blood vessels in the jaw and may contribute to the development of ONJ.

Ranpura et al reviewed data from 16 randomized clinical trials of bevacizumab that enrolled 10,217 patients and identified a 2.5% risk of fatal adverse events. Hemorrhage was the most common cause of fatality in 23.5% of cases, followed by febrile neutropenia in 12.2%, and gastrointestinal tract perforation in 7.1%.

**Discussion**

The development of targeted agents for use in oncology is challenging. Agents such as bevacizumab and trastuzumab have no significant single-agent activity and are always administered concurrently with cytotoxic agents, making it impossible to determine which patients are benefiting from the addition of the targeted agent. Trastuzumab was approved for management of advanced HER2-positive breast cancer on the basis of an improvement in OS in women with immunohistochemical (IHC) 2+/3+ disease. The definition of HER2 positivity was subsequently defined as IHC 3+ or gene amplification by fluorescent in situ hybridization (FISH). Although HER2 status is useful in identifying a population of patients who are likely to benefit from
trastuzumab, it does not indicate who may benefit. In the case of bevacizumab, a clear clinical target that can be assayed and used to identify which patients may be likely to benefit from therapy has yet to be identified.

Following the approval of trastuzumab, an FDA panel convened to make recommendations on requirements for approval of new agents in advanced breast cancer. Its recommendation was that an improvement in OS be required for the approval of first-line therapy in advanced breast cancer. Although many of the bevacizumab trials in breast cancer reported improvements in response rates or PFS in metastatic disease, none demonstrated an OS advantage. In other disease sites, PFS may be considered adequate for approval of a new agent, although its value as a primary endpoint is being challenged.36

A number of important lessons have been learned from the clinical trials leading to the approval of bevacizumab in some diseases but not others. Well-conducted phase II studies often, but not always, provide important information to guide the design of phase III studies. By identifying fatal hemoptysis in patients with squamous cell cancers, tumor necrosis and caviation, and lesions located near major blood vessels, such patients were excluded from study participation, and toxicity from bevacizumab was minimized.5,8,37

In contrast, toxicity data from a phase II trial of bevacizumab in ovarian cancer may have been misleading, as a high incidence of gastrointestinal perforation was observed.25 The unique pattern of metastasis throughout the peritoneum raised concerns in the oncology community that perforation was related to regression of tumor involving the bowel wall. In fact, the incidence of gastrointestinal perforation in 12,294 patients enrolled in 17 randomized controlled trials was 0.9% and is associated with a mortality rate of 21.7%.25 With additional experience using bevacizumab, it is clear that gastrointestinal perforation is a toxicity observed with this drug, regardless of the primary tumor site or location of metastatic disease.

The initial clinical experience with bevacizumab raised concerns about administering the drug in the immediate postoperative setting due to initial reports that patients experienced more postoperative bleeding and compromised wound healing. To determine the risk of central nervous system bleeding, Besse et al38 reviewed 13 randomized controlled trials that enrolled 8,443 patients. Occult brain metastases were identified in 187 participants, 91 of whom were assigned to receive bevacizumab. Three of the bevacizumab-treated patients developed grade 4 cerebral hemorrhage (3.3%) compared with 1 of 96 patients (1%) in the control arm. Consideration should be given to include select patients with tumor involving the brain.

Conclusions
Side effects of treatment may provide important information about drug mechanism and efficacy. While bleeding is a recognized complication of bevacizumab therapy, the most dramatic bleeding reported was in patients with non–small cell lung cancer of squamous cell histology, cerevical lesions, and tumors located near large blood vessels. The specificity of this toxicity may eventually help to inform us about biologic mechanisms. When administering noncurative therapy, it is critical to balance the potential risks with the benefits. In the case of breast cancer, the risk-benefit ratio is too great to recommend bevacizumab as a standard of care, despite a strong signal of activity. Bevacizumab is clearly an important agent in oncology and is likely to become more significant once a clinical or pathological marker to predict its efficacy has been identified.

References


