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

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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. While these therapies have changed the natural course of many cancers, several may also lead to cardiovascular complications. Many new anti-cancer drugs approved over the past decade are “targeted” kinase inhibitors that interfere with intracellular signaling contributing to tumor progression. Unexpected cardiovascular and cardio-metabolic effects following 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 as well as other specific cellular and metabolic pathways are being developed and tested in

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oncology clinical trials. Some of these drugs may impact the cardiovascular system in detrimental 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 cardio-metabolic changes due to 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 anti-cancer therapies as well as for cardiovascular research and drug discovery.

Keywords

cardiology; drug trials; preeclampsia/pregnancy; cardio-Oncology; precision Medicine; targeted therapy; oncology; cancer

Introduction

Human 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, i.e. humans, and working backwards 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. That is, to start at the cardiovascular phenotype in humans, and take a reductionist approach in preclinical models to understand the cardiovascular and cardio-metabolic pathways in the heart and vasculature.

Novel targeted therapies have changed the natural history of many cancers in the past two decades. Their success has spawned the theme of survivorship in oncologic care. The field of cardio-oncology (the cardiovascular-focused study and care of cancer patients) has emerged due to the increasing recognition that traditional and novel mechanism-based therapies to treat cancer also have the potential to affect the cardiovascular system and 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, as well as 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 about the cardiovascular system that arise from clinical trials in cancer patients can begin to shed light on these shared functional pathways. In this perspective, we will illustrate several examples where 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 substrates.^{4,5} TKs play a critical role in eukaryotic cellular signaling and their aberrant activation has been implicated in multiple types of cancer. There are two

broad classes of TKs: Receptor TKs (RTK), which are transmembrane proteins with a ligand-binding extracellular domain and a catalytic intracellular kinase, and intracellular (non-receptor) TKs. In both cases, the enzymatic activity of TKs is tightly regulated, generally leading to low levels of phosphorylated proteins in non-proliferating 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 and/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 inhibitors of tyrosine kinases.⁴ RTKs can be inhibited by antibodies that either target the receptor ligand or the extracellular domain receptor TK itself, and as a result, block ligand binding, prevent receptor dimerization, and/or lead to receptor downregulation (Figure 2). As 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 which rather selectively inhibits the *BCR-ABL1* tyrosine kinase, found in chronic myeloid leukemia (CML), as well as a limited number of other TKs, was the first major therapeutic success using this strategy.⁶ Because the ATP-binding pocket can be similar in one or more kinases, small molecular inhibitors can target more than one RTK. This concept can have implications for both efficacy but also safety of the small molecular inhibitors. Such is the case with imatinib where specificity against ABL1 kinase allows its use in chronic myelogenous leukemia (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) where the KIT RTK is mutationally activated in the majority of cases.⁷

The explosion of kinase inhibitors and their use in patients with cancer has 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. Since 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 (EGF) receptor family, is overexpressed in more

than 20% of breast cancers and is associated with poor prognosis⁸ 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 in comparison to 8% of patients receiving anthracycline chemotherapy alone.¹¹ The effect was not limited to patients receiving anthracyclines, a known cardiac toxin, as 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 anti-cancer effect of trastuzumab treatment.

This unexpected clinical observation of cardiomyopathy following 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 clinical trials of trastuzumab, HER2 was known to be critical to cardiac development, but expression in adult cardiomyocytes was relatively low compared to the HER2-overexpressing tumors, and a physiologic role of the low levels of HER2 protein in the adult heart was not appreciated.^{13,14} Subsequent to the early clinical trials involving trastuzumab, however, emerging data suggested that HER2 serves as a co-receptor for neuregulin-1 (NRG-1)-activated ERBB3 (HER3) or ERBB4 (HER4) RTKs¹⁵. Endogenous NRG-1 is a paracrine factor released by cardiac endothelial cells which influences survival of cardiomyocytes. In neonatal and adult ventricular cardiomyocytes, NRG-1 signaling via ERBB2-containing heterodimers activates cellular hypertrophy and cell survival through downstream signaling pathways that involve activation of the phosphoinositide 3-kinase (PI-3-K) and AKT pathways as well as the mitogen-activated protein kinase cascade.¹⁶ Importantly, recombinant NRG-1 has been shown to protect cardiomyocytes from the myofibrillar disarray caused by anthracyclines in culture.¹⁷ Further *in vivo* studies using mice where 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 pre-clinical 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 potentiates injury from other stressors such as cardiotoxic agents, and that NRG-1 signaling can facilitate cardiac adaptation to stress in pre-clinical 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 NRG-1 beta isoform in a large cohort of patients with systolic heart failure of a variety of etiologies including both

ischemic and non-ischemic cardiomyopathy showed a correlation between increasing serum levels and disease severity.¹⁹ Infusion of a recombinant neuregulin-1 beta peptide fragment into four different animal models of heart failure (a rat infarct model, a rat anthracycline cardiomyopathy model, a rat myocarditis model, and a dog rapid pacing model) demonstrated improved hemodynamics and improved survival with effect sizes comparable to, or superior to, that seen with angiotensin inhibitors.²⁰ These exciting results have prompted 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 directly led 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 (Figure 2)¹⁵. The precise mechanisms by which trastuzumab causes cardiomyopathy and by which NRG-1 affords cardiac protection are not understood. Also not fully understood is why trastuzumab causes cardiomyopathy more frequently than some of the newer HER2 signaling pathway inhibitors. Nevertheless, this well-told “bedside to bench, and back to bedside” story may represent the tip of the iceberg in terms of how targeted therapies in cancer may provide insight into human cardiovascular biology.

VEGF Signaling Pathways (VSP) 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 transcription of a number of angiogenic factors including vascular endothelial growth factor-A (VEGF-A) (hereafter called VEGF) and Platelet Derived Growth Factors (PDGF) 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 (VEGFR) was shown to limit tumor growth in pre-clinical models.²⁶ In 2004, the FDA approved bevacizumab (Avastin), a monoclonal antibody specifically inhibiting soluble VEGF-A, 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, which traps soluble VEGF. In other cases VSP inhibitors are less selective (euphemistically known as “multi-targeted”) tyrosine kinase inhibitors (TKIs) with potent activity against the VEGFR or PDGF receptors (sunitinib, sorafenib, pazopanib, regorafenib, axitinib, vandetanib, cabozantinib, lenvatinib, ponatinib).²⁷ These small molecular 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 both for 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 VEGF Signaling Pathway (VSP) inhibitors.

Adverse cardiovascular events, particularly systemic arterial hypertension, have been associated with VSP inhibitors since the initial clinical trials involving bevacizumab.^{27,30,31} 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 19–24%.^{32,33} Hypertension may be more frequent and more severe with the more potent second-generation tyrosine kinase inhibitors.³⁴ In addition, an interesting and unexpected pattern of adverse events to 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 is 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 two 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 anti-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 (sEng) inhibits the TGF- β pathway, which is involved in the development of pericytes, and is also secreted by the injured placenta. These two placental factors, sFLT-1 and sEng, are strongly associated with development of pre-eclampsia and its severity,³⁹ rising weeks before 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.⁴⁰

Therefore, two 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 in pre-eclampsia was greatly strengthened by the observation of a similar phenotype in humans receiving exogenous VSP inhibitors for treatment of cancer. These observations have now come full circle with a current study investigating removal of sFlt1 as a novel targeted therapy of preeclampsia.⁴² A phase 2 clinical trial is enrolling patients with the goal of determining whether removal of circulating sFlt1 in patients with severe early preeclampsia improves perinatal death rates. Women with very early severe preeclampsia at less than 26 weeks gestation undergo twice weekly extracorporeal apheresis using 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, pre-clinical 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 hypoxia-inducible factor (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 often 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 anti-vascular fragment and the secretion of sFLT-1 from placenta.^{51,52} Indeed, 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 due to an imbalance between pro-angiogenic factors and anti-angiogenic 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 peripartum cardiomyopathy patients have substantial recovery of left ventricular systolic function. These data suggest that alteration of VEGF and/or PDGF signaling in the heart may be a common mechanism between cardiomyopathy associated with VSP inhibitors and peripartum cardiomyopathy.^{Abraham:2000tt} 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 peripartum cardiomyopathy. It would also be interesting to know if 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}

Multi-targeted Tyrosine Kinase inhibition: A complex picture in the cardiovascular system

Although the small molecule TKI imatinib was initially developed as an inhibitor of PDGFR, its clinical utility was subsequently developed by rationally using the inhibitory activity against ABL1 kinase, which becomes constitutively active in CML, as well as against the mutationally-activated KIT and PDGFRA kinases in GIST.⁵⁶ Due to its remarkable efficacy in these cancer types in initial clinical trials, imatinib was FDA approved in 2001 for CML, in 2002 for GIST, and in 2006 for six other rare TK-associated

cancers. Imatinib significantly changed the natural course of these cancers. Prior to imatinib, for example, median survival of CML patients treated with previous therapies (usually an interferon α -based regimen) was 4–5 years, justifying the recommendation of allogeneic stem cell transplant, a costly procedure with significant morbidity and mortality. With imatinib, 5-year survival rates of newly diagnosed CML is about 90% and those patients who attain either cytogenetic or molecular response to imatinib have similar survival compared to an aged-matched normal population.⁵⁷ Unfortunately, it has also been shown that the ABL1 kinase can mutate rendering it resistant to imatinib therapy. As a result, second (2G) and third (3G) generation therapies, such as dasatinib, nilotinib, bosutinib, and ponatinib, were developed and approved for imatinib-resistant CML. As 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 to 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;⁵⁸ however, further retrospective and prospective studies have provided compelling evidence that there is 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 cardiovascular physiology of mice versus humans or the fact that exceedingly high exposures to imatinib were used in the initial mouse studies.^{63,64} On the other hand, experimental evidence suggests that imatinib may have favorable metabolic and vascular effects. Treatment of pre-diabetic and new-onset diabetic mice with imatinib prevented and, in some cases, reversed type 1 diabetes⁶⁵ and attenuated diabetes-induced atherosclerosis.⁶⁶ This effect was not felt to be due to inhibition of ABL or KIT but rather due to inhibition of PDGFR.⁶⁵ However, in humans this beneficial metabolic effect of imatinib has only been noted 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 to patients not treated with TKI or patients treated with newer TKIs such as nilotinib⁶⁸ 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 speculated to be the known ability of imatinib to inhibit PDGFR signaling in the pulmonary vasculature, since 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 (PAH). In one prospective clinical trial of imatinib as an add-on drug to conventional PAH therapy, imatinib improved exercise

capacity and hemodynamics.⁷¹ However, unlike in patients with cancer, imatinib was poorly tolerated in patients with PAH and one-third of patients withdrew from the study due to 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 out of 144 patients) was observed in the imatinib treated group. Many patients with advance pulmonary hypertension may be on anti-coagulation, which could explain this unusual side effect in the imatinib-treated group. The possibility that multi-targeted 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 to imatinib, may have adverse metabolic effects⁵⁹ 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” FDA 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 FDA, it was temporarily taken off the market in 2013 due to the high number of vascular events. It remains to be seen what is the specific pathophysiology of the vascular events with ponatinib (thrombosis, accelerated atherosclerosis or another vascular event, such as a vasospasm). 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 induction of vascular events is intriguing in that ponatinib is also a potent VEGFR inhibitor, comparable to the VSP inhibitors such as sunitinib or sorafenib.^{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 CML patients 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 cardio-metabolic endpoints in selected cancer clinical trials may inform about the biology of specific signaling pathways targeted in humans, 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 cardiomyopathy⁵⁸. These efforts would require a closer collaboration between cardiologists and oncologists, especially in the initial design of clinical trials.

In the future, better pre-clinical 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 (CTCAE) were developed to standardize reporting of adverse reactions of cancer treatments. However, CTCAE definitions of cardiotoxicity are often different than 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 trials⁸⁰. 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) versus that 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 phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway contributes to the survival and proliferative advantage of many malignant cells and also 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.⁸² 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 been commonly observed in early phase trials with PI3K inhibitors.^{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 or even borderline-high fasting glucose. If these drugs are found to be effective and are approved, there will be a dearth of data regarding 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 that 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 one of the approved

drugs, carfilzomib, having been associated with a range of cardiovascular complications.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.^{86,87} Lenalidomide has significant risk for thrombosis necessitating prophylactic treatment with either aspirin or LMW heparin. As modulators of specific E3 ubiquitin ligase gain further traction in cancer therapy,⁸⁸ there will be immense potential to learn about ubiquitin biology in the cardiovascular system.

Additionally, fibroblast growth factor receptor (FGFR) inhibitors are now in clinical development since this pathway is deregulated in numerous solid tumors.⁸⁹ The most frequent side effect observed in patients receiving these drugs is hyperphosphatemia, presumably reflecting inhibition of kidney FGFRs which mediate phosphate excretion. In a recent phase 1 trial of the pan-FGFR inhibitor JNJ-42756493, 57% of patients developed new hyperphosphatemia over the course of the study.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 FGFR 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” (e.g. 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 one documented case of autoimmune myocarditis after melanoma treatment with a PD-1 inhibitor.⁹⁴ 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 for 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 oncologic 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 has been the case 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 possible cardiotoxicity of drugs and observe possible cardiovascular or cardio-metabolic 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 anti-cancer therapies.

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Figure 1.

Depiction of Cardio-Oncology as a platform for investigation and comparison to human genetics and traditional "bottom up" basic science. Human genetics has been a rich source for discovery in part because the initial observation occurs at a human level. Genetic identification of a heritable phenotype leads to subsequent *in vitro* and animal studies as a means of novel drug development. On the other hand, traditional "bottom up" basic science starts at the level of a molecule with subsequent experimental models testing the relevance of the molecule *in vivo* with the hope that this will ultimately prove relevant to humans. The latter may not be the case for many reasons. On the other hand, cardio-oncology inspired drug discovery may prove more similar to genetics given that the initial observation occurs in humans.

Figure 2.

An overview of pathways that are activated in cancer and regulate cardiovascular homeostasis. Example of different kinase inhibitors used in cancer treatment. Extracellular antibodies include receptor inhibitors (e.g. trastuzumab), dimerization inhibitors (e.g. pertuzumab) or ligand inhibitors (e.g. bevacizumab). Small molecule multi-target inhibitors include tyrosine kinase inhibitors (which often bind to more than one receptor tyrosine kinase) or other small molecule inhibitors. An emerging group of therapies includes drugs that modulate protein degradation machinery including drugs like immunomodulators (e.g. lenalidomide) that activate an E3 ubiquitin ligase targeting one or more proteins for proteasome-mediated degradation.

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 VEGF Signaling Pathway Inhibition: Similarities to cardiovascular complications that can occur during pregnancy. Central role for VEGF signaling in both models.

Figure 4.

A schematic of cardio-oncology in the future which incorporates various aspects of a clinical cardiology division, as well as basic and clinical investigation.