Reversible Cardiotoxicity With Tyrosine Kinase Inhibitors

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Introduction

Tyrosine kinase inhibitors (TKIs) that target the BCR-ABL gene have recently been utilized as selectively targeted noncytotoxic therapy for a variety of malignant conditions, including chronic myelogenous leukemia (CML), gastrointestinal stromal tumor (GIST), chronic eosinophilic leukemia, systemic mastocytosis, chronic myelomonocytic leukemia, and Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL).[1] Cardiotoxicity has been noted as an infrequent occurrence with BCR-ABL TKIs.[2] TKIs have received regulatory approval on the basis of studies with relatively few patients, and the true frequency of cardiotoxicity could have been under-recognized. Reversible cardiotoxicity has been documented in the literature, with normalization in some cases without supportive treatment.

Several aspects of the association between cardiotoxicity and the BCR-ABL TKIs are yet to be fully understood. Although there are growing data linking imatinib (Gleevec, Novartis) to cardiac toxicity, the frequency of such events—in other words a "class effect"—with newer generation TKIs (dasatinib [Sprycel, Bristol-Myers Squibb] and nilotinib [Tasigna, Novartis]) is not known. Reports have described TKI-induced cardiomyopathy in patients with CML, and there are such anecdotal accounts in patients with GIST and chronic eosinophilic leukemia, but not ALL. There is a lack of clear understanding of the pathogenesis of the cardiomyopathy and of the appropriate therapy. Finally, there is controversy regarding susceptibility: Is it idiosyncratic or dependent on pre-existing cardiac comorbidities? We report on the instructive case of a young, athletic patient who had 3 discrete episodes of documented cardiomyopathy in relation to treatment with imatinib, nilotinib, and dasatinib.

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Case Report

Methods

A previously healthy 27-year-old athletic female was diagnosed with Ph+ ALL in June 2004, when she presented with recurrent infections, weight loss, and a total white blood cell count of 56 × 10^9/L. Lumbar puncture excluded central nervous system involvement. Induction therapy was per Cancer and Leukemia Group B (CALGB) protocol 9111.[3] The cumulative dose was 135 mg/m^2 for daunorubicin and 1,200 mg/m^2 for cyclophosphamide.

The patient was then enrolled in CALGB 10001, a phase II trial of sequential chemotherapy and imatinib.[4] Because a fully matched donor was unavailable, the patient underwent an autologous stem cell transplant. Her left ventricular ejection fraction (LVEF) prior to the autologous transplant was 60%. The myeloablative conditioning regimen, administered in December 2004, included total body irradiation (1,320 cGy in 11 fractions), cyclophosphamide (100 mg/kg), and etoposide. This hospitalization was complicated by typhlitis as well as by *Streptococcus viridans* and *Escherichia coli* septicemia that required vasopressor support. The patient was restarted on imatinib maintenance therapy at 400 mg twice daily after count recovery.

One year following her autologous transplant (November 2005), the patient developed a persistent headache and was diagnosed with central nervous system

relapse. No marrow involvement was detected. Imatinib was discontinued after 17 months of therapy, and the patient was treated with cranial irradiation (150 cGy × 8 fractions), followed by re-induction with high-dose cytarabine and mitoxantrone.[5] This treatment was complicated by septic shock with gram-negative bacteremia that required vasopressor support for 1 day. Three days later, a diastolic murmur prompted administration of an echocardiogram that revealed a dilated hypokinetic left ventricle with an ejection fraction of 20–25%; no vegetations were noted. Cardiac enzymes were within normal limits, but brain natriuretic peptide (BNP) was elevated at 470 pg/mL (normal range, 0–100 pg/mL). An electrocardiogram showed sinus tachycardia without signs of ischemia. The patient was placed under watchful observation, and she experienced a dramatic recovery with a repeat ejection fraction of 50% 1 week later. The patient was discharged in a stable condition 2 weeks later.

Maintenance nilotinib (400 mg twice daily) therapy was started in January 2006 and lasted for 3 months. In April 2006, the patient underwent a 9/10 human leukocyte antigen–matched unrelated donor transplant. The conditioning regimen included fludarabine (25 mg/m^2 x 5 days) and melphalan (70 mg/m^2 × 2 days). Severe mucositis required intubation and ventilatory support for 1 week. Upon extubation, the patient required bilevel positive airway pressure for another week when she was re-intubated for increasing shortness of breath related to congestive heart failure. An echocardiogram showed an LVEF of 30% with an elevated BNP of 3,725 pg/mL. Cardiac enzymes revealed minor elevations in the creatine kinase muscle-brain fraction to 9.8 ng/mL (normal range, 0.0–5.0) and in troponin I to 1.99 ng/mL (normal range, 0.0–0.10). The patient was treated with invasive hemodynamic monitoring–guided use of vasopressors and nicardipine. She was successfully extubated 8 days later, with normalization of the LVEF to 55% and the BNP to 84 pg/mL. She was discharged 3 weeks after extubation.

In August 2006, the patient was initiated on maintenance dasatinib 70 mg orally twice daily. Skin and gastrointestinal graft versus host disease required immunosuppressive therapy, including steroids. Ten months after initiation of dasatinib therapy, the patient was admitted with worsening bilateral pleural effusions and progressive shortness of breath. Dasatinib was discontinued on admission. However, on the fourth day of hospitalization, the patient became unresponsive with pulseless electrical activity. Aggressive cardiopulmonary resuscitation included emergent intubation. On arrival in the intensive care unit, an echocardiogram revealed an LVEF of 10–15%. A continuous cardiac output, fiberoptic pulmonary artery catheter was placed. The initial hemodynamic parameters included a cardiac output/index of 1.6 L/min and 1.0 L/min, a pulmonary artery wedge pressure of 36 mm Hg, and a systolic arterial pressure of 120 mm Hg. A dobutamine infusion was initiated, and on intensive care unit day 3, a nicardipine drip was added. Her cardiac output tripled over this time, and filling pressures returned toward normal. The patient was also treated with high-dose corticosteroids and was extubated 11 days later. A repeat echocardiogram, 4 days later, showed an ejection fraction of 55%. The patient was discharged after 4 weeks. Shortly thereafter, she developed recurrent central nervous system relapse and expired suddenly.

Discussion

Our young patient, who had a history of modest anthracycline exposure, developed several episodes of severe reversible cardiomyopathy after 17 months of imatinib therapy, 3 months of nilotinib therapy, and 10 months of dasatinib therapy. The episodes occurred within 2 weeks after discontinuation of imatinib, 3 weeks after discontinuation of nilotinib, and 4 days after discontinuation of dasatinib. The unique aspects of this case were the multiple episodes that occurred in a single patient, the fulminant onset of symptoms within days after the TKI was stopped, severity that required either ventilatory and/or vasopressor support in all 3 instances, and rapid reversibility. There could have been alternative contributing factors to the transient reduction in left ventricular systolic function, including gram-negative sepsis in the first episode, afterload reduction by nicardipine producing a negative inotropic effect in the second episode, and a stunned myocardium following cardiac arrest in the third episode. Additionally, this unfortunate woman received anthracyclines and was later treated with mitoxantrone. All of these agents are known to result in the cumulative-dose type of cardiotoxicity that results in cell death. The patient then went on to receive TKIs. The recurrence of cardiomyopathy with different TKIs suggests that our patient had some underlying susceptibility, as traditional coronary risk factors—such as old age, male sex, diabetes mellitus, hypertension, dyslipidemia, smoking, and family history of disease—were absent.

The clinical development of TKI therapies has been accompanied by growing awareness of rare but serious cardiac toxicity (Table 1). Kerkelä and colleagues discussed 10 patients who developed significant left ventricular dysfunction during their course of therapy with imatinib.[6] All 10 patients had normal left ventricular function before imatinib therapy but presented after a mean of 7.2 plus/minus 5.4 months of therapy with heart failure, including significant volume overload and symptoms corresponding to New York Heart Association class 3–4 heart failure. Several letters in response

Table 1. Cardiovascular Toxicities in Studies of Tyrosine Kinase Inhibitors

Year	Reference	Number of Patients	Study Type	Methods	TKI Investigated	Results
2002	Barton et al[22]	1	Case report	Echocardiography	Imatinib	Large pericardial effusion with normal LVEF (70%)
2005	Breccia et al[23]	3	Case series	Echocardiography	Imatinib	Pericardial and pleural effusions
2006	Park et al[9]	2	Case series	BNP levels	Imatinib	2 patients experienced an increase in BNP
2006	Kerkelä et al[6]	10	Case series	LVEF; myocardial biopsies	Imatinib	10 patients experienced depressed LVEF
2006	Dasatinib package insert[24]	2,182	Prospective	Cardiac events; CHF	Dasatinib	2% of patients experienced CHF/cardiac dysfunction
2007	Chu et al[25]	75	Retrospective	Cardiac events; CHF	Sunitinib	11% cardiac events; 8% CHF
2007	Atallah et al[26]	1,276	Prospective	CHF symptoms; echocardiography; MUGA	Imatinib	1.8% (22/1,276 patients) had symptoms that could be attributed to systolic heart failure
2007	Rosti et al[7]	833	Prospective	Fatal MI (no signs of LV dysfunction)	Imatinib	3 cases of fatal myocardial infarction (0.4%)
2008	Perik et al[10]	55	Prospective	NT-BNP levels	Imatinib	1 patient showed increase in NT-BNP and CHF symptoms
2008	Ribeiro et al[13]	103	Prospective	BNP levels and LVEF	Imatinib	4 patients showed increased BNP, 1 showed depressed LVEF
2008	Tiribelli et al[14]	49	Prospective	BNP levels	Imatinib	No change in BNP level
2008	Schmidinger et al[20]	86	Prospective	Cardiac events; EKG changes; symptoms	Sunitinib and sorafenib	33.8% cardiac event; 40.5% EKG changes; 18% symptoms

BNP=brain natriuretic peptide; CHF=congestive heart failure; EKG=electrocardiogram; LV=left ventricular; LVEF=left ventricular ejection fraction; MI=myocardial infarction; MUGA=multigated acquisition scan; NT-BNP=N-terminal brain natriuretic peptide; TKI=tyrosine kinase inhibitor.

to this article emphasized that of the 10 patients, 3 had been previously diagnosed with coronary artery disease, 7 had hypertension, and 4 had diabetes; the frequency of other cardiovascular risk factors, such as smoking and hyperlipidemia, was not reported.[7,8] Two case reports discussed by Park and coworkers showed sudden, dramatic, reversible cardiomyopathy after 4 weeks of imatinib in a GIST patient and after 5 weeks of imatinib in a chronic-phase CML patient.[9] Both patients had hypertension and diabetes. Perik and coauthors, however, demonstrated in 55 patients with GIST that imatinib did not increase plasma proBNP levels, and that prospective monitoring of proBNP and cardiac troponins could not identify imatinib-induced cardiotoxicity.[10]

Imatinib is a small-molecule inhibitor of the fusion protein BCR-ABL, an inhibitor of the tyrosine kinase enzyme. It is used widely in the treatment of patients with CML, GIST, Ph+ chromosome ALL, and systemic mastocytosis associated with chronic eosinophilic leukemia, a myeloproliferative variant of idiopathic hypereosinophilic syndrome. It has demonstrated clinical and hematologic response in the last 2 diseases without inducing cardiotoxicity.[11,12] Ribeiro and associates showed that imatinib was not related to systemic deterioration of cardiac function in their study of 103 CML

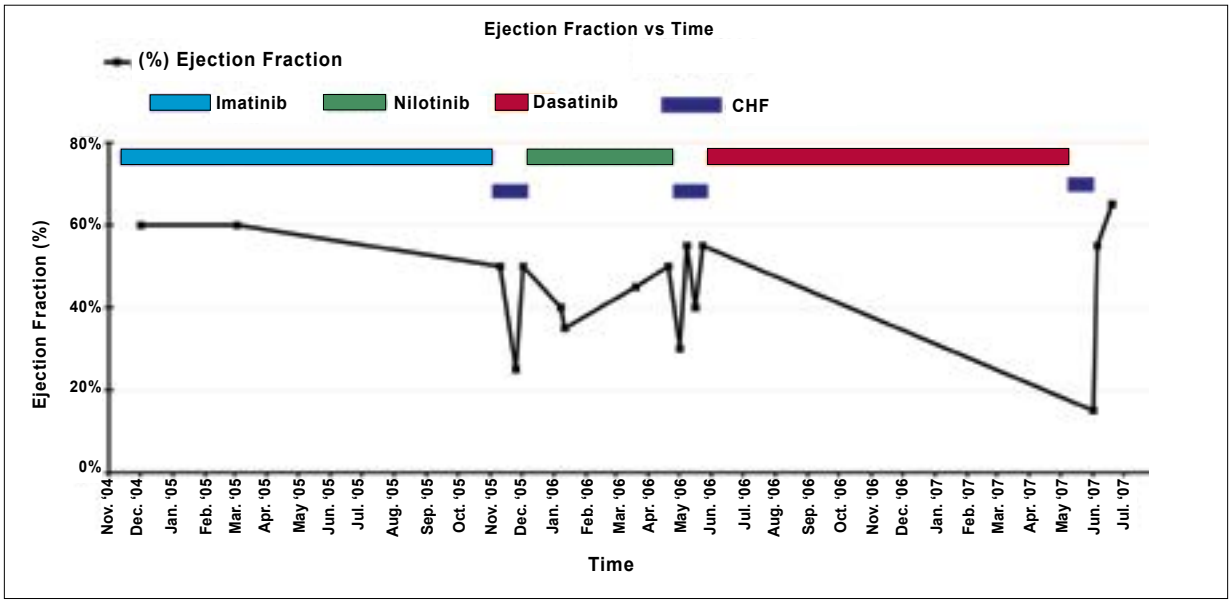

Figure 1. The patient's left ventricular ejection fraction in relation to therapy with the tyrosine kinase inhibitors imatinib, nilotinib, and dasatinib.

CHF=congestive heart failure.

patients.[13] Furthermore, Tiribelli and colleagues also confirmed that there was no evidence of cardiotoxicity in CML patients who were treated with imatinib.[14]

Our patient, unlike the reported cases in the literature, was a Ph+ ALL patient who probably experienced cardiotoxicity induced by multiple TKIs compounded by other clinical factors (cardiotoxins such as anthracycline exposure and/or sepsis). Although the association was most dramatically noted with dasatinib, in retrospect it became clear that the patient's previous episodes of decompensation were likely related to prior imatinib and nilotinib therapy. As seen in other cases, this response was manifested by development of congestive heart failure characterized by a drop in ejection fraction and an increase in BNP indicative of volume and pressure overload (Figure 1).[9,13] However, in sharp contrast to the gradual deterioration seen in most cases, our patient had sudden and severe episodes of cardiac decompensation. The delay between TKI therapy and the onset of cardiac failure in our patient has not been described previously.

Questions arise regarding the relationship between TKI-induced cardiotoxicity and exposure to an anthracycline. In the report by Atallah and colleagues, of the 22 subjects with congestive heart failure, only 3 had prior anthracycline exposure, 12 had received prior interferon therapy, and 18 had pre-existing medical comorbidities predisposing to cardiac disease.[8] Anthracycline cardiotoxicity has been recently reviewed by Gianni and coworkers.[15] Putative mechanisms of anthracycline-mediated cardiotoxicity include not only reactive oxidative species but also mitochondrial DNA damage and acquired dystrophin mutations. Anthracycline toxicity is dose-dependant, with an average incidence of 5.1% at 400 mg/m^2. Limitation of cumulative anthracycline exposure has worked as a strategy in the past; however, this approach has come into question lately in the setting of long-term survivors and in combination with newer therapies. Doses as low as 100 mg/m^2 in childhood cancer survivors increase the risk of reduced fractional shortening and increased afterload.[16,17] The targeted inhibitors, such as the anti-HER2 antibody trastuzumab (Herceptin, Genentech), unexpectedly synergize to cause cardiotoxicity.[18] This activity suggests that trophic stimulation by tyrosine kinase growth factor pathways plays a role in overcoming anthracycline-mediated damage. Inhibition of the tyrosine kinase growth factor pathway may well have played a role in our patient.

Cardiotoxicity seen with imatinib has been studied in vivo and in vitro. Electron microscopy revealed mitochondrial abnormalities and accumulation of membrane whorls in vacuoles and the endoplasmic reticulum, findings that suggest a toxic myopathy.[6] Cardiomyocytes, when treated with imatinib in vitro, have shown activation of the endoplasmic reticulum stress response, activation of the intrinsic pathway of apoptosis, and, subsequently, cell death. Insertion of an imatinib-resistant c-ABL mutant reversed endoplasmic reticulum stress and rescued the cardiomyocytes.[6] The mitochondrial damage with the

BCR-ABL TKIs may be a downstream effect. Direct mitochondrial toxicity assays utilizing the multitargeted TKIs imatinib, dasatinib, sunitinib (Sutent, Pfizer), and sorafenib (Nexavar, Bayer Healthcare) have shown that only sorafenib induced direct mitochondrial dysfunction.[19] Recent reports also stated that cardiotoxicity may be noted in TKIs targeting pathways distinct from BCR-ABL.[20] Schmidinger and associates performed aggressive cardiac monitoring in 86 patients with metastatic renal cell carcinoma treated with sunitinib or sorafenib and found that cardiac dysfunction with these agents was highly underestimated: approximately 34% of patients experienced a cardiac event, 40% had electrocardiogram changes, and 18% were symptomatic.[20]

Clinical trials leading to the development of TKIs have not focused on exhaustive monitoring of cardiac safety, but have relied mostly on symptoms and cardiac events. Cardiac symptoms are unreliable in the oncology setting and are easily confounded by other explanations. Subclinical cardiac dysfunction is probably more prevalent than previously thought. The best way to monitor patients for cardiac dysfunction in the setting of TKI administration is not known. Reversibility was seen in our patient as well as in the larger case series with sunitinib and sorafenib reported by Schmidinger and associates,[20] suggesting that cardiac dysfunction alone need not be an absolute contraindication for the use of such agents.

Conclusion

It is prudent to monitor cardiac function in a patient on treatment with TKIs over the long-term, and it is imperative to act immediately if the patient develops signs or symptoms of heart failure.[13,21] Prior exposure to anthracyclines may increase susceptibility to TKI-mediated cardiotoxicity. It is reassuring that our patient recovered rapidly from all 3 episodes of severe cardiomyopathy with supportive care alone. Our patient's unique history suggests that patients who are susceptible to cardiomyopathy with 1 TKI may be sensitive to others as a "class effect."

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Review

Cardiovascular Toxicities Due to Molecularly Targeted Cancer Therapeutics

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The promise of molecularly targeted cancer therapy is based upon the premise that by specifically inhibiting molecules associated with tumor growth, such therapies will be highly effective in treating cancer without adversely affecting normal organs. This action is in contrast to that of traditional chemotherapeutic agents, such as anthracyclines, which are very effective in the treatment of a number of malignancies, yet often result in a cancer survivor with devastating cardiac disease. Cardiotoxicity associated with anthracycline cancer therapies has been recognized since the 1970s,[1] and the cardiotoxic effects have been extensively studied in both clinical and preclinical settings.[2] Although such studies have been instrumental in the development of management strategies to minimize the cardiotoxic effects of anthracyclines, the dose-dependent, irreversible cytotoxic effects of these drugs on various noncancerous tissues, including the heart, is still a major concern.

Targeted cancer therapies such as tyrosine kinase inhibitors (TKIs) are typically aimed at molecules that are overexpressed in cancer cells,[3] but the fact remains that many such molecules are biologically active in noncancerous tissues and may play a role in the normal physiology of diverse organ systems, including the cardiovascular system. Many drugs currently in development or in clinical trials would be predicted, on theoretical grounds, to lead to cardiotoxicity (Table 1). These drugs are designated as "potentially cardiotoxic" based upon murine loss of function studies using tissue-specific knockout mouse models in which deletion of the indicated target results in cardiac pathology under basal conditions or under stress.

Francis and colleagues report on cardiotoxicity manifesting as reversible, severe cardiac dysfunction in a young woman with acute lymphoblastic leukemia treated sequentially with several small-molecule TKIs.[4] All of the agents in this case study (imatinib [Gleevec, Novartis], nilotinib [Tasigna, Novartis], and dasatinib [Sprycel, Bristol-Myers Squibb]) target the ABL tyrosine kinase, although each agent has inhibitory activity against several other tyrosine kinases as well. Of these agents, imatinib is the most well-studied in regard to cardiovascular effects. Kerkelä and coworkers reported that cardiac dysfunction in a small group of imatinib-treated patients showed compelling mechanistic overlap with toxicity in imatinib-treated mice at clinically relevant dosages.[5] They attributed this toxicity to inhibitory effects on ABL kinase in the heart, which result in activation of the cardiac endoplasmic reticulum stress response. Subsequently, we and others have demonstrated that in patients with gastrointestinal stromal tumor[6] or chronic myelogenous leukemia,[7] clinically significant cardiotoxicity due to imatinib monotherapy is uncommon. However, our study also revealed that hearts from imatinib-treated mice had a substantial reduction in activation of established cardioprotective kinases.[6]

Taken together, the findings from our group and from Kerkelä and coworkers[5] suggest that imatinib may impair aspects of cardiac function that are directly relevant to the adult cardiac response to pathologic stressors. Such mechanistic insights may have significant relevance to the reversible cardiomyopathy due to imatinib and other ABL kinase inhibitors described by Francis and colleagues.[4] Notably, in contrast to the first-line monotherapy approach used in chronic myelogenous leukemia and gastrointestinal stromal tumor, the patient described was aggressively pretreated with multiple cytotoxic chemotherapies, including anthracycline-based chemotherapy and mitoxantrone. Furthermore, the patient developed cardiomyopathy against the background of other superimposed stressors, such as septic shock, cardiac arrest of unclear etiology, and severe mucositis requiring intubation. Thus, it is possible that the implicated TKIs may have contributed to cardiomyopathy in an additive manner in combination with prior anthracycline exposure, impairing the cardiac response to stress in the form of severe, noncardiac illness.

Such a possibility is of considerable relevance as the use of imatinib and other targeted therapies expands and these drugs become part of a combination regimen that includes other cytotoxic chemotherapeutic agents, an approach being explored in newer clinical trials.[8] It is possible that in this setting, imatinib may be associated with a clinically significant cardiotoxicity, an effect not seen to date when imatinib has been used as monotherapy.

Mechanistically, it appears that cardiotoxicity due to TKIs is unlikely to be a generic "class effect," as pro-

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Table 1. Examples of Potentially Cardiotoxic Anticancer Agents Currently Used in Clinical Practice or Under Clinical Investigation

Drugs	Target	Cancer	Cardiac Loss of Function Phenotype
AZD6244 RDEA-119	MEK/ERK 1/2	Leukemia Melanoma Lung	Myocyte apoptosis and heart failure in response to overload stress
Vorinostat Depsipeptide MGCD0103	Class I/II Histone Deacetylases	Lymphoma Myeloma Leukemia Central nervous system	Pathologic hypertrophy and ventricular dilatation in response to overload stress
Perifosine GSK6909693	Akt	Sarcoma Ovarian Central nervous system	Inhibition of physiologic cardiac growth
IMC-A12 CP 751871	IGF-1R	Head/neck Lung	Inhibition of exercise-induced cardiac growth
BEZ235 XL765	PI3K	Metastatic Breast Lung	Dilated cardiomyopathy in response to pressure overload
Lapatinib	ErbB2	Breast Lung	Basal cardiomyopathy with high mortality due to stress

posed by Francis and colleagues[4] and others who have designated such nonanthracycline-related cardiac toxicities as "type II cardiotoxicities."[9] Such a view overlooks the molecular specificity of the individual targeted agents. It is much more likely that the net cardiotoxicity of an individual TKI will be determined by its effects on critical pathways that regulate normal cardiovascular physiology or the cardiovascular stress response. For example, agents whose targets include vascular endothelial growth factor (VEGF) receptor, including the small-molecule inhibitors sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Bayer Healthcare) and the monoclonal antibody bevacizumab (Avastin, Genentech), are all associated with a striking incidence of hypertension, which in some studies has occurred in nearly 50% of patients.[10] The VEGF/VEGF receptor signaling system has been demonstrated in preclinical studies to be an important regulator of systemic vascular tone.[11] Thus, hypertension due to such agents underscores the relevance of this signaling system in the maintenance of normal blood pressure in patients with cancer, and, perhaps, in patients without cancer. Similarly, both sunitinib and sorafenib, whose targets include platelet-derived growth factor receptor (PDGFR), have been reported to lead to clinically significant cardiac dysfunction in subsets of treated patients,[10,12,13] suggesting that PDGFR signaling in the cardiomyocyte may play an important role in the cardiac response to stressors, such as hypertension, that are seen at high frequency with these agents.

Ultimately, precise molecular understanding of the identity and function of targets within the cardiovascular system whose inhibition leads to cardiovascular toxicity associated with novel targeted anticancer therapies will set the stage for the development of strategies to identify patients at high risk of cardiac toxicity due to these agents and to prevent such toxicities. Furthermore, the identity of such targets may be incorporated into future drug development efforts aimed at producing novel, highly effective cancer therapeutics with minimal cardiovascular toxicities. As more patients survive their cancer, the development of new therapies that are effective and have minimal long-term adverse cardiac effects is of the utmost importance.

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