New Anticancer Drugs Can Trigger Hypertension

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NEW YORK — Several new and effective anticancer drugs have produced the unexpected and potentially serious side effect of hypertension in many patients.

Drugs that work by inhibiting the vascular endothelial growth factor signaling pathway (VSP), such as bevacizumab (Avastin), sunitinib (Sutent), and sorafenib (Nexavar), all have been documented to trigger hypertension in roughly 10%-40% of patients, in many cases leading to grade 3 hypertension, with blood pressure rising over 180/110 mm Hg, Dr. Michael L. Maitland said at a symposium on cardiovascular disease in cancer patients, sponsored by the University of Texas M.D. Anderson Cancer Center, Houston. In some cases patients also developed heart failure, which was severe in some instances.

Although the magnitude of the problem of hypertension that is triggered by these drugs remains poorly understood, several rules for their safe use have emerged:

- ► Candidates for VSP inhibitor therapy should have a pretreatment risk assessment.
- ► The blood pressure goal for patients on a VSP inhibitor is a maximum of 140/90 mm Hg.
- ► Blood pressure should be measured accurately, early, and often in patients on one of these drugs.
- ► If hypertension develops, it should be promptly treated.

If a patient's blood pressure spikes, the treatment with the VSP inhibitor should be immediately stopped until his or her pressure can be normalized, said Dr. Maitland, an oncologist and pharmacologist at the University of Chicago.

Not enough is currently known about VSP inhibitor–triggered hypertension to guide a rational management approach. Consensus management recommendations are being written, Dr. Maitland said in an interview. Until these guidelines are issued, "treat it like conventional hypertension," using agents such as ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, and β-blockers, he said.

"Aggressive treatment of blood pressure may substantially minimize the cardiotoxicity" of new anticancer drugs, including sunitinib and imatinib, another anticancer drug that's been implicated in causing heart damage, Dr. Aarif Y. Khakoo, a cardiologist at M.D. Anderson Cancer Center in Houston, said in a separate talk at the meeting, which also was sponsored by the American College of Cardiology and the Society of Geriatric Cardiology. "If caught early, the sunitinib toxicity may be reversible," Dr. Khakoo added.

The consequences of a profound spike in blood pressure and possibly other physiological changes caused by drugs like sunitinib have been documented in results from recent studies. A review of 75 patients with metastatic GI stromal tumors treated with sunitinib for a median of 34 weeks showed that 35 (47%) eventually became hypertensive (compared with a 6% prevalence of hypertension at baseline), with several developing grade 3 hypertension. Eight (11%) of the sunitinib-treated patients had a cardiovascular event, including six with heart failure (8%) and one with a myocardial infarction. Of the 65 sunitinib-treated patients who underwent LVEF monitoring, 13 (20%) had their left ventricular ejection fraction fall below 50% (Lancet 2007;370:2011-9).

A multivariate analysis of the outcomes identified a history of coronary artery disease as the only significant independent predictor of a cardiovascular event in the sunitinib recipients. Patients with this history were about 40-fold more likely to have a cardiovascular event.

In most patients, the declines in left ventricular function rapidly reversed once treatment with sunitinib stopped, said Dr. Ming Hui Chen, a cardiologist at Brigham and Women's Hospital in Boston and a collaborator on this sunitinib study.

In a second review of 224 patients who were treated with sunitinib at M.D. Anderson Cancer Center, 6 patients (3%) developed significant heart failure within 4-44 days after treatment began, according to a recent report from Dr. Khakoo and his associates (Cancer 2008;112:2500-6). Three patients developed New York Heart Association class IV failure, two had class III heart failure, and the sixth patient developed class II heart failure. One patient died because of this adverse effect, which was linked to sunitinib treatment. All six patients also had increased blood pressure, and the effect of the drug did not fully resolve when treatment stopped. ■