Contemporary Reviews in Cardiovascular Medicine

Cardio-Oncology
How New Targeted Cancer Therapies and Precision Medicine Can Inform Cardiovascular Discovery

Andrew M. Bellinger, MD, PhD; Carlos L. Arteaga, MD; Thomas Force, MD; Benjamin D. Humphreys, MD, PhD; George D. Demetri, MD; Brian J. Druker, MD; Javid J. Moslehi, MD

Abstract—Cardio-oncology (the cardiovascular care of cancer patients) has developed as a new translational and clinical field based on the expanding repertoire of mechanism-based cancer therapies. Although these therapies have changed the natural course of many cancers, several may also lead to cardiovascular complications. Many new anticancer drugs approved over the past decade are “targeted” kinase inhibitors that interfere with intracellular signaling contributing to tumor progression. Unexpected cardiovascular and cardiometabolic effects of patient treatment with these inhibitors have provided unique insights into the role of kinases in human cardiovascular biology. Today, an ever-expanding number of cancer therapies targeting novel kinases and other specific cellular and metabolic pathways are being developed and tested in oncology clinical trials. Some of these drugs may affect the cardiovascular system in detrimental ways and others perhaps in beneficial ways. We propose that the numerous ongoing oncology clinical trials are an opportunity for closer collaboration between cardiologists and oncologists to study the cardiovascular and cardiometabolic changes caused by the modulation of these pathways in patients. In this regard, cardio-oncology represents an opportunity and a novel platform for basic and translational investigation and can serve as a potential avenue for optimization of anticancer therapies and for cardiovascular research and drug discovery. (Circulation. 2015;132:2248-2258. DOI: 10.1161/CIRCULATIONAHA.115.010484.)

Key Words: cardiotoxicity ■ drug evaluation ■ molecular targeted therapy ■ pre-eclampsia ■ protein-tyrosine kinases ■ translational medical research

H uman genetics represents a rich vein for mining discovery into molecular mechanisms of disease with subsequent translation into novel therapeutics. The power of human genetics derives, at least in part, from starting at the clinical phenotype in the organism of interest, that is, humans, and working backward to a mechanism in lower organisms (Figure 1). Cardiovascular sequelae in oncology trials of novel therapies that target specific signaling pathways offer, as an unexpected side benefit to the identification of effective cancer therapies, a similar opportunity to start at the cardiovascular phenotype in humans and take a reductionist approach in preclinical models to understand the cardiovascular and cardiometabolic pathways in the heart and vasculature.

Novel targeted therapies have changed the natural history of many cancers in the past 2 decades. Their success has spawned the theme of survivorship in oncological care. The field of cardio-oncology (the cardiovascular-focused study and care of cancer patients) has emerged as a result of the increasing recognition that traditional and novel mechanism-based therapies to treat cancer also have the potential to affect the cardiovascular system and to cause clinical complications; indeed, these complications represent a leading cause of morbidity and mortality in cancer survivors.1-3 This fact is attributed to a combination of the reduction in mortality from cancer and the observation that pathways that are targeted by cancer therapies also appear to play important roles in the cardiovascular system. Why cancers and the cardiovascular system share common pathways is a fascinating question that is not fully understood. Nevertheless, insights into the cardiovascular system that arise from clinical trials in cancer patients can begin to shed light on these shared functional pathways. Here, we illustrate several examples of instances when recognition of unexpected cardiovascular toxicity has guided basic science to unravel mechanisms of toxicity and has steered new possibilities for cardiovascular therapeutics.

Targeting Tyrosine Kinases for Cancer Therapy
Protein tyrosine kinases (TKs) are enzymes that catalyze the transfer of phosphate from ATP to tyrosines in cellular

From Department of Medicine, Brigham and Women’s Hospital, Boston, MA (A.M.B., G.D.D.); Vanderbilt-Ingram Cancer Center (C.L.A., J.M.); Cardiovascular Division (T.F., J.J.M.), and Cardio-Oncology Program (C.L.A., T.F., J.J.M.), Vanderbilt University School of Medicine, Nashville, TN; Department of Medicine, Washington University Medical Center, St. Louis, MO (B.D.H., J.M.); Dana-Farber Cancer Institute and Ludwig Center at Harvard, Harvard Medical School, Boston, MA (G.D.D.); and Knight Cancer Institute, Oregon Health & Science University and Howard Hughes Medical Institute, Portland, OR (B.J.D.).
Correspondence to Javid J. Moslehi, MD, Cardio-Oncology Program, Vanderbilt University Medical Center, 2220 Pierce Ave, Nashville, TN 37232.
E-mail javid.moslehi@vanderbilt.edu
© 2015 American Heart Association, Inc.
Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.115.010484

Downloaded from http://circ.ahajournals.org/ at Vanderbilt University Eskind Biomedical Library on December 7, 2015
TKs play a critical role in eukaryotic cellular signaling, and their aberrant activation has been implicated in multiple types of cancer. There are 2 broad classes of TKs: receptor TKs (RTKs), which are transmembrane proteins with a ligand-binding extracellular domain and a catalytic intracellular kinase, and intracellular (nonreceptor) TKs. In both cases, the enzymatic activity of TKs is tightly regulated, generally leading to low levels of phosphorylated proteins in nonproliferating cells. In cancer, TKs can become hyperactive by several means: the fusion of TK to a partner protein (often as a result of a chromosomal translocation), point mutations/insertions that confer ligand-independent constitutive activity or a gain of fitness, gene amplification, RTK ligand overexpression, or deletion of genes that negatively regulate TK function, among others.

Given the central role that TKs play in the development of cancer, it is of no surprise that there have been intense efforts to develop TK inhibitors (TKIs). RTKs can be inhibited by antibodies that target either the receptor ligand or the extracellular domain RTK itself and, as a result, block ligand binding, prevent receptor dimerization, or lead to receptor downregulation (Figure 2). Because many RTKs require dimerization for activation of enzymatic function, dimerization inhibitors have also been developed. The strategy of targeting kinases expanded after the discovery that small molecules can directly inhibit the catalytic activity of TKs by directly interfering with the binding of ATP to a structurally unique pocket or alternatively by allosteric inhibition. Imatinib (Gleevec), a small molecule that inhibits the BCR-ABL1 TK, found in chronic myeloid leukemia (CML) and a limited number of other TKs, was the first major therapeutic success with this strategy. Because the ATP-binding pocket can be similar in ≥1 kinases, small-molecular inhibitors can target >1 RTK. This concept can have implications for both the efficacy and safety of the small-molecular inhibitors. Such is the case with imatinib: Its specificity against ABL1 kinase allows its use in CML. However, its activity against another RTK, KIT, renders it effective in the treatment of a completely distinct form of cancer, gastrointestinal stromal tumor (GIST), for which the KIT RTK is mutationally activated in the majority of cases.

The explosion of kinase inhibitors and their use in patients with cancer have introduced another concept that is less discussed. Cardiovascular or cardiometabolic sequelae (both good and bad) as a result of these novel targeted therapies can provide unexpected insights into the functional roles played by numerous kinases in the cardiovascular system. Because the initial observations occur in patients, much like genetics, they represent real-world “experiments” of human physiology. These initial observations introduce concepts that can then be studied mechanistically in experimental model systems. As has already been the case with specific TKs, modulation of various pathways may then be translated back to bedside, providing novel platforms for cardiovascular therapeutics. This concept was initially appreciated in a subset of breast cancer patients who benefit from treatment with the HER2 (ERBB2)-directed antibody trastuzumab (Herceptin).

**HER2-Targeted Therapies**

The observation in 1987 that the ERBB2 oncogene, which encodes the HER2/neu RTK, a member of the epidermal...
growth factor receptor family, is overexpressed in >20% of breast cancers and is associated with poor prognosis opened the door for the development of oncogene-targeted therapies in breast cancer (Figure 2). Trastuzumab, a monoclonal antibody recognizing an extracellular domain of the HER2, was found to markedly improve survival in patients with HER2-overexpressing breast cancer and has revolutionized the treatment of HER2-positive breast cancer.9,10 In the first human trials of trastuzumab, however, an unexpected cardiac toxicity was identified: 27% of patients receiving trastuzumab concurrently with anthracycline-containing chemotherapy developed either asymptomatic cardiomyopathy or clinical heart failure compared with 8% of patients receiving anthracycline chemotherapy alone.11 The effect was not limited to patients receiving anthracyclines, a known cardiac toxin; 13% of patients receiving trastuzumab plus the microtubule inhibitor paclitaxel also exhibited cardiac dysfunction.9 Fortunately, in many cases, the cardiac dysfunction was asymptomatic, and further clinical trials indicated that in the absence of concomitant anthracycline treatment, the incidence of cardiac dysfunction was relatively low during treatment with trastuzumab and generally transient after completion of therapy.12 In addition, the cardiac risks were outweighed overall by the potent anticancer effect of trastuzumab treatment.

This unexpected clinical observation of cardiomyopathy after trastuzumab therapy resulted in a flurry of basic research into the role of HER2 in the heart. HER2 is a non–ligand-binding RTK expressed in a variety of tissues, including the heart. At the time of the first trials of trastuzumab, HER2 was known to be critical to cardiac development, but expression in adult cardiomyocytes was relatively low compared with the HER2-overexpressing tumors, and a physiological role of the low levels of HER2 protein in the adult heart was not appreciated.13,14 After the early clinical trials involving trastuzumab, however, emerging data suggested that HER2 serves as a coreceptor for neuregulin-1–activated ERBB3 (HER3) or ERBB4 (HER4) RTKs.15 Endogenous neuregulin-1 is a paracrine factor released by cardiac endothelial cells that influences the survival of cardiomyocytes. In neonatal and adult ventricular cardiomyocytes, neuregulin-1 signaling via ERBB2-containing heterodimers activates cellular hypertrophy and cell survival through downstream signaling pathways that involve activation of the phosphoinositide-3-kinase (PI3K) and AKT pathways, as well as the mitogen-activated protein kinase cascade.16 Importantly, recombinant neuregulin-1 has been shown to protect cardiomyocytes from the myofibrillar disarray caused by anthracyclines in culture.17 Further in vivo studies using mice in which HER2 was genetically knocked out specifically in cardiomyocytes showed development of a spontaneous cardiomyopathy; these mice were also more sensitive to other triggers of cardiomyopathy, including pressure overload and anthracyclines.18 Collectively, these preclinical data suggest that the HER2 pathway serves as a critical pro-survival signaling mechanism in the heart, especially under stress conditions.

The combined observations that inhibition of HER2 with trastuzumab causes cardiomyopathy in humans and potentially injury from other stressors such as cardiotoxic agents and that neuregulin-1 signaling can facilitate cardiac adaptation to stress in preclinical models presented several other intriguing possibilities: Is neuregulin signaling altered in human heart failure in general, and could it be modulated for therapeutic
purposes in heart failure? Measurement of circulating serum levels of the potent neuregulin-1β isoform in a large cohort of patients with systolic heart failure of a variety of causes, including both ischemic and nonischemic cardiomyopathy, showed a correlation between increasing serum levels and disease severity.\(^{20}\) Infusion of a recombinant neuregulin-1β peptide fragment into 4 different animal models of heart failure (a rat infarct model, a rat anthraclycine cardiomyopathy model, a rat myocardiitis model, and a dog rapid-pacing model) demonstrated improved hemodynamics and improved survival with effect sizes comparable or superior to that seen with angiotensin inhibitors.\(^{20}\) These exciting results have prompted the initiation of human clinical trials of recombinant neuregulin in heart failure. A phase 1 trial of recombinant neuregulin in 15 patients who received daily infusion for 11 days produced favorable hemodynamic changes and a sustained small increase in left ventricular ejection fraction at 12 weeks.\(^{21}\) Larger clinical trials are expected.

The initial observation of unexpected cardiomyopathy in the first clinical trials of trastuzumab in breast cancer led directly to novel insights into the importance and role of HER2 signaling in other forms of clinical heart failure and hence to a possible new class of therapeutic agents for heart failure. A phase 1 trial of recombinant neuregulin in 15 patients who received daily infusion for 11 days produced favorable hemodynamic changes and a sustained small increase in left ventricular ejection fraction at 12 weeks.\(^{21}\) Larger clinical trials are expected.

VEGF Signaling Pathway Inhibitors

Four decades after Judah Folkman proposed that tumor growth is dependent on formation of new blood vessels through secreted factors,\(^22,23\) aberrantly active angiogenesis has emerged as a therapeutic target in the treatment of cancer and other diseases.\(^{24}\) Decades of work on the tumor microenvironment suggested that tumor hypoxia leads to the stabilization and activation of the master transcription factor, hypoxia-inducible factor (HIF), leading to the transcription of a number of angiogenic factors, including vascular endothelial growth factor (VEGF)-A (hereafter called VEGF) and platelet-derived growth factors (PDGFs) as regulators and inducers of tumor microvasculature.\(^{25}\) These secreted factors act as ligands on respective RTKs on the endothelium and propagate the growth and maturation of new blood vessels that then feed the tumor. Inhibiting either the circulating VEGF or the VEGF receptor was shown to limit tumor growth in preclinical models.\(^{26}\) In 2004, the US Food and Drug Administration approved bevacizumab (Avastin), a monoclonal antibody specifically inhibiting soluble VEGF, in combination with chemotherapy for patients with metastatic colon cancer. In 2015, 11 inhibitors of the VEGF signaling pathway (collectively known as VSP inhibitors) are in clinical use (Figure 2). In some cases, these therapies are antibodies that target soluble VEGF (bevacizumab) or the VEGF receptor (ramucirumab). Aflibercept is a genetically engineered receptor fusion protein that traps soluble VEGF. In other cases, VSP inhibitors are less selective (euphemistically known as multitargeted) TKIs with potent activity against the VEGF receptor or PDGF receptors (sunitinib, sorafenib, pazopanib, regorafenib, axitinib, vandetanib, cabozantinib, lenvatinib, and ponatinib).\(^27\) These small-molecule inhibitors, by virtue of binding to the ATP-binding molecular pocket, which is relatively conserved among different kinases, often inhibit multiple TKs. This target promiscuity has implications for both efficacy and safety. For example, the ability of sunitinib to inhibit KIT with unique structural affinity provides treatment efficacy against GIST.\(^28,29\) On the other hand, the effects of TKIs on other kinases have implications for their variable and dose-limiting side-effect profiles. Nevertheless, collectively, these drugs are referred to as VSP inhibitors.

Adverse cardiovascular events, particularly systemic arterial hypertension, have been associated with VSP inhibitors since the initial clinical trials involving bevacizumab.\(^{30,31}\) Indeed, systemic hypertension has been shown to be a class effect found with nearly all members of the VSP inhibitor family.\(^{27,31}\) The incidence of clinical hypertension has been estimated in meta-analyses to be 19% to 24%.\(^32,33\) Hypertension may be more frequent and more severe with the more potent second-generation TKIs.\(^34\) In addition, an interesting and unexpected pattern of adverse events for VSP inhibitors has emerged, consisting of proteinuria combined with systolic hypertension.\(^35\) Less frequently, VSP inhibitors can be associated with thrombosis and cardiomyopathy.\(^27,31\)

Concomitant hypertension and proteinuria observed in patients soon after starting treatment with VSP inhibitors are reminiscent of another condition associated with endothelial dysfunction, pre-eclampsia, a disorder of pregnancy characterized by elevated blood pressure and proteinuria. Pre-eclampsia is thought to occur in 2 stages: inadequate placental perfusion, resulting in a hypoxic placenta, followed by widespread endothelial dysfunction, resulting in hypertension and proteinuria.\(^36\) Work over the last decade suggests a unifying basis for seeming disjointed stages. Two identified angiogenic factors secreted by the hypoxic placenta are thought to mediate pre-eclampsia.\(^37,38\) Soluble FLT-1 (sFLT-1) is a secreted VEGF receptor lacking the signaling transmembrane domain. Therefore, sFLT-1 acts as an endogenous circulating “trap” for VEGF, competitively inhibiting free circulating VEGF. Soluble endoglin inhibits the transforming growth factor-β pathway, which is involved in the development of pericytes, and is secreted by the injured placenta. These 2 placental factors, sFLT-1 and soluble endoglin, are strongly associated with the development of pre-eclampsia and its severity,\(^39\) rising weeks before the appearance of overt clinical manifestations of the disease.\(^40,41\) Exogenous treatment with sFLT-1 induces hypertension, nephrotic-range proteinuria, and generalized endothelial dysfunction, thus strongly suggesting that the mechanism of pre-eclampsia is through loss of VEGF signaling on maternal endothelium in the kidney and the arterial tree.\(^42\)

Therefore, 2 avenues of scientific exploration, both beginning with a pathological phenotype observed in humans (VSP inhibition causing hypertension and proteinuria, and pre-eclampsia causing a similar phenotype) were united. The hypothesis that endogenous sFLT-1 was the causative agent
Cardiovascular Complications Associated with VEGF Signaling Pathway (VSP) Inhibition

VSP inhibitors
- Hypertension
- Proteinuria
- Thrombosis
- Cardiomyopathy

Pregnancy
- Hypertension
- Proteinuria
- Thrombosis
- Cardiomyopathy

Figure 3. Cardiovascular complications associated with vascular endothelial growth factor (VEGF) signaling pathway inhibition: similarities to cardiovascular complications that can occur during pregnancy. Central role for VEGF signaling in both models. Adapted from Häggström.53a

in pre-eclampsia was greatly strengthened by the observation of a similar phenotype in humans receiving exogenous VSP inhibitors for the treatment of cancer. These observations have now come full circle, with a current study investigating removal of sFlt1 as a novel targeted therapy of pre-eclampsia.42 A phase 2 clinical trial is enrolling patients with the goal of determining whether removal of circulating sFlt1 in patients with severe early pre-eclampsia improves perinatal death rates. Women with very early severe pre-eclampsia at <26 weeks’ gestation undergo twice-weekly extracorporeal apheresis with a charged dextran sulfate cellulose column, which adsorbs sFLT1. Therapy is continued until 34 weeks’ gestation, and the primary outcome is whether the baby is discharged alive or alive at 6 months if hospitalized.43

In addition to proteinuria and hypertension, certain VSP inhibitors have been associated with contributing to systolic heart failure.31,44–46 It was not immediately clear why these drugs would lead to cardiomyopathy; however, with the guiding knowledge of the drug targets, preclinical models have proven informative. Inhibition of VEGF or PDGF signaling, either genetically or pharmacologically via VSP inhibitors such as sunitinib, leads to microvascular dysfunction in the heart, induction of hypoxia and HIF in the myocardium, and a reversible cardiomyopathy.47,48 Stabilization of HIF in the heart is sufficient to cause a reversible cardiomyopathy in mice.49,50 Indeed, clinical cardiomyopathy resulting from VSP inhibitors often is reversible.44,46 Similarly, perturbations in the HIF-VEGF signaling were shown to play a causal role in peripartum cardiomyopathy (PPCM), another cardiovascular complication associated with pregnancy.51 PPCM in mice is triggered by insults to the cardiac vasculature that occur during late pregnancy and the postpartum period, including inappropriate cleavage in the heart of circulating prolactin into a potentially antivascular fragment and the secretion of sFLT-1 from placenta.51,52 Indeed, the incidence of PPCM is increased in patients with pre-eclampsia and in patients with higher levels of circulating sFLT-1.51 Emerging data suggest that PPCM is a vascular disease, with the mechanism probably attributable to an imbalance between proangiogenic factors and antiangiogenic factors in the heart, leading to a reduction in vascular density and microvascular dysfunction. It remains to be seen whether HIF signaling per se is involved in PPCM. Similar to the cardiomyopathy associated with VSP inhibitors, between one third and one half of patients with PPCM have substantial recovery of left ventricular systolic function. These data suggest that alteration of VEGF or PDGF signaling in the heart may be a common mechanism between cardiomyopathy associated with VSP inhibitors and PPCM.53 These similarities also suggest several testable hypotheses, including linking the hypertension and proteinuria and the subsequent cardiomyopathy in both models (Figure 3). It remains to be seen whether modulation of this pathway has therapeutic potential in PPCM. It would also be interesting to know whether dysregulation of this pathway plays a pathogenic role in other forms of cardiomyopathy. Finally, with respect to emerging cancer therapies, endoglin inhibitors are being tested for cancer therapy (in some cases, in combination with VSP inhibitors); it would be interesting to see the cardiac and vascular sequelae of such combination therapies.54,55

Multitargeted TKIs: A Complex Picture in the Cardiovascular System

Although the small-molecule TKI imatinib was initially developed as an inhibitor of PDGF receptor (PDGFR), its...
clinical utility was subsequently developed by rationally using the inhibitory activity against ABL1 kinase, which becomes constitutively active in CML, and against the mutually activated KIT and PDGFRA kinases in GIST.63 As a result of its remarkable efficacy in these cancer types in initial clinical trials, imatinib was approved by the US Food and Drug Administration in 2001 for CML, in 2002 for GIST, and in 2006 for 6 other rare TK-associated cancers. Imatinib significantly changed the natural course of these cancers. Before imatinib, for example, the median survival of CML patients treated with previous therapies (usually an interferon α-based regimen) was 4 to 5 years, justifying the recommendation of allogeneic stem cell transplantation, a costly procedure with significant morbidity and mortality. With imatinib, the 5-year survival rate of newly diagnosed CML is >90%, and those patients who attain either cytogenetic or molecular response to imatinib have a survival similar to that of an aged-matched healthy population.57 Unfortunately, it has also been shown that the ABL1 kinase can mutate, rendering it resistant to imatinib therapy. As a result, second- and third-generation therapies such as dasatinib, nilotinib, bosutinib, and ponatinib were developed and approved for imatinib-resistant CML. Because most of these newer TKIs are more effective against ABL1, the drugs were shown to lead to more effective molecular responses in CML patients. On the other hand, the newer TKIs target other kinases with different degrees of specificity compared with imatinib, introducing a degree of complexity with respect to side effects, including cardiovascular complications.

The cardiovascular safety profile associated with imatinib has evolved significantly over the past decade and has been an interesting and moving target. In 2006, it was shown that imatinib induces a toxic cardiomyopathy in vitro and in mice;54 however, further retrospective and prospective studies have provided little evidence of imatinib-associated cardiomyopathy in humans.59–62 The discordance between murine studies and the experience with imatinib in humans may be explained by differences in the cardiovascular physiology of mice and humans or the fact that high concentrations to imatinib were used in the initial mouse studies.53,64 On the other hand, experimental evidence suggests that imatinib may have favorable metabolic and vascular effects. Treatment of prediabetic mice and mice with new-onset diabetes mellitus with imatinib prevented and, in some cases, reversed type 1 diabetes mellitus63 and attenuated diabetes mellitus–induced atherosclerosis.64 This effect was not felt to be attributable to inhibition of ABL or KIT but rather to inhibition of PDGFR.65 However, in humans, this beneficial metabolic effect of imatinib has been noted only in anecdotal case reports.67 Longer-term observations from phase 3 studies have revealed a lower incidence of cardiovascular events in patients treated with imatinib compared with patients not treated with TKI or patients treated with newer TKIs such as nilotinib,66 suggesting that perhaps imatinib itself may be inherently protective against vascular events. However, appropriately powered, prospective, controlled comparisons are lacking.

Further evidence of a beneficial vascular effect of imatinib came from a case report of a patient with familial idiopathic pulmonary arterial hypertension who was deteriorating on maximal existing medical therapy but who had improved exercise capacity and hemodynamics after treatment with imatinib.69 The presumed mechanism for this benefit was inhibition of PDGFR signaling in the pulmonary vasculature; PDGF can cause increased proliferation and migration of pulmonary vascular smooth muscle cells. Indeed, imatinib reversed experimentally induced pulmonary hypertension and had favorable pulmonary vasodilatory effects in animal models of pulmonary hypertension,70 prompting several prospective clinical trials of imatinib for patients with pulmonary arterial hypertension. In a prospective clinical trial of imatinib as an add-on drug to conventional pulmonary arterial hypertension therapy, imatinib improved exercise capacity and hemodynamics.71 However, unlike in patients with cancer, imatinib was poorly tolerated in patients with pulmonary arterial hypertension, and one third of the patients withdrew from the study as a result of intolerance.71,72 Imatinib therapy was associated with more severe forms of previously reported side effects, including edema, vomiting, and anemia. Unexpectedly, an increased incidence of subdural hematoma (8 of 144 patients) was observed in the imatinib-treated group. Many patients with advance pulmonary hypertension may be on anticoagulation, which could explain this unusual side effect in the imatinib-treated group. The possibility that multitargeted kinase inhibitors can be used for pulmonary hypertension treatment has prompted testing of more selective PDGFR inhibitors administered by inhalation to minimize the systemic side effects.73

Clinical observations from the more recent TKIs used for CML therapy introduce a more complex picture with respect to vascular or pulmonary vascular effects. Initial clinical trials with dasatinib suggested that a percentage of patients are susceptible to pericardial and pleural effusions.74 More concerning, recent data from a French registry point to a signal for dasatinib-induced pulmonary hypertension, marked by severe symptoms and marked hemodynamic compromise.75 Nilotinib, a more potent ABL1 kinase inhibitor compared with imatinib, may have adverse metabolic effects50 and recently has been associated with peripheral arterial vascular events.76,77 Vascular toxicity issues have come to the forefront in CML therapy in the case of ponatinib, which was designed to inhibit a common resistant mutation of BCR-ABL1 and was thought to be “the best of the bunch” among TKIs.78 Despite early signs of efficacy (granting ponatinib an accelerated US Food and Drug Administration approval), a concerning signal for a number of arterial vascular events (including cardiovascular, cerebrovascular, and peripheral vascular events) was present in the seminal phase 2 clinical trial in patients who had failed other TKIs. In total, after 24 months, 12% of patients had vascular events requiring at least an admission to the hospital.79,80 Although ponatinib had been granted accelerated approval by the US Food and Drug Administration, it was temporarily taken off the market in 2013 because of the high number of vascular events. The specific pathophysiology of the vascular events with ponatinib (thrombosis, accelerated atherosclerosis, or another vascular event such as a vasospasm) remains to be seen. It also would be interesting to see if other cardiac risk factors such as hypertension contribute to vascular events. The possibility that hypertension may play a causal role in the induction of
vascular events is intriguing in that ponatinib is also a potent VEGF receptor inhibitor, comparable to VSP inhibitors such as sunitinib or sorafenib.\textsuperscript{80,81}

The cardiovascular experience with the TKIs for the treatment of CML introduces several important concepts that may pertain to other drug classes in other cancer types. First, given the good overall prognosis of patients with CML and the relatively high incidence of cardiovascular disease in the general population, it is important to dissect drug-dependent and drug-independent cardiovascular events. Second, incorporation of appropriate cardiovascular and cardiometabolic end points in selected cancer clinical trials may inform about the biology of specific signaling pathways targeted in humans, may better assess cardiac toxicities, and could lead to better detection of a net cardiovascular benefit (if the latter exists). Third, given that the specific targeted pathways are partially known, the clinical observations, if rigorous, would provide testable hypotheses in the laboratory, where the precise mechanisms can be better elucidated. These bedside-to-bench transitions necessitate stringent clinical adjudication, not possibly biased case series or case reports, as may have been the case with imatinib when it was initially linked to cardiomyopathy.\textsuperscript{58} These efforts would require a closer collaboration between cardiologists and oncologists, especially in the initial design of clinical trials.

In the future, better preclinical models of cardiovascular toxicity and phenotyping of the cardiovascular complications in oncology clinical trials will be necessary to define more clearly the potential cardiovascular toxicities of cancer therapies. For oncology clinical trials, the National Cancer Institute Common Terminology Criteria for Adverse Events were developed to standardize reporting of adverse reactions of cancer treatments. However, these definitions of cardiotoxicity are often different from definitions used for cardiovascular drug trials. In addition, cardiovascular drug trials often require comprehensive adjudication of cardiotoxicity by clinical events committees, something that is not incorporated into oncology clinical trials.\textsuperscript{90} All grading of cardiotoxicity with oncology clinical trials must take into consideration the net benefit that may result from the cancer therapy. For example, the threshold for cardiotoxicity may be different for a compound being tested in renal cell carcinoma (which generally portends a poor prognosis) than for the same compound being tested in CML. Cardio-oncology, in 2015, represents an opportunity to integrate several clinical aspects of a cardiovascular division with both basic and translational investigations (Figure 4).

**Novel Targeted Therapies**

In 2015, a multiplicity of targeted therapies are being tested in humans for various types of cancers. It remains to be seen how effective each agent will be in treating cancer. Even more unclear are the potential cardiovascular and cardiometabolic effects of each agent. For example, the PI3K/protein kinase B (AKT)/mammalian target of rapamycin signaling pathway contributes to the survival and proliferative advantage of many malignant cells and confers resistance to chemotherapy in various malignancies. As a result, a number of PI3K inhibitors have been developed and are in late-stage clinical development in patients with advanced cancers.\textsuperscript{62} However, PI3K signaling is critical for regulation of glucose homeostasis through its modulation of insulin-insulin receptor signaling in cellular metabolism. Elevated levels of C peptide and hyperglycemia have commonly been observed in early-phase trials with PI3K inhibitors.\textsuperscript{83,84} Indeed, relative insulin resistance is considered a necessary pharmacodynamics marker and expected side effect of this class of drugs. As a result, early clinical trials involving PI3K inhibitors have excluded patients with diabetes mellitus or even borderline-high fasting glucose. If these drugs are found to be effective and are approved, there will be a dearth of data on the safety and tolerability for the 30,000,000 diabetics in the United States. Observations in patients treated with this class may further inform our field about the role of PI3K signaling in human metabolism and potentially expand the number of cancer patients who can benefit from treatment with PI3K inhibitors.

Many new classes of cancer therapies target other key cellular pathways. A growing number of cancer therapies target components of the ubiquitin system. Proteasome inhibitors have been approved for the treatment of multiple myeloma, with at least 1 of the approved drugs, carfilzomib, having been associated with a range of cardiovascular complications.\textsuperscript{85} So-called immunomodulators such as thalidomide and lenalidomide are also now known to target the E3 ubiquitin ligase, leading to degradation of the IKAROS family of B-cell transcription factors.\textsuperscript{86,87} Lenalidomide has significant risk for thrombosis, necessitating prophylactic treatment with either aspirin or low-molecular-weight heparin. As modulators of specific E3 ubiquitin ligase gain traction in cancer therapy,\textsuperscript{88} there will be immense potential to learn about ubiquitin biology in the cardiovascular system.

Additionally, fibroblast growth factor (FGF) receptor inhibitors are now in clinical development because this pathway is deregulated in numerous solid tumors.\textsuperscript{89} The most frequent side effect observed in patients receiving these drugs is hyperphosphatemia, presumably reflecting inhibition of kidney FGF receptors that mediate phosphate excretion. In a recent phase 1 trial of the pan–FGF receptor inhibitor JNJ-42756493, 57% of patients developed new hyperphosphatemia over the course of the study.\textsuperscript{90} FGF23, secreted by osteocytes, normally acts to reduce proximal tubule phosphate reabsorption; therefore, blockade of this pathway is expected to increase serum phosphate through reduced kidney
excretion. Hyperphosphatemia is a well-known risk factor for vascular calcification, and whether patients treated with FGF receptor inhibitors may be at increased risk of this complication is unknown at this point.

Finally, some of the most exciting work in oncology is the development of cancer immunotherapies such as the immune checkpoint inhibitors (eg, CTLA4 and the PD1/PD-L1 system).91,92 These agents have exhibited unprecedented activity and even long-term cures in certain highly resistant cancers such as metastatic melanomas. The cardiovascular adverse events associated with cancer immunotherapy are unclear at this point, given the novelty of these therapies. However, basic studies suggest possible cardiovascular sequelae. For example, disruption of PD-1 in mice results in autoimmune dilated cardiomyopathy and sudden death.93 There has been at least 1 documented case of autoimmune myocarditis after melanoma treatment with a PD-1 inhibitor.41 Cardiovascular sequelae of cancer immunotherapy should be an important consideration, particularly with the use of combinations of these agents, as well as with TKIs. This offers yet another set of insights into cardiovascular biology in conjunction with rational activation of cellular immunity.

**Summary: A Novel Platform for Cardiovascular Drug Discovery**

It is estimated as many as 600 targeted oncological therapies are currently in development, representing the undersea portion of the iceberg. Many of these will be, or have recently been, administered to patients with cancer. In effect, these clinical trials sum to a massive exploration of the cardiovascular implications of modulation of signaling pathways ranging from HER2 to PI3K to HDAC to the proteasome. Indeed, a similar case could be made for other organ systems commonly affected such as the kidney.

We propose that as a result of the therapeutic targeting of the signaling pathways in cancer, novel roles of these pathways will likely be recognized in the cardiovascular system. As with trastuzumab, it may even be the case that unexpected observations will lead to insights into novel mechanisms of cardiovascular biology and new potential cardiovascular therapies. The field of cardio-oncology has evolved over the past decade as a clinical field addressing the cardiovascular issues that arise from cancer therapies. However, incorporation of cardio-oncology practice into early studies is necessary to detect the possible cardiotoxicity of drugs and to observe possible cardiovascular or cardiometabolic benefits. Astute clinicians are necessary to tease out the signal from the noise, and basic and translational scientists are necessary to connect these adverse events back to molecular mechanisms. There is a tremendous opportunity, as well as responsibility, to glean as much information and new knowledge as we can from the thousands of patients willing to undergo investigational anticancer therapies.

**Acknowledgments**

The authors thank Dr Weijuan Li for help with layout of Figure 1.

**Sources of Funding**

Dr Bellinger was supported in part by National Institutes of Health grant T32. 5T32HL007604-29. Dr Druker is an investigator for the Howard Hughes Medical Institute. Dr Demetri is supported by the following: Ludwig Center at Harvard, The Pan Mass Challenge via Paul’s Posse, the Russo Family Fund for GIST Research, and Gastrointestinal Cancer SPORE grant 1P50CA127003-05 at the Dana-Farber Cancer Institute from the US National Cancer Institute.

**Disclosures**

Dr Arteaga has received grants for clinical research from Amgen, AstraZeneca Pharmaceuticals, Exelixis, and Merck and has served as an advisor or consultant for InNexus Biotechnology Inc, Monogram Biosciences, Inc, and Roche Laboratories Inc. Dr Force has served as a consultant for Amgen and Bristol-Myers Squibb. Dr. Druker is currently principal investigator or coinvestigator on Novartis, Bristol-Myers Squibb, and ARIAD clinical trials. His institution has contracts with these companies to pay for patient costs, nurse and data manager salaries, and institutional overhead. He does not derive salary, nor does his laboratory receive funds from these contracts. Oregon Health Sciences University and Dr Druker have a financial interest in MolecularMD. Technology used in some of these studies has been licensed to MolecularMD by Oregon Health Sciences University. This potential individual and institutional conflict of interest has been reviewed and managed by Oregon Health Sciences University. Dr Demetri has served as a consultant and clinical investigator with Novartis, Pfizer, Bayer, GlaxoSmithKline, EMD/Serono, Threshold Pharma, PharmaMar, and Janssen/JNJ. He has received a small royalty from Dana-Farber Cancer Institute on a patent licensed from Dana-Farber and Oregon Health Sciences University on imatinib use in GIST. He has also served as a consultant for Ariad, ZioPharm, and Sanofi; serves on the Board of Directors and Scientific Advisory Board of Blueprint Medicines with a minor equity interest; and is on the Scientific Advisory Board of Kolltan Pharmaceuticals with a minor equity interest. These potential individual conflicts of interest have been reviewed and managed by Dana-Farber Cancer Institute. Dr Moslehi has served as a consultant for Novartis, Pfizer, Bristol-Myers Squibb, ARIAD, Millennium, and Acceleron. Drs Bellinger and Humphreys report no conflicts.

**References**


Cardio-Oncology: How New Targeted Cancer Therapies and Precision Medicine Can Inform Cardiovascular Discovery
Andrew M. Bellinger, Carlos L. Arteaga, Thomas Force, Benjamin D. Humphreys, George D. Demetri, Brian J. Druker and Javid J. Moslehi

_Circulation_. 2015;132:2248-2258
doi: 10.1161/CIRCULATIONAHA.115.010484
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/23/2248

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/