Success of Bevacizumab Trials Raises Questions for Future Studies

The fortunes of antiangiogenesis therapies have swung between promises of glory and dashed hopes. Now, with several large-scale clinical trials finding that combination regimens that include the drug bevacizumab (Avastin) improve progression-free survival and overall survival in certain cancers, reality seems to have settled somewhere in the middle. It is clear that bevacizumab, the only angiogenesis inhibitor with U.S. Food and Drug Administration approval, seems to be effective in multiple cancers, but just when and how clinicians should use it for optimal results are still up for discussion.

The popularity of and interest in angiogenesis inhibitors soared in 1998 when the New York Times published a front-page story reporting that Judah Folkman, M.D., a professor at Harvard Medical School, and Michael O’Reilly, M.D., now of the University of Texas M. D. Anderson Cancer Center in Houston, and colleagues used the drugs endostatin and angiostatin to successfully treat metastatic disease in mice after resection of the primary tumor. Unfortunately, phase I studies of endostatin published in September 2002 showed that the drug was safe but had only minimal efficacy in humans.

So why has bevacizumab been successful? The difference between results from early trials with angiogenesis inhibitors, such as endostatin, and newer drugs that are now showing promise in phase I and II studies is because of differences in both the drug and the regimens tested, said Robert A. Burger, M.D., an associate professor of gynecology and oncology at the University of California Irvine Medical Center.

Burger has received speaker honoraria from Genentech. “My general impression has been that in many cases relatively impotent drugs were being used in the early trials,” he said. The drugs had a short half-life, weren’t readily bioavailable, or didn’t target vascular endothelial growth factor (VEGF), the major growth factor in the angiogenesis pathway. Bevacizumab is a recombinant humanized monoclonal antibody against VEGF with a half-life of 17–21 days, which gives the drug distinct advantages over its predecessors. It was approved by the FDA last year for use in combination with chemotherapy in the treatment of metastatic colorectal cancer.

One of the several bevacizumab trials presented at this year’s annual meeting of the American Society of Clinical Oncology was a phase II Gynecologic Oncology Group (GOG) trial that tested single-agent bevacizumab in ovarian cancer. The drug was given every 3 weeks in women with recurrent or persistent ovarian cancer, all of whom had measurable disease and at least one prior platinum therapy. Three women (4.8%) of 62 had complete responses and eight (12.9%) had partial responses by RECIST criteria. The median response duration was about 10 months, and 24 patients (38.7%) were progression free at 6 months.

Combination Therapy

But such results with single-agent bevacizumab do not appear to be the norm, a fact that led some researchers to think that the GOG would be better off using combination therapy. “I think we should learn from [experience with] other tumors,” said Peter G. Harper, M.D., of Guys Hospital in London, who discussed the GOG trial at the ASCO meeting. He pointed out that patients on single-agent bevacizumab therapy in studies of breast cancer, prostate cancer, and a variety of phase I dose-finding studies did not have substantial response rates.

In addition, treating patients earlier in their course of disease rather than later may be critical for bevacizumab’s efficacy, as seen in two large phase III trials in breast cancer. In the first trial published earlier this year, researchers enrolled heavily pretreated patients with metastatic disease and compared bevacizumab plus standard chemotherapy with chemotherapy alone. Although response rates increased substantially in the bevacizumab arm, the responses did not translate into prolonged progression-free survival or overall survival.

By comparison, a second trial in women with previously untreated metastatic breast cancer showed that the addition of bevacizumab to standard chemotherapy did increase progression-free survival and overall survival. Kathy D. Miller, M.D., an assistant professor at Indiana University Cancer Center, presented results of the first planned interim analysis of the trial at this year’s ASCO meeting. With 715 patients included in the analysis, the median progression-free survival was 11 months in the bevacizumab arm compared with 6 months in the chemotherapy-alone arm. The women treated with bevacizumab plus chemotherapy also had a 23% reduction in risk of death, relative to those in the control arm.

Folkman isn’t surprised by these data. About 60% of early breast cancers produce VEGF but not other angiogenesis factors, he said. As the disease progresses, tumors produce more types of angiogenesis growth factors, including fibroblast growth factor (FGF). “Tumors may express as many as six different
growth factors that stimulate angiogenesis, but the drug only targets VEGF, so it doesn’t inhibit the other growth factors,” said Folkman. That suggests that multiple antiangiogenesis drugs in combination may be required to treat advanced disease.

Such combination studies are already in the works. A phase II trial testing erlotinib (Tarceva) and bevacizumab in 40 patients with refractory non–squamous-cell, non–small-cell lung cancer showed objective responses in 20% of patients. Roy Herbst, M.D., Ph.D., chief of thoracic oncology at the University of Texas M. D. Anderson Cancer Center in Houston, who presented these results, said that the design of a phase III comparator trial was already under discussion. (Herbst receives laboratory support from Genentech, makers of Avastin.)

The logic behind the combination is twofold. Erlotinib should block activation of the epidermal growth factor receptor (EGFR) and thereby slow tumor growth. In addition, the drugs may work together to repress angiogenesis, with bevacizumab working on VEGF and erlotinib blocking EGFR, which would down-regulate the amount of VEGF, FGF, and transforming growth factor α (TGF-α) produced by the tumor.

Napoleone Ferrara, M.D., of Genentech, said that many combinations of biologics were being explored in the clinic, including bevacizumab with cetuximab, sorafenib, bortezomib, imatinib mesylate, trastuzumab, and rituximab.

Toxicity

One of the driving forces behind such combinations is the relative lack of toxicity the biologic drugs have compared with traditional cytotoxic agents. However, the phase II and III trials presented at ASCO demonstrated that bevacizumab does have toxic effects. For example, in the trial that tested the drug in previously untreated metastatic breast cancer patients, 13% of the women in the bevacizumab arm developed hypertension that required treatment, while none of the women in the control arm did. Similarly, bleeding, proteinuria, or a drop in left-ventricular ejection fraction occurred in up to 2% of patients treated with bevacizumab. The side effects were seen in the trial population despite the researchers’ efforts to exclude patients at substantial risk for such problems, suggesting that clinicians will encounter such problems when using the drug in practice.

But just how bevacizumab works isn’t entirely clear yet, which may make predicting the effect of drug combinations more complicated. Lee Ellis, M.D., a professor of surgical oncology at M. D. Anderson Cancer Center, presented evidence at the ASCO meeting indicating that bevacizumab may not work just by blocking vascularization but may also kill tumor cells directly by blocking activation of a VEGF receptor family member called neuropilin. Neuropilin promotes survival and migration and is found on the surface of colorectal cancer cells but not on healthy neighbors or the endothelial cells that make up the vasculature. Addition of bevacizumab to tumor cells in culture induces cell death, indicating there is a direct tumor cell response to the antibody. That response, whether it is via neuropilin or some other currently unrecognized mechanism, may account for the increased response rate detected in the bevacizumab-plus-chemotherapy arms of clinical trials, compared with chemotherapy alone, said Ellis, who is an ad hoc consultant to Genentech.

Dosing

It is also not clear what the optimal dose of the drug is. “In most of the trials, the higher the dose, the better the response,” said Ellis. However, in at least one trial in colorectal cancer, the group treated with the lower dose of bevacizumab did better than the group treated at a higher dose. Those results are complicated by the fact that the lower-dose group had more women, who tend to outperform male counterparts on these trials, and more patients with higher performance status at baseline. In the case of colorectal cancer, a dose of 5 mg/kg of body weight every 2 weeks has been used.

“I think it is going to be incredibly difficult to sort out the difference between 5 and 10 mg in terms of efficacy in colorectal cancer because the number of patients needed to answer that question would be astronomical,” Ellis said. These data and the fact that the maximum effect on the vasculature is related to the maximum tolerated dose in preclinical trials leads him to say that dosing needs to be determined by evidence of target suppression at both the peak and trough of drug concentrations in the blood.

Another issue that both Folkman and Burger raised in discussions of bevacizumab is how success should be measured. In the GOG trial Burger led, the team used standard RECIST criteria for tumor shrinkage and they saw a 17.7% overall response rate. They also saw 54% stable disease, which is not traditionally considered a response, and yet some of these patients had substantial improvements in quality of life. Antiangiogenic drugs, like several other biologics, are not likely to induce rapid tumor shrinkage, making interpretation of measurements by the RECIST criteria difficult.

“We have to look for more subtle clues of activity with single-agent antiangiogenic therapy in phase II trials in order to find active agents, rather than expect the sort of result we had in [the GOG trial],” said Burger. “We need to also realize there is a definite interaction between these antiangiogenic agents and the cytotoxic agents that are effective to treat those malignancies, so it may be more important to study the combined effects of cytotoxics and biologics even if single-agent activity for the antiangiogenic drug seemed to be minimal in those disease sites.” —Rabiya S. Tuma