Antiangiogenesis Research Is Booming, As Questions and Studies Proliferate

By Vicki Brower

In a recent analysis of a large observational study, bevacizumab (Avastin), an inhibitor of angiogenesis, was associated with favorable survival rates in patients whose colorectal cancer had already progressed. Those taking bevacizumab with chemotherapy had a median overall survival of 32 months, compared with 20 months for those who did not receive bevacizumab beyond first-line therapy. The difference was statistically significant.

The analysis, published in November, was based on data from a patient registry known as BRiTE, which is designed primarily to gather information on adverse events and secondarily on progression-free and overall survival. Nevertheless, the positive results buoyed researchers.

“We did not expect patients to receive such a magnitude of benefit,” said lead investigator Axel Grothey, M.D., a professor at the Mayo Clinic in Rochester, Minn. The researchers concluded that bevacizumab beyond initial disease progression might benefit patients who have metastatic colorectal cancer.

But compare the BRiTE results to those of a prospective controlled trial—considered a stronger study design—in patients with metastatic colorectal cancer, also published last year. In this multicenter, phase III trial, patients were randomized to either first-line treatment with bevacizumab and chemotherapy until disease progression or chemotherapy alone. Patients taking the combination had a disappointing median overall survival of 21.3 months compared with those taking only chemotherapy, who lived a median 19.9 months. The difference was not statistically significant.

The lead investigator in this trial, Leonard Saltz, M.D., at Memorial Sloan–Kettering Cancer Center in New York, is less optimistic than Grothey that the agents will live up to expectations. “Antiangiogenesis is an elegant concept, and bevacizumab, like other angiogenesis inhibitors [AIs], is a real but modest step, but it isn’t a breakthrough drug and it isn’t a home run,” he said.

The conflicting results—and attitudes—point to some of the current questions surrounding AIs 5 years after the first one, bevacizumab, was approved by the U.S. Food and Drug Administration.

And with many questions unanswered, AI research is booming. There are currently about 800 trials under way, according to David Waxman, Ph.D., professor of medicine at Boston University School of Medicine, writing in the December 2008 Molecular Cancer Therapeutics. Trials are testing the drugs alone and in combination with each other and with chemotherapy agents, as third, second, and more recently first-line therapy.

Since 2004, the FDA has approved other AIs, including sunitinib (Sutent) for renal cancer and gastrointestinal stromal tumor and sorafenib (Nexavar) for liver cancer. In March, a phase III trial of sunitinib was stopped early after the drug demonstrated substantially better progression-free survival than placebo in patients with pancreatic neuroendocrine tumors. Other AIs in development include axitinib and vandetanib.

Despite such activity, or perhaps because of it, scientists do not agree about the potential of AIs to control cancer, or how to best use them, or even how best to gauge their efficacy.

Treatment After Progression?

One of the immediate questions surrounding bevacizumab, for instance, is whether it should be given after cancers have progressed, as suggested by the results of the BRiTE analysis.

The community-based BRiTE registry contains data on 1,953 colorectal cancer patients treated with bevacizumab. It is not a randomized trial, but it does gather data on patients in the real world, who may be sicker, older, and have more comorbidities than those in a pivotal trial, according to the Mayo Clinic’s Grothey, who also serves as vice chair of the North Central Cancer Treatment Group and as an adviser to Genentech, the maker of bevacizumab.

“This [finding] is interesting but also leaves a lot of unanswered questions, such as how long these drugs should be continued with and beyond chemotherapy,” said Joan Schiller, M.D., deputy director of the Simmons Cancer Center at the University of Texas Southwestern Medical Center in Dallas. “If a patient’s disease progresses, if he’s not on bevacizumab, do you put him on that or on another angiogenesis inhibitor?”

In an editorial accompanying the BRiTE study, Lee Ellis, M.D., of the University of Texas M. D. Anderson Cancer Center in Houston, and Daniel Haller, M.D., of the University of Pennsylvania, Philadelphia, discuss mechanisms that might account for the apparent benefit of using bevacizumab beyond progression. They suggest that changing the chemotherapy and adding bevacizumab might sensitize the endothelial cells of tumor blood vessels, making them more vulnerable to chemotherapy. They also speculate that had Grothey analyzed tumors, he might have determined whether using bevacizumab past progression was effective in certain patients with a particular genetic mutation.

A related question is how best to combine AIs with chemotherapy. Most experts
agree that the drugs have only a moderate effect on cancer when given by themselves or even in combination with other AIs.

The idea of combining AIs with low-dose and continuous, or metronomic, chemotherapy intrigues some researchers. Francisco Bertolini, M.D., Ph.D., of the European Institute of Oncology’s hematology–oncology laboratory in Milan, Italy, has conducted several phase II, single-arm trials with metronomic chemotherapy and bevacizumab in patients with advanced breast cancer. “In these trials, over 70% of patients showed disease stabilization for over 6 months, with few side effects, including no negative effects on their bone marrow,” Bertolini said.

Measuring AI Effects

Another major issue is how best to gauge the efficacy of bevacizumab and other AIs. This is a particular challenge, because inhibiting angiogenesis is a slow process, and the antiangiogenic therapies do not produce immediate tumor shrinkage, even if the treatment is effective. “Some of my patients show tumor shrinkage only after 3–4 months,” said Giannoula Klement, M.D., attending pediatric oncologist at Boston’s Children’s Hospital. “It’s sort of like dying by a gunshot, immediately, versus by starvation, which can take weeks to months.”

Finding biomarkers that can determine whether an AI agent is working has become an important quest. Measuring blood levels of angiogenesis proteins, such as vascular endothelial growth factor, has not led to reliable indicators. “One issue in testing these drugs is that we lack good biomarkers...We may never find them, or we may be looking in the wrong place,” Grothey said.

How They Work

Researchers also continue to investigate exactly how these drugs work. Early investigators, led by Folkman, thought that targeting tumor blood vessels would kill tumors by strangling their blood supply. But Folkman’s Harvard University Medical School colleague, Rakesh Jain, Ph.D., has demonstrated that AIs appear to first normalize leaky blood vessels, enabling chemotherapy to reach and kill tumors.

Other research shows that chronic angiogenic inhibition eventually reduces tumor uptake of chemotherapy, suggesting a need to optimize the window of AI treatment. The use of endothelial receptor antagonists to dilate tumor vessels before chemotherapy is one possible approach, Waxman said.

However, Jain noted that AIs also work as originally thought, eventually cutting off the blood vessels feeding the tumor. Overall, “angiogenesis-induced tumor cell starvation does increase antitumor activity despite a decrease in cytotoxic drug exposure,” he said.

Rebound Effect

Another issue is that stopping antiangiogenic therapy, either periodically or permanently, can result in accelerated tumor growth, according to Donald McDonald, M.D., Ph.D., of the University of California at San Francisco. McDonald’s work on this “rebound effect” indicates that pericytes—relatively undifferentiated cells that support small blood vessels—provide a scaffold for rapid revascularization of tumors after stopping AIs. As such, they are a potential therapeutic target, McDonald said.

A French group, led by François Goldwasser, Ph.D., has also observed the rebound effect, finding that tumor growth in patients with metastatic colon cancer was faster, after interrupting bevacizumab and chemotherapy for a few months, than the growth rate before bevacizumab was given. But McDonald’s group has demonstrated that when treatment is resumed after a break, vessels regress as much as the first time.

Some physicians, disillusioned with antiangiogenic drug results to date, maintain that they have not lived up to their expectations and hype. “Cytostatic means they don’t work well enough [to kill cancer cells]. Arresting tumor growth is not enough,” said Saltz. Wanting bevacizumab to validate this approach doesn’t make it so, he added.

However, proponents of AIs are optimistic that they will be able to improve on mostly modest gains by trying new drug combinations, developing reliable biomarkers, determining which drugs work best for certain cancers, and changing the duration of treatment and rest periods.

Klement takes a long view of the field. “No single agent or even combination will work with every tumor, especially in late-stage cancer, just as no one antibiotic will work for a critically ill patient in the ICU,” she said. In her judgment, new combinations of chemotherapies and AIs, and maintenance therapy with AIs, will be needed to make substantial progress.