

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Cardiovascular Toxicity of New Agents

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H&O How has the link between cardiovascular toxicities and new anticancer agents been researched?

MM Aside from agents developed specifically to treat breast cancer, such as trastuzumab (Herceptin, Genentech), the link between cardiovascular toxicities and new anticancer agents has been researched erratically. In the past, patients with significant cardiovascular comorbidities were typically excluded from trials of new anticancer agents and patients with advanced cancer were likewise excluded from trials of agents for the management of cardiovascular morbidities. During early drug development, the oncology community has not paid much attention to cardiovascular adverse events of new anticancer agents. With the exception of the chronic effects of anthracyclines, we have had low sensitivity for detecting cardiovascular toxicities. Besides individual investigators' observation skills, we rely on structured reporting of adverse events in clinical trial databases. Many cardiovascular toxicities are somewhat arbitrarily categorized and their reporting is based on not only an investigator's recognition but also subjective categorization. Consequently, the currently reported frequencies of cardiovascular toxicities of novel anticancer agents, such as inhibitors of the vascular endothelial growth factor (VEGF) signaling pathway (VSP), is probably an underestimate of the true effect.

Some early-drug development investigators recognized an unusually high frequency of hypertension with VSP inhibitors (ie, bevacizumab [Avastin, Genentech], sorafenib [Nexavar, Bayer], and sunitinib [Sutent, Pfizer]) and unexplained lower extremity edema, fatigue, and dyspnea on exertion with some kinase inhibitors (most prominently sunitinib and imatinib [Gleevec, Novartis]). These findings have led to 3 investigational approaches: 1) small, focused prospective studies in patients receiving these drugs (eg, a study of blood pressure and sorafenib by Veronese et al); 2) mechanism-based studies relying primarily on animal models and in vitro studies (eg, studies of imatinib by Kerkelä et al); 3) now that these concerns have been raised, more systematic retrospective analyses (eg, the study of sunitinib and left-ventricular dysfunction by Chu et al published in *Lancet* in 2007). Moving forward, with this research, it will become possible to discern the extent to which one agent causes such adverse events more than another.

H&O What are the cardiovascular toxicities associated with new agents?

MM There are many cardiovascular toxicities associated with new agents. The toxicities are likely interrelated, but by as yet unknown mechanisms, and they might represent a continuum of severity. Focusing on the VSP inhibitors, there appear to be 3 primary cardiovascular toxicities: elevation in blood pressure, left-ventricular dysfunction, and bleeding/thrombosis.

H&O What hypotheses have been proposed to explain the mechanism of cardiovascular toxicities resulting from VEGF receptor-2 inhibitors?

MM VEGF signaling is necessary for many aspects of normal endothelial cell function and survival, not just tumor angiogenesis. For example, production of nitric oxide, a gaseous mediator of vascular smooth muscle relaxation is directly regulated by the VSP. To explain the first toxicity, blood pressure elevations, there are 2 leading hypotheses: vasoconstriction resulting from almost immediate effects on endothelial cell production of nitric oxide, and over the longer term, increased rigidity of the systemic vasculature due to the diminished presence of endothelial cells and their many roles in stabilizing microvessels and regulating response of the vasculature to changes in blood flow.

For ventricular dysfunction, the outcome results from complex effects of these agents on the systemic vasculature and direct effects on cardiac myocyte signaling. Disruption of VEGF signaling by itself does not appear to lead to ventricular dysfunction, and this toxicity has not been associated with bevacizumab, which binds the VEGF ligand itself. The kinase inhibitors sorafenib and sunitinib inhibit many kinases other than VEGF receptor-2 (VEGFR2), including platelet derived growth factor receptor (PDGFR) and c-Abl. Studies of imatinib (which inhibits many kinases but not VEGFR2) by Kerkelä and colleagues and Fernández and associates suggest that disruption of Abl signaling increases the likelihood that a cardiac myocyte will undergo apoptosis. Both groups demonstrated that bypassing or removing the blockade of Abl signaling abrogates this effect. Khakoo and colleagues have reviewed the protective role that PDGFR plays in ventricular remodeling in response to stress. In fact, recombinant PDGFR has shown therapeutic benefit in animal models of heart failure. These investigators hypothesized that sunitinib delivers a “one-two punch” to the left ventricle. First, by elevating systemic blood pressure through VSP inhibition, the drug increases afterload. The second hit, blocking PDGFR signaling, leaves cardiac myocytes impaired for response to this stress, and leads to ventricular dysfunction. An extension of this hypothesis would be that effective control of the blood pressure elevation caused by sunitinib’s VSP inhibition could minimize the afterload stress and prevent development of ventricular dysfunction. This hypothesis needs to be tested prospectively, as excessive preemptive blood pressure reduction could cause its own complications.

With bleeding and thrombosis, the specific mechanisms are less clear. In general, blockade of the VSP disrupts microvascular architecture, which might lead to increased capillary fragility and bleeding. Severe bleed-

Table 1. Ongoing Trials Evaluating Cardiovascular Toxicity of Anticancer Agents

Clinicaltrials.gov Identifier	Title
NCT00259129	Effect of BAY 43-9006 (Sorafenib) on Cardiovascular Safety Parameters in Cancer Patients
NCT00691730	Kidney and Blood Pressure Changes in Patients Receiving Bevacizumab, Aflibercept, Sunitinib, or Cediranib for Cancer
NCT00532064	Early Detection of Cardiotoxicity During Sunitinib or Sorafenib Chemotherapy Using Cardiac Biomarkers

ing events have been associated with tumors that are in close proximity to major blood vessels, implying that degradation of a tumor that had previously eroded a blood vessel led to the event. Inhibitors of the VSP have been associated with a higher rate of arterial thrombotic events. As the incidence of venous thrombosis events in cancer patients is already quite high, it is not yet clear that exposure to VSP inhibitors increases the risk. It is also unclear whether the thrombotic events result directly from VSP inhibition or are a consequence of decreased endothelial cell coverage of vessel lumen surfaces, and, in turn, increased shear stresses from damaged microvessels and elevated blood pressure.

H&O Until further research is complete, how should clinicians think about the risk of cardiovascular toxicities?

MM There are ongoing prospective studies evaluating cardiovascular toxicity with specific agents (Table 1). Until the results of these trials are available, clinicians need guidance on how to treat patients. Because the cancer patient population is aging and surviving longer, more patients are likely to have preexisting cardiovascular morbidity, and thus, agents that cause cardiovascular toxicities can lead to significant adverse events for our patients. The greater questions are how clinicians should determine which patients are at increased risk of incurring these problems and which patients are at risk for the most severe adverse events. Catastrophic cardiovascular events might be avoided if patients are thoroughly evaluated, and those most sensitive to the stresses expected from exposure to VSP inhibitors might best be managed in collaboration with a cardiovascular specialist.

H&O How should the knowledge of the risk of cardiovascular toxicities be used in the future?

MM In the near term, the oncology community can improve its profiling of patients in terms of who needs more attentive care. We should readily take advantage of the immense body of knowledge regarding the management of cardiovascular conditions. In my opinion, oncologists have tended not to pay enough attention to managing patients with hypertension or evaluating patients with hyperlipidemia, which is an element of risk for coronary artery disease. In fact, Piccirillo and colleagues suggested in *JAMA* in 2004 that more attentive management of comorbidities may be as important to cancer-related mortality as the stage of cancer at which a patient presents. It is important, therefore, to ensure that patients receiving VSP inhibitors undergo a thorough history and exam to assess cardiovascular risk. This assessment might not be quite as intense as preoperative evaluations commonplace to patients undergoing surgery, but the spirit should be the same. Identifying risks and optimizing their control—for example, controlling blood pressure—might have a significant effect on all associated cardiovascular morbidities, including significant decreases in ventricular function, myocardial infarction, and severe bleeding.

In the future, with knowledge of which currently available agents carry an increased risk of causing specific cardiovascular toxicities, it will be possible to select an agent associated with less risk for a particular patient, given that patient's profile. Another possibility, following from the research of Fernández and colleagues, is the development of next-generation agents that eliminate one particular off-target effect associated with a given toxicity.

H&O Are there other anticancer agents in development that are associated with cardiovascular toxicities?

MM Although angiogenesis inhibitors interfere with the branching of new blood vessels necessary to support tumor growth, the vascular-disrupting agents comprise a group of drugs designed to damage directly the existing tumor vasculature based on its abnormal structure. The mechanisms by which these agents act are independent of VSP targeting, but similarly, these drugs have overlapping effects on the normal vasculature. Cardiac ischemia, electrocardiogram changes, and decreases in ejection fraction have been reported with these agents. As these agents are earlier in development, based on the experience with VSP inhibitors, the oncology community will hopefully be more proactive in recognizing and preventing cardiovascular toxicities of these drugs as they are developed.

Suggested Readings

Chu TF, Rupnick MA, Kerkelä R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet*. 2007;370:2011-2019.

Fernández A, Sanguino A, Peng Z, et al. An anticancer C-Kit kinase inhibitor is reengineered to make it more active and less cardiotoxic. *J Clin Invest*. 2007;117:4044-4054.

Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12:908-916.

Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. *Cancer*. 2008;112:2500-2508.

Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA*. 2004;291:2441-24417.

van Heeckeren WJ, Ortiz J, Cooney MM, Remick SC. Promise of new vascular-disrupting agents balanced with cardiac toxicity: is it time for oncologists to get to know their cardiologists? *J Clin Oncol*. 2006;24:1485-1488.

Veronese ML, Mosenkis A, Flaherty KT, et al. Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol*. 2006;24:1363-1369.