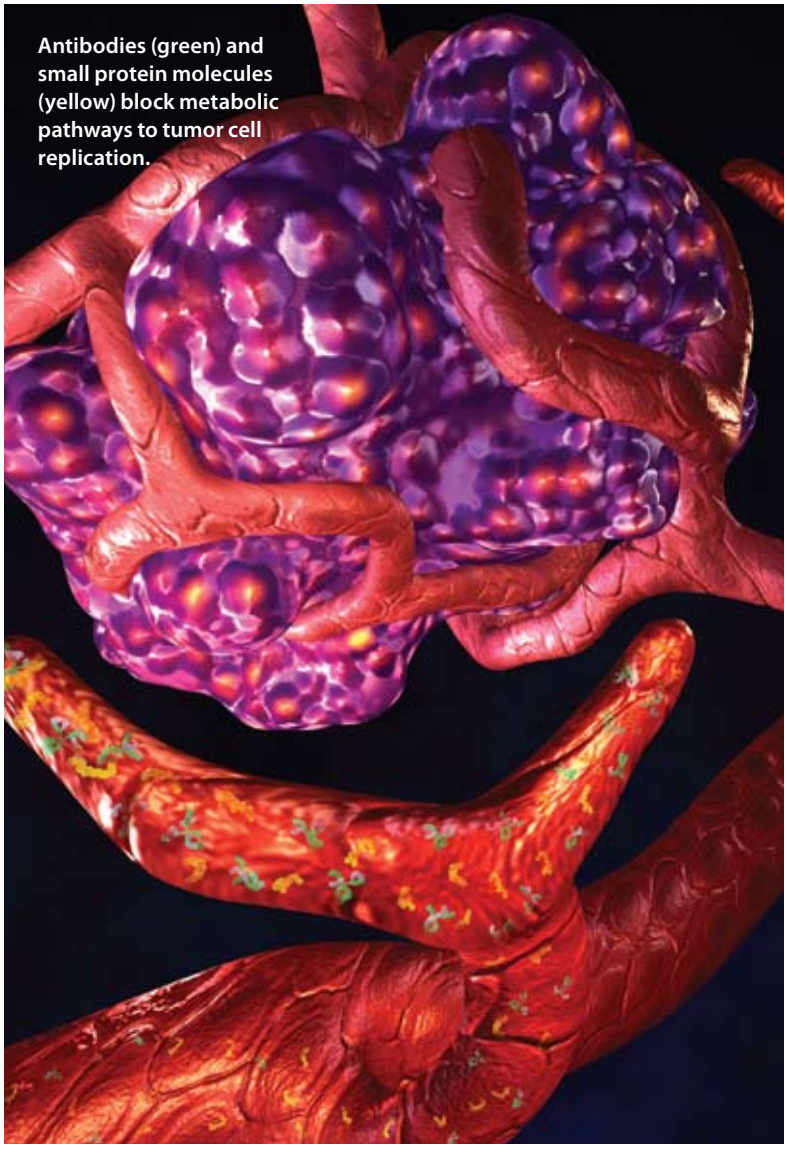
VEGF blockade: Optimizing chemotherapy drug uptake

New research is showing that sequence and timing have significant impact on the efficacy of therapeutic regimens that include bevacizumab.



Antibodies (green) and small protein molecules (yellow) block metabolic pathways to tumor cell replication.

BRYANT FURLOW

A growing arsenal of humanized monoclonal antibodies is providing targeted therapies that can disrupt specific molecular steps in carcinogenesis and the growth and spread of tumors—a critical step toward personalized clinical oncology. But the mechanisms of action of these agents are far more dauntingly complex, controversial, and less well-understood than those of systemic cytotoxic therapies, and researchers are still debating monoclonal antibodies' biomolecular effects and clinical outcomes—and even how best to measure these effects.[1,2]

Among the best-known monoclonal antibodies is bevacizumab (Avastin), which blocks receptor binding by vascular endothelial growth factor A (VEGF-A, or simply VEGF) and in this way disrupts tumor angiogenesis (the growth of new blood vessels). VEGF is over-expressed in many cancers, making it an attractive target for drug development over the past decade.[2] Despite its early promise, anti-VEGF monotherapies have demonstrated relatively limited evidence of overall survival benefits for patients, prompting studies of its use in combination with standard anticancer chemotherapies.[3]

But now, a new study appears to challenge longstanding beliefs about how bevacizumab VEGF blockade affects tumor perfusion with cytotoxic chemotherapeutic agents.[2] This and other new research suggests that both the timing of VEGF blockade and pairing anti-VEGF agents with c-Met-blocking monoclonal antibody

therapies, demand further study as potentially crucial factors in optimizing VEGF blockade for cancer control.[1]

VEGF BLOCKADE: PROMISE AND CHALLENGES

The Food and Drug Administration (FDA) approved bevacizumab for use in combination with standard chemotherapy for metastatic colon cancer, for recurring glioblastoma multiforme brain cancer, and as a first-line therapy for advanced nonsquamous non-small-cell lung (NSCLC) and renal cell cancer.[4,5] The FDA also provisionally approved bevacizumab for treatment of HER2-negative metastatic breast cancer, despite an FDA advisory panel's recommendation against approval.[1]

The provisional approval for bevacizumab's breast cancer indication was revoked in November 2011, citing insufficient evidence of efficacy and concern about adverse effects.[6] Approvals for bevacizumab indications for colon, kidney, glioblastoma, and non-small-cell lung cancers were not affected.[6] Subsequently published clinical trials have reported modest breast tumor pathological complete response to bevacizumab, with the variation possibly representing differences in study design and participant eligibility criteria.[1] For example, one of these studies defined pathological complete response as the absence of residual tumor in both breast tissue and lymph nodes, yielding a 3.5% response rate; the other analyzed only tumor response within breast tissue, yielding a 6.3% response rate. When node tumor response was applied to data from the second study, the response rate fell to statistical nonsignificance.[1]

Compared to blood vessels in healthy tissues, tumors' vessels are profoundly disorganized and irregular.[5] Tumor vessels are highly variable in size and cell wall structure, and tend to be tortuous, resulting in inefficient tumor perfusion with oxygen—and frequently impairing tumor uptake of anticancer drugs.[5] Vascular inefficiency and tumor cell hypoxia can trigger increased angiogenesis and the development of more aggressive cancer clones.[5]

VEGF blockade therapy's central promise in combination with chemotherapy is that it inhibits angiogenesis and blood vessel branching, and triggers vascular pruning. This normalization of tumor vasculature is temporary but should improve drug perfusion by tumor tissues, Harvard Professor of Tumor Biology Rakesh K. Jain, PhD, and others have reasoned.[7,8]

IS TIMING EVERYTHING?

Despite early findings over recent years that seem to support the normalization model, before this year, no clinical studies had described the effects of VEGF blockade on chemotherapy drug uptake by tumors in humans.[2] Now, the first such study, by researchers in the Netherlands, appears to challenge the widely accepted normalization model. Contrary to expectation, the new study found that VEGF blockade can impair rather than improve the delivery of chemotherapy drugs to tumors.[2] The researchers used positron emission tomography (PET) to track radiolabeled docetaxel in patients with NSCLC. Surprisingly, they found that administering bevacizumab before docetaxel significantly reduced the perfusion and influx rate of taxane to tumors, an effect that lasted 4 days.[2]

"The clinical relevance of these findings is notable, as there was no evidence for a substantial improvement in drug delivery to tumors," the authors reported.[2] "These findings highlight the importance of drug scheduling and advocate further studies to optimize scheduling of antiangiogenic drugs."

New randomized, controlled clinical trials are needed to identify the optimal schedule for bevacizumab plus cytotoxic chemotherapy, and animal studies may prove instrumental in identifying the molecular mechanisms explaining her team's findings, lead author Astrid Van der Veldt, MD, of the VU Medical Center in Amsterdam, told *Oncology Nurse Advisor.*

"The authors should be congratulated for performing this study and examining a very important question about anti-VEGF treatment in human tumors," Jain, a pioneer of the normalization model, told *Oncology Nurse Advisor.* "There has been a relative dearth of translational studies examining the physiological effects of anti-VEGF treatment in cancer patients, largely due to logistical difficulties—and more such studies are urgently needed to shed further light on this important question."

Previous clinical and preclinical animal studies that seemed to support the normalization model of VEGF blockade and improved tumor drug uptake, may have yielded misleading results because they tracked tumor perfusion using radiolabeled *glucose* (using FDG PET tumor imaging), rather than radiolabeled chemotherapy drugs, Van der Veldt suspects.

> "There is a large number of variables that can modulate the effects of anti-VEGF therapy on drug delivery. The most important of these is dose."

"The kinetics of ^{18}F-FDG are fundamentally different from those of anticancer drugs, as ^{18}F-FDG reflects glucose metabolism," she explained.

"This is an interesting and important study that contradicts much of the previous literature … and has significant clinical

and translational implications," said Professor Timothy Cripe, MD, PhD, Director of Hematology/Oncology and Bone Marrow Transplant at Nationwide Children's Hospital, Columbus, Ohio.

The new findings need to be further explored and validated, Cripe and Jain both emphasized. The new study is preliminary and exploratory, Jain told *Oncology Nurse Advisor*, and timing of VEGF blockade is not the only consideration.

"There are a large number of variables that can modulate the effects of anti-VEGF therapy on drug delivery," Jain said. "The most important of these is *dose*. A lower dose could normalize vessels and improve drug delivery, whereas a higher dose could reduce both perfusion and drug delivery. The question of an appropriate [VEGF blockade] dose is a complete black box in the setting of human tumors and the results of this study should be interpreted with caution."

"It would have been better if the authors had compared a larger group of patients and tested several doses in this study, and compared changes in perfusion with the treatment outcome—response rate, progression-free survival, [or] overall survival," Jain said.

And while the new study found statistically significant impairment of tumor drug uptake, these may not prove to be *clinically* significant, Cripe argued. "The effects of combined therapy on the tumor microenvironment might offset the effects of loss of drug delivery, so that in the end schedule might not matter," he said.

Tumor uptake of chemotherapy drugs is not the only factor that determines therapeutic efficacy, Cripe added. VEGF blockade appears to decrease the influx of innate inflammatory cells that contribute to a microenvironment favoring tumor growth, he noted. "By decreasing the influx of such cells, the antitumor effects of bevacizumab may be more profound than the loss of chemotherapy exposure," he said. The effects of VEGF blockade plus chemotherapy may be "quite different among different tumor types," such that the new study of non-small-cell lung tumor responses will not generalize to all cancers, Cripe added.

While tumor necrosis could impair docetaxel uptake late in the study period (eg, day 4), early impairment of tumors' drug uptake was evident within hours of bevacizumab infusion, suggesting a more immediate mechanism is also at play, even if tumor necrosis occurs later.[2] Van der Veldt and her colleagues suspect rapid vasoconstriction of tumor vasculature in response to bevacizumab administration is one likely explanation. If vasoconstriction is involved, administering cytotoxic drugs first and then administering bevacizumab could improve tumor retention of chemotherapy agents, they suggest.

"Given previous clinical trials of bevacizumab and irinotecan in colorectal patients having some success, the results are counterintuitive," said Michael Lewis, PhD, associate professor of Oncology for Tumor Biology at the University of Missouri. "An interesting possibility raised by these authors is to reverse the order of treatments: administer chemotherapy first, followed by antiangiogenic treatment. Based on their findings, a decrease in tumor perfusion caused by the antiangiogenic agent might increase retention of cytotoxic drugs in tumors."

Indeed, that is just what Cripe and colleagues found in an animal study of how VEGF blockade affected the uptake of an oncolytic herpes virus, conducted at the Cincinnati Children's Hospital Medical Center and published in 2010.[9]

Vascular pruning, hypoxia, and *c-Met* activation all play a role in VEGF blockade-associated tumor escape to new tissues.

That study showed that VEGF blockade hampered tumor uptake of an anticancer viral agent in mice when it preceded intravenous delivery of the oncolytic virus.[9] But when VEGF blockade *followed* oncolytic virotherapy, the efficacy of virotherapy improved significantly.[9]

"In that case, the schedule did make a difference on the antitumor effect," Cripe said. "Whether or not the mechanism inhibiting uptake [between bevacizumab and oncolytic virus] is similar, is unknown. In terms of the posited mechanism of vasoconstriction, it seems reasonable given the rapid timeframe that is really too early to allow for any major changes in gene or protein expression. Again, though, that effect may be transient and might be different at days 2 or 3."

BLOCKING TUMOR CELL ESCAPE WITH C-MET

The sequence or timing of VEGF blockade is not the only hurdle to optimizing its efficacy as an anticancer therapy. Ironically, preclinical studies indicate that VEGF blockade can actually increase the risk of tumor spread and metastasis.[10] Tumor cell hypoxia can activate the *c-Met* gene, for example, which upregulates production of the hepatocyte growth factor receptor proteins involved in tumor invasion and metastasis.[10] c-Met activation increases cell proliferation and motility, potentially hastening tumor invasion and metastasis to distant organs.[10]

Tumor cell hypoxia has been shown to be associated with a higher risk of metastasis and poor prognosis.[11] And in a recently published study of VEGF blockade and tumor spread in a mouse

pancreas model, researchers at the University of California San Francisco reported that VEGF blockade–associated tumor cell hypoxia led to upregulated c-Met and greater tumor aggressiveness and more severe liver metastasis.[10] The study confirmed that vascular pruning, hypoxia, and c-Met activation all play a role in VEGF blockade–associated tumor escape to new tissues.[10] The study showed that an engineered antibody—cabozantinib—inhibits c-Met activation and reduces tumor aggressiveness, reflecting remarkable promise as a potential monotherapy for suppressing tumor angiogenesis, growth, invasion, and metastasis by simultaneously blocking both c-Met and VEGF-mediated angiogenesis.[10] (Also see *Oncology Nurse Advisor,* In the News, August/September 2010, p. 8.) Whether other mechanisms also cause VEGF-blockade therapies to provoke metastatic processes leading to the regional lymph node or distant spread of tumors is not yet known.[12]

To counter the potential risk of tumor cell escape and spread during VEGF blockade, bevacizumab manufacturer Genentech is already conducting clinical trials of combined therapy with bevacizumab plus the c-MET receptor-blocking antibody onartuzumab in advanced NSCLC patients, and patients with advanced cases of triple-negative breast cancer and metastatic colorectal cancer.[12] ■

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