Bevacizumab Treatment for Solid Tumors
Boon or Bust?

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IN 1971, FOLKMANN PROPOSED THAT MALIGNANCIES COULD only grow to a significant size, or metastasize to other organs, by stimulating new blood vessel growth. This process, designated angiogenesis or neovascularization, is now accepted as necessary for cancers to extend beyond the in situ state and metastasize to distant sites. Tumor-induced angiogenesis requires a complex interplay between the cancer cell and surrounding stroma at the primary cancer site and at the metastasis site, including recruitment of bone marrow–derived, circulating endothelial cell precursors.

Folkman’s proposed mechanism led to development of therapeutic agents that target tumor vasculature, including antibodies against endothelial cell growth factor receptors and inhibitors of tyrosine kinases that are presumed to contribute to neovascularization. Arguably the most successful strategy to target cancer-associated neovascularization consists of a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) A. This antibody, bevacizumab, was shown in early phase 1 studies to induce occasional responses as a single agent and to enhance chemotherapy-induced tumor shrinkage.

The subsequent clinical development of bevacizumab has included successes and disappointing failures. Following promising phase 2 trials, a randomized controlled trial (RCT) of capcitabine with or without bevacizumab demonstrated a doubling of response rates in participants receiving bevacizumab but no difference in progression-free or overall survival among women with metastatic breast cancer whose disease had previously progressed during standard anthracycline- and taxane-based therapies. Favorable results for patients with colorectal cancer, non–small cell lung cancer (NSCLC), and renal cell cancer suggested that bevacizumab had a role in treatment of patients with these malignancies, whereas negative RCT results for patients with pancreatic and prostate cancers tempered enthusiasm. Perhaps the most promising findings for bevacizumab were observed by investigators from the Eastern Cooperative Oncology Group (ECOG), who reported that, when administered with paclitaxel as first-line chemotherapy for patients with measurable metastatic breast cancer, the antibody not only increased response rates but appeared to double the time to progression.

Curiously, few of these studies demonstrated a survival benefit from the addition of bevacizumab to chemotherapy. Explanations for this observation included early follow-up, insufficient statistical power, and the confounding effects of subsequent postprogression treatments. Nonetheless, the US Food and Drug Administration (FDA) approved bevacizumab for treatment of colorectal cancer, NSCLC, and renal cell cancer. The FDA approval for breast cancer was controversial, including an initial rejection based on concern that the ECOG study was not placebo-controlled. After an objective, third-party review of the radiographs used for this determination provided similarly favorable findings, the FDA provided accelerated approval of bevacizumab for metastatic breast cancer, overriding the recommendation against approval made by the Oncology Drug Advisory Committee (ODAC). The ODAC expressed particular concern about the lack of overall survival benefit and the rare but occasional life-threatening toxic effects reported with bevacizumab. Recently, the FDA has rescinded its approval of bevacizumab for metastatic breast cancer, based on the results of 2 other RCTs that were less favorable and suggested uncommon but occasional lethal adverse events.

The findings for metastatic disease stimulated the conduct of several RCTs of bevacizumab in the adjuvant setting. Again, results have been mixed. Results were favorable for progression-free survival, but not overall survival, for gynecologic cancers. However, results were negative for all end points in colorectal cancers. These inconsistent results raise important questions: Does bevacizumab have cancer-specific benefits? Is it more effective when combined with a chemotherapeutic partner, and if so, is this benefit specific for different agents? Why, despite the impressively solid preclinical data and the promising early clinical results, has bevacizumab not been more successful in improving overall survival?
The answers to these questions, especially the last, are not easily discerned. Many investigators have questioned whether progression-free or disease-free survival (as opposed to overall survival) is the best end point for large-scale cancer therapeutic trials. The biology of anti-VEGF therapy may make the choice of end points a critical issue. Angiogenesis, like most endocrine processes, is complex and includes positive and negative feedback loops. It is possible that suppressing VEGF signaling may enhance VEGF expression, either systemically or locally, resulting in a rebound effect of enhanced neovascularization and tumor growth when suppression is discontinued.

Casual, but not statistically rigorous, review of the Kaplan-Meier curves from many bevacizumab clinical trials suggest that such an effect may occur. In the ECOG metastatic breast and National Surgical Adjuvant Breast and Bowel Project adjuvant colorectal trials, visual inspection of the survival curves suggests an early difference in progression-free or disease-free survival that is attenuated after the drug is discontinued. The hypothesis that longer therapy might be more advantageous is supported by recent results from the Gynecologic Oncology Group adjuvant ovarian cancer trial. These results suggest that longer treatment is better and that early benefits in progression-free or disease-free survival may be lost when the drug is stopped.

If longer bevacizumab therapy is better than shorter, at what cost? Bevacizumab is not associated with the degree of adverse effects encountered with most anticancer therapies. However, as reported in the meta-analysis by Ranpura et al in this issue of JAMA, bevacizumab therapy is associated with a higher rate of fatal adverse events (FAEs) than expected with chemotherapy alone. Ranpura et al report that approximately 2.5% of bevacizumab-treated patients experienced FAEs and that the rate of FAEs was 1.5 times more frequent among patients receiving chemotherapy plus bevacizumab compared with those receiving chemotherapy alone. The most common FAEs were hemorrhage (23.5%), neutropenia with lethal infection (12.2%), gastrointestinal tract perforation (7.1%), pulmonary embolism (5.1%), and cerebrovascular accident (5.1%). Their analysis also suggests that FAEs may occur more commonly when bevacizumab is used to treat specific tumor types (prostate and lung vs renal cell and breast) or when bevacizumab is used in conjunction with specific chemotherapy partners (taxanes and platinum compounds). A higher rate of FAEs was not more common with higher bevacizumab doses.

These observations raise a conundrum. Optimal treatment with bevacizumab may require years of frequent (every 2 to 3 weeks) intravenous therapy, perhaps combined with toxic chemotherapy. Although oral adjuvant endocrine therapy for 5 or more years and intravenous adjuvant trastuzumab for 1 year have been feasible in breast cancer, frequent intravenous administration of bevacizumab and chemotherapy is logistically challenging and potentially associated with substantial toxic effects. The increased FAE rate with prolonged bevacizumab administration might negate any survival benefit.

Moreover, bevacizumab comes with an enormous price tag. The drug alone costs more than $50,000 per year. Intravenous administration, coadministration with a chemotherapy partner, and routine monitoring may easily exceed $100,000 per patient per year. Food and Drug Administration review is independent of economic considerations. However, individual clinical decisions are not. Should bevacizumab be removed from the treatment options available for patients with breast or other cancers? Available data suggest that bevacizumab is biologically active in most but not all solid tumors. However, the benefits of extended adjuvant bevacizumab in unselected populations may not be justified by the modest disease-free survival and questionable overall survival benefits reported thus far.

Careful review of response rates to bevacizumab suggest that bevacizumab works well, but only in selected patients. This phenomenon may be similar to that observed with endocrine therapy, which is only effective in women with estrogen receptor–positive breast cancer. Even though more than 10,000 patients have been enrolled in RCTs of bevacizumab, few insights are available about specific subgroups of patients who may benefit. Perhaps the most promising observations were reported by Schneider et al, who found that inherited, germline single-nucleotide polymorphisms in genes encoding for components of the VEGF pathway are associated with either benefit (progression-free and overall survival) or toxic effects (hypertension) from bevacizumab in women with metastatic breast cancer. These preliminary results suggest that it may be possible to focus bevacizumab treatment in patients most likely to benefit and avoid treatment of patients unlikely to benefit or more likely to experience toxic effects. However, because tissue or germline DNA was rarely collected in most manufacturer-sponsored trials, these results will be difficult to validate. Even more concerning is that the manufacturer has insisted on reviewing and approving any correlative studies performed using specimens that were collected within trials sponsored by the National Cancer Institute but with whom the sponsor has a Cooperative Research and Development Agreement.

Is bevacizumab a boon or a bust? The jury is still out. Although bevacizumab has benefit, it is currently not possible to determine in whom or for how long. Thus, oncologists are forced to dilute the potential effects of bevacizumab by exposing all treated patients, and society, to enormous costs and occasional life-threatening toxic effects. These unfortunate circumstances are sad for those who pay the bills—and sadder for patients with solid tumors.
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REFERENCES