

IN EVERY ISSUE

# Patients on Angiogenesis Inhibitors Should Be Monitored for Heart Issues

BY KATHY LATOUR

Researchers studying the side effects of new cancer treatments have determined that patients taking a class of drugs that target the VEGF pathway should be monitored for cardiac issues that include high blood pressure, heart attack and congestive heart failure.

The issue is not to stop the drugs' use but to make oncologists aware that patients taking these drugs need monitoring, says Javid Moslehi, MD, co-director of the Cardio-Oncology Program at the Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston.

VEGF, or vascular endothelial growth factor, is a protein released more abundantly by tumors, which signals the growth of blood vessels to feed the tumor, a process called angiogenesis. The increasing numbers of angiogenesis inhibitors in development have made this an important area of research, Moslehi says. During the past seven years, four drugs that target the VEGF pathway have been approved by the Food and Drug Administration for use in a number of cancers, including brain, colon, lung, kidney, liver and gastrointestinal tumors. In addition to Avastin (bevacizumab), the FDA has approved Nexavar (sorafenib), Sutent (sunitinib) and Votrient (pazopanib).

"It has been recognized that these drugs cause hypertension," Moslehi says, "but it was often ignored because they were treating the patient for cancer. But hypertension can be a long-term issue and lead to a number of cardiovascular diseases, including heart failure and stroke."

A study reported earlier this year in the *Journal of Clinical Oncology* examined five randomized trials, which compared 3,784 women with metastatic breast cancer who received chemotherapy regimens containing Avastin with women given regimens that did not include the drug.

"This analysis showed a significant increase in [risk for] high-grade congestive heart failure in women taking Avastin—almost five times higher," says Toni Choueiri, MD, assistant professor of medicine at Harvard Medical School and lead researcher. "This is clinically significant." Only 1.6 percent of women taking Avastin actually had high-grade congestive heart failure, so while it's important to note there is a significantly increased risk, there is still a low incidence overall.

In the study, Choueiri points to research on mice indicating that those lacking the VEGF gene have thinned myocardial walls. "What we know is that VEGF may have cardioprotective effects, and when you block it you may get a certain cardiac

toxicity,” Choueiri says, adding that physicians may not have attributed symptoms associated with heart failure to Avastin since symptoms could be attributed to other causes, particularly in the breast cancer population where women may have received other treatments recognized as having cardiac toxicity. For this reason, he says, incidents may not have been cited in the studies.

Moslehi and Choueiri point to the trial process for the newer drugs as a time to identify potential cardiac side effects, learn how they can be managed and determine whether they are reversible.

In October, Moslehi and colleagues published a letter in *The New England Journal of Medicine* that indicated in certain cases that the heart failure seen with Nexavar and Sutent is reversible. “But more studies are needed that prospectively examine these unwarranted side effects.”

Moslehi and Choueiri have joined forces and combined their expertise—cardiology and oncology—to examine the effects of VEGF inhibitors on the cardiovascular system.

“Ultimately, treating the cardiovascular effects of novel chemotherapies requires a team effort between various physicians working together for the benefit of the patient,” Moslehi says.