Cardio-Oncology: It Takes Two to Translate

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Heart-related toxicities from targeted cancer therapies shed light on the biology of cardiovascular disease in humans (Chintalgattu et al., this issue).

As an emerging discipline focused on the cardiovascular care of cancer patients, cardio-oncology represents a novel platform for translational investigations. Toxic effects on the heart and vasculature caused by targeted cancer therapies can reveal insights into the biology of cardiovascular disease in humans. This phenomenon was first observed with trastuzumab, a monoclonal antibody that targets the receptor HER2, which is overexpressed in a subset of breast cancers (1). After early, unexpected reports that trastuzumab treatment predisposed patients to cardiomyopathy, preclinical studies uncovered a critical role of HER2 signaling in the cardiac myocyte stress response. Later research suggested that activation of HER2 signaling has therapeutic potential in the treatment of heart failure, an idea that is currently being tested in clinical trials with neuregulin (1).

Mechanistic insights into vascular and myocardial pathobiology, such as those inadvertently exposed by trastuzumab treatment, are likely just the tip of the iceberg (Fig. 1). The oncology community has now seen the rapid emergence of multiple novel targeted therapies, including agents such as sunitinib, a novel tyrosine kinase inhibitor initially approved for kidney cancer treatment. In this issue of Science Translational Medicine, Chintalgattu et al. report the intriguing results of a study of sunitinib in a rat model that not only elucidates potential mechanisms for associated cardiomyopathy but also introduces a new basis for the regulation of coronary microvascular function via cardiac pericyte cells (2).

INSIGHTS FROM ANGIogenesis

Originally proposed by Folkman more than 40 years ago, the inhibition of angiogenesis by targeting specific proangiogenic factors has been a major focus of cancer drug development over the past decade (3). Angiogenesis is mediated by stabilization of a master transcription regulatory protein hypoxia-inducible factor–α (HIF-α), which drives transcription of pro-tumorigenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Bevacizumab, a monoclonal antibody targeting the soluble VEGF protein, was the first drug in this class approved by the U.S. Food and Drug Administration (FDA); however, newer drugs such as sunitinib and sorafenib target tyrosine kinase receptors that are activated by VEGF, PDGF, and other factors—referred to collectively as VEGF signaling pathway (VSP) inhibitors. However, the term “VSP inhibitor” is somewhat misleading given the relative receptor promiscuity of some of these drugs.

Over the past several years, it has become increasingly clear that VSP inhibitors are associated with increased risk for hypertension, vascular events, and cardiomyopathy (4). Sunitinib, the first tyrosine kinase inhibitor developed in this class, is FDA-approved for the treatment of advanced renal cell carcinoma, gastrointestinal stromal tumor, and advanced pancreatic neuroendocrine tumors. Sunitinib, in particular, has been associated with risk for heart failure in retrospective single-institution studies and in meta-analyses of clinical trials. Observational data from trials involving sunitinib also suggest an increased risk for asymmetric cardiomyopathy, with one study reporting up to 28% of patients having an absolute decrease in ejection fraction of at least 10% (5). The mechanisms of sunitinib-associated cardiomyopathy are not well understood, but the known biological targets of sunitinib offer some clues. Sunitinib targets several vasculature-associated tyrosine kinases receptors, including all three VEGF receptors (VEGFR1, VEGFR2, and VEGFR3), PDGF receptor α (PDGFRα) and PDGFRβ, KIT, and FLT3. Thus, the molecular targets of these therapies invoke a vascular mechanism for the associated cardiomyopathy.

ON-TARGET

In their previous work, Chintalgattu and colleagues demonstrated a critical role for PDGFRβ in stress-induced cardiac angiogenesis (6). In the current study (2), the authors established a mouse model of sunitinib-associated cardiomyopathy and showed a marked decrease in coronary-flow reserve after sunitinib treatment. Sunitinib mediates coronary microvascular dysfunction by targeting PDGFRβ on cardiac pericytes—contractile cells that wrap around blood vessels through contact with their endothelial cells.

The authors then performed several elegant experiments demonstrating specificity and causality. For example, they showed that the cardiomyopathy feature of their mouse model is specifically induced by sunitinib because doxorubicin—another cancer chemotherapy associated with cardiac dysfunction—did not affect PDGFRβ signaling in cardiac pericytes despite an effect on the microvasculature and an observed decrease in cardiac function. Moreover, CP-673451, another PDGFR inhibitor, recapitulated sunitinib-associated effects on the microcirculation and pericytes in the mouse model, whereas concomitant treatment with thalidomide, an inducer of pericytes, ameliorated sunitinib-induced cardiomyopathy and microvascular dysfunction. Finally, consistent with the cardiomyopathy seen in humans treated with sunitinib, the authors’ model for sunitinib-induced cardiomyopathy was reversible, with normalization of cardiac and microvascular dysfunction 2 weeks after drug withdrawal, corresponding to restoration of pericytes in the heart.

A few unanswered questions remain. One concern is the lack of an effect on blood pressure after sunitinib treatment in the authors’ mouse model. Elevation in blood pressure, in some cases leading to hypertension, is an outcome that occurs in the majority of patients treated with sunitinib (7). Although it is unclear whether hypertension occurs in the same patients that display cardiomyopathy, hypertension is likely an on-target effect and may predict tumor response after sunitinib treatment (7). It is also unclear what role VEGF receptor targeting plays in the development of sunitinib-induced cardiomyopathy. A preclinical model by Keshet and colleagues expresses a “tunable” transgene that encodes a VEGF trap (in a sense, recapitulating the effects of bevacizumab) that, when induced, leads to decreased myocardial capillary
density (capillary rarefaction), induction of hypoxia and hypoxia-inducible genes in the myocardium, and cardiac dysfunction; this dysfunction is reversible upon removal of the transgene in a manner consistent with the cardiomyopathy that results from many VSP inhibitors (8). This model suggests that VEGF-targeting by sunitinib may recapitulate many of the hallmarks of sunitinib-associated cardiomyopathy, including reversibility. Because VEGF inhibition is a central feature of VSP inhibitors and cardiomyopathy has been described with other drugs in this class, it is possible that VEGFR and PDGFR inhibition work synergistically in the development of heart failure.

**WIDENING THE LENS**

The current study by Chintalgattu et al. (2) has implications that extend beyond sunitinib-induced cardiomyopathy. For instance, the microvascular dysfunction seen in the current study may be applicable to other conditions, such as diabetes, which can also lead to cardiomyopathy. The authors’ preliminary data suggest that sunitinib treatment leads to myocardial hypoxia and induction of hypoxia-inducible genes. These findings raise the intriguing possibility that hypoxia-inducible pathways lead to cardiac abnormalities, and their induction is a common final pathway leading to cardiomyopathy as a result of microvascular dysfunction from any cause. Indeed, chronic stabilization of HIFα in the heart is necessary and sufficient to induce reversible cardiomyopathy in mice (9, 10). The current study also highlights a critical and previously underappreciated role for pericytes in the regulation of microvascular function in the heart. Pericytes are a heterogeneous group of extensively branched perivascular cells previously thought to function merely as scaffolding structures. However, the authors’ findings add to a growing literature that suggests a functional and regulatory role for these cells. The precise mechanisms by which pericytes affect coronary microvascular function remain unknown and could result from direct physical contact with the endothelium or from paracrine effects.

The generalizability of the current findings to other VSP inhibitors is not yet clear. It would be interesting to see whether the results observed with sunitinib apply to other drugs that also inhibit both VEGF and PDGF receptors (such as sorafenib). Indeed, VSP inhibitors arguably represent the fastest growing class of drugs for cancer therapy; the number of FDA-approved VSP inhibitors doubled in the last year, and more await approval (4). However, if there is one lesson to be learned from our experience with targeted therapies, it is that the “one size fits all” approach does not apply. The cardiomyopathies that arise from doxorubicin, trastuzumab, or sunitinib may all result in cardiac systolic dysfunction, but it is increasingly clear that the mechanisms behind each cardiomyopathy differ. Thus, further progress in this arena will require scientific as well as clinical vigilance. Diligently screening for hypertension, thrombosis, and other cardiovascular toxicities is mandatory for optimal patient care when administering new anticancer drugs. Concurrently investigating the precise mechanisms that underlie these potential adverse cardiovascular sequelae...
may lead to interventions for attenuating cardiovascular risk, while also serving to further elucidate the interplay between vascular and myocardial biology.

REFERENCES