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 registry known as BRiTE, which is designed primarily to gather information on adverse events and secondary 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, che-
motherapy intrigues some researchers.
Francisco Bertolini, M.D., Ph.D., of the
European Institute of Oncology’s hematol-
ogy–oncology laboratory in Milan, Italy, has
conducted several phase II, single-arm trials
with metronomic chemotherapy and bevaci-
zumab 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 inhib-
itng 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 starva-
tion, 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 biomark-
ers...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 investi-
gators, led by Folkman, thought that target-
ing 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 nor-
malize leaky blood vessels, enabling che-
motherapy to reach and kill tumors.

Other research shows that chronic angio-
genic 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,
“antiangiogenesis-induced tumor cell starva-
tion does increase antitumor activity despite a
decrease in cytotoxic drug exposure,” he said.

Rebound Effect
Another issue is that stopping antiangio-
genic therapy, either periodically or per-
manently, 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 revasculariza-
tion 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 anti-
angiogenic drug results to date, maintain
that they have not lived up to their expecta-
tions 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 opti-
mistic that they will be able to improve on
mostly modest gains by trying new drug
combinations, developing reliable biomark-
kers, 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 combina-
tions of chemotherapies and AIs, and main-
tenance therapy with AIs, will be needed to
make substantial progress.

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