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The Frequency and Severity of Cardiovascular Toxicity From Targeted Therapy in Advanced Renal Cell Carcinoma Patients

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Objectives The purpose of this study was to document the incidence and extent of cardiovascular toxicity among advanced renal cell carcinoma patients treated with newer targeted cancer agents.

Background The potential for targeted cancer agents to induce cardiovascular toxicity has been increasingly recognized, but the overall incidence and extent of toxicity have not been well characterized. Early detection of asymptomatic patients could preempt symptomatic toxicity and reduce treatment-related morbidity and mortality.

Methods The incidence of hypertension, left ventricular dysfunction, and heart failure was assessed for all advanced renal cell carcinoma patients treated with targeted therapies at our institution between 2004 and 2011. Grading was performed according to the Common Terminology Criteria for Adverse Events version 4.0.

Results Cardiovascular toxicity developed in 116 of 159 patients (73%), including 52 of 159 patients (33%) when hypertension was excluded. Toxicity varied from occurrences of asymptomatic drops in left ventricular ejection fraction to rises in N-terminal-pro-B-type natriuretic peptide to severe heart failure. The tyrosine kinase inhibitor sunitinib was the agent most frequently used, with 66 of 101 sunitinib-treated patients (65%) developing a form of cardiovascular toxicity, including 32 of 101 patients (32%), excluding hypertension. Other VEGF inhibitors such as bevacizumab, sorafenib, and pazopanib also elicited significant cardiovascular toxicity with incidences ranging from 51% to 68%.

Conclusions The frequency and severity of cardiovascular toxicity in advanced renal cell carcinoma patients treated with targeted cancer therapies are high. (J Am Coll Cardiol HF 2013;1:72–8) © 2013 by the American College of Cardiology Foundation

Recognition and management of treatment-related cardiovascular toxicity has become tightly integrated with routine cancer care (1,2). The introduction of targeted therapies, which inhibit molecular pathways implicated in oncogenesis and growth, has revolutionized the treatment of many malignancies. However, along with the benefits of disease stabilization, toxicities have been increasingly recognized, particularly cardiovascular toxicities (3).

Renal cell carcinoma (RCC) is one of the malignancies most impacted by the new targeted therapies. Seven agents that target hypoxia-inducible and mammalian target of rapamycin (mTOR) axes have been approved by the U.S. Food and Drug Administration (FDA) in the last 6 years, and more agents are on the horizon. Currently available therapies include the multitargeted tyrosine kinase inhibitors (TKIs) sunitinib, axitinib, sorafenib, and pazopanib; the antibodies to vascular endothelial growth factor (VEGF) such as bevacizumab; and the mTOR inhibitors everolimus and temsirolimus (4). Increasing use of these drugs has led to the recognition of significant cardiovascular adverse events, but the extent of toxicity needs further characterization and definition, particularly in "real-world" patient populations, which include individuals who would not have been eligible for clinical trials.

Of the targeted therapies available for the treatment of RCC, sunitinib has been most frequently associated with cardiovascular toxicity (1,3,5–11). Sunitinib is currently approved for the treatment of RCC, gastrointestinal stromal tumors (GISTs), and pancreatic neuroendocrine tumors and is being investigated in many other malignancies (12–16). The phase III trials leading to FDA approval did not highlight heart failure as a significant adverse event, but subsequent retrospective and prospective studies have since illuminated the significantly elevated risk of heart failure (6,7,16–19).

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The Stanford Cancer Institute maintains a database of records of advanced metastatic RCC patients who have been treated with targeted therapies, including approved and investigational agents. Since 2007, many patients treated with these agents have undergone prospective cardiac monitoring using a regular monitoring protocol. We performed an analysis of our institution's experience to better characterize the incidence and extent of cardiovascular toxicity in RCC patients treated with targeted therapies.

Methods

After Institutional Review Board approval, we identified consecutive patients with advanced RCC treated with targeted therapies from the Stanford RCC database. The targeted therapies included FDA-approved agents such as the TKIs sunitinib, sorafenib, and pazopanib; the VEGF inhibitor bevacizumab; the mTOR inhibitors everolimus and temsirolimus; and other investigational agents. The medical records of these patients were reviewed for clinical, demographic, toxicity, and outcome data. Age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, pre-existing comorbidities, and treatment dates and duration were obtained for each patient. Since the potential for sunitinib-induced cardiotoxicity was recognized in 2007, a TKI monitoring algorithm has been in place in the Stanford genitourinary oncology clinics. This algorithm includes baseline electrocardiography and peritreatment echocardiography, serum levels of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and troponin I. Blood pressure readings were obtained every month during treatment, while LVEF assessments, NT-proBNP levels, and troponin levels were typically obtained every 2 to 3 months while patients were receiving treatment. Development of heart failure symptoms and initiation of any antihypertensive or heart failure medications during treatment were recorded.

For this study, cardiovascular toxicities were characterized and graded using Common Terminology Criteria for Adverse Events version 4.0 (CTCAE version 4.0), which grades adverse events from 1 to 5 according to severity (Table 1) (20). This tool has nearly universal acceptance for defining adverse events in oncologic clinical trials. The adverse events chosen for inclusion in this study included "Heart Failure," "Cardiac Troponin I Increased," "Ejection Fraction Decreased," and "Hypertension." CTCAE defines asymptomatic heart failure (grade 1) as the presence of detectable cardiac imaging or laboratory abnormalities. Imaging abnormalities were defined using "Ejection Fraction Decreased" criteria. Laboratory abnormalities were defined as the on-treatment detection of an abnormally elevated NT-proBNP levels (>300 pg/ml) or an increase by at least 100% of a previously elevated level. Prehypertension (grade 1 hypertension) was not included as an adverse event in this study due to its questionable clinical utility.

In patients who had received two or more therapies, we assessed the treatment-related toxicity with each drug administered. In addition to the overall incidence of adverse events, among all 159 patients, we separately calculated the incidence of treatment-related toxicity for each drug among the subset of patients who received that drug.

Abbreviations and Acronyms

BNP = B-type natriuretic peptide

CTCAE = Common Terminology Criteria for Adverse Events

ECOG = Eastern Cooperative Oncology Group

GIST = gastrointestinal stromal tumor

LVEF = left ventricular ejection fraction

mTOR = mammalian target of rapamycin

RCC = renal cell carcinoma

TKI = tyrosine kinase inhibitor

VEGF = vascular endothelial growth factor

Results

Patient characteristics. Between 2004 and 2011, 159 patients received targeted therapies for metastatic RCC. Baseline characteristics of the patients are listed in Table 2, presented in aggregate and by individual drug administered. Incidence of pre-existing hypertension was relatively high (47%), but only 3% of patients had a history of heart failure. The TKIs were the most commonly used agents (92% of patients received at least one TKI), and sunitinib was the most commonly used therapy (64% of patients).

Frequency of monitoring. Of the 159 patients included, 100% had at least 1 blood pressure recording during treatment, 89 (56%) had at least 1 assessment of LVEF, 90 (57%) had at least 1 NT-proBNP level test, and 98 (62%) had at least 1 troponin I level test. Patients received a mean of 17 blood pressure readings, 2 LVEF assessments, 4 NT-proBNP assessments, and 4 troponin assessments. Among the 89 patients who received at least 1 assessment of LVEF, the average number of LVEF assessments was 3.

Incidence of cardiotoxicity. Across all targeted therapies, 116 of 159 patients (73%) experienced some form of cardiovascular toxicity (Table 3, Fig. 1). Most of these adverse events were related to the development of hypertension or worsening of pre-existing hypertension during treatment. Eighty-five percent of patients required treatment with at least one antihypertensive agent, and 52% of patients required two or more antihypertensive agents. Data regarding the classes of antihypertensive agents used are included in Table 4.

Excluding hypertension as an adverse event, 52 of 159 patients (33%) developed another form of cardiotoxicity, ranging from asymptomatic elevation of NT-proBNP level to severe heart failure. Most events resulted from an asymptomatic drop in LVEF or a rise in NT-pro-BNP. Five patients (3%) developed symptomatic heart failure, with 2 patients (1%) developing high-grade heart failure. Of 38 patients who developed abnormal NT-pro-BNP levels during treatment, 12 also developed decreases in LVEF. Among these patients, 10 developed abnormal values at the same time, while 2 patients had a rise in NT-pro-BNP prior to the decrease in LVEF. Detection of elevated troponin occurred in only 4 of 159 patients (3%) and was only once associated with symptoms.

Of the 23 patients with a drop in LVEF, 19 patients received standard heart failure therapy (beta-blockers and

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Table 1 Definitions of Adverse Events

Heart Failure
Grade 1: Asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities
Grade 2: Symptoms with mild to moderate exertion
Grade 3: Severe with symptoms at rest or with minimal activity or exertion, intervention indicated
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Grade 5: Death
Ejection Fraction Decreased
Grade 1: Not defined
Grade 2: Resting EF 50%–40%; 10%–19% drop from baseline
Grade 3: Resting EF 39%–20%; >20% drop from baseline
Grade 4: Resting EF <20%
Cardiac Troponin I Increased
Grade 1: Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer
Grade 2: Not defined
Grade 3: Levels consistent with myocardial infarction as defined by the manufacturer
Grade 4: Not defined
Hypertension
Grade 1: Pre-hypertension (systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg)
Grade 2: Stage 1 hypertension (systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg); medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated
Grade 3: Stage 2 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg); medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated
Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Grade 5: Death

Adapted from CTCAE version 4.0 (20).
BNP = B-type natriuretic peptide; BP = blood pressure; EF = ejection fraction; IV = intravenous; WNL = within normal limits.

angiotensin-converting enzyme inhibitors or angiotensin receptor blocker agents). Nine of these 19 patients experienced improvements in subsequent LVEF assessments, 6 had no change in subsequent LVEF, and 4 had no further LVEF assessments performed. Of the remaining 4 patients, 2 experienced LVEF improvements with cessation of the targeted cancer therapy alone, and 2 had no further reassessments due to entering hospice for end-stage malignancy.

The TKI sunitinib was the agent most frequently used, with 66 of 101 sunitinib-treated patients (65%) developing a form of cardiovascular toxicity, including 32 of 101 patients (32%) when hypertension was excluded as a toxicity. The other TKIs (sorafenib and pazopanib) and the VEGF inhibitor bevacizumab also elicited similar incidences of cardiovascular toxicity ranging from 51% to 68%.

The subsets of patients who received mTOR inhibitors also developed frequent cardiovascular adverse events during treatment. Of the patients treated with everolimus, 17% developed grade 1 heart failure, and 24% of the patients treated with temsirolimus developed grade 3 hypertension during treatment.

Discussion

Among the targeted therapies, nonhypertensive cardiovascular toxicity has been most widely documented with sunitinib (1,3,5–11). First detailed in 2007, a review of a phase

Table 2 Baseline Characteristics

	All Therapies	Sunitinib	Sorafenib	Pazopanib	Bevacizumab	Everolimus	Temsirolimus
Patients (n)	159	101	73	43	31	24	17
Age (yrs)	60.8	59.2	62.9	62.7	61.0	60.5	58.4
Men	122 (77%)	78 (77%)	60 (82%)	34 (79%)	24 (77%)	20 (83%)	16 (94%)
Women	37 (23%)	23 (23%)	13 (18%)	9 (21%)	7 (23%)	4 (17%)	1 (6%)
ECOG performance status	1	1	1	1	1	1	1
Heart Failure	5 (3%)	2 (2%)	3 (4%)	1 (2%)	0 (0%)	1 (4%)	0 (0%)
Hypertension	74 (47%)	44 (44%)	38 (52%)	21 (49%)	16 (52%)	12 (50%)	6 (35%)
Coronary artery disease	10 (6%)	9 (9%)	4 (5%)	1 (2%)	1 (3%)	2 (8%)	0 (0%)
Diabetes mellitus	19 (12%)	14 (14%)	10 (14%)	7 (16%)	3 (10%)	2 (8%)	2 (12%)
Hyperlipidemia	38 (24%)	25 (25%)	19 (26%)	16 (37%)	6 (19%)	10 (42%)	2 (12%)
Atrial fibrillation	6 (4%)	1 (1%)	3 (4%)	2 (5%)	3 (10%)	1 (4%)	1 (6%)
Previous stroke or TIA	3 (2%)	1 (1%)	2 (3%)	0 (0%)	0 (0%)	1 (4%)	1 (6%)
Additional malignancy	5 (3%)	4 (4%)	1 (1%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)

Note: patients who received multiple therapies in succession are counted only once in "All Therapies."
ECOG = Eastern Cooperative Oncology Group; TIA = transient ischemic attack.

Table 3 Results

	All Therapies	Sunitinib	Sorafenib	Pazopanib	Bevacizumab	Everolimus	Temsirolimus
Patients (n)	159	101	73	43	31	24	17
Any toxicity	116 (73%)	66 (65%)	50 (68%)	22 (51%)	21 (68%)	8 (33%)	6 (38%)
Any toxicity, excluding hypertension	52 (33%)	32 (32%)	15 (21%)	13 (30%)	7 (23%)	4 (17%)	3 (18%)
Abnormal NT-proBNP	38 (24%)	25 (25%)	11 (15%)	11 (26%)	5 (16%)	4 (17%)	1 (6%)
Grade 1 heart failure	43 (27%)	28 (28%)	13 (18%)	11 (26%)	6 (19%)	4 (17%)	2 (12%)
Grade 2 heart failure	5 (3%)	3 (3%)	1 (1%)	1 (2%)	1 (3%)	0 (0%)	0 (0%)
Grade 3 heart failure	2 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
Grade 2 EF decreased	16 (10%)	10 (10%)	3 (4%)	3 (7%)	2 (6%)	0 (0%)	1 (6%)
Grade 3 EF decreased	6 (4%)	4 (4%)	0 (0%)	0 (0%)	2 (6%)	1 (4%)	1 (6%)
Grade 4 EF decreased	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 2 hypertension	37 (23%)	16 (16%)	16 (22%)	4 (9%)	7 (23%)	3 (13%)	1 (6%)
Grade 3 hypertension	66 (42%)	37 (37%)	26 (36%)	12 (28%)	8 (26%)	2 (8%)	4 (24%)
Grade 4 hypertension	2 (1%)	0 (0%)	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Grade 1 elevated troponin	4 (3%)	1 (1%)	1 (1%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)

Note: patients who received multiple therapies in succession are counted only once in "All Therapies." Because some patients received multiple agents, rates of toxicity for "All Therapies" may be higher than for any individual agent.

Abbreviations as in Table 1.

I/II clinical trial of sunitinib in GIST patients identified adverse cardiac events in 8 of 75 patients (11%), with heart failure accounting for six of the eight events (7). A subsequent case series of patients treated with sunitinib identified 6 of 224 patients (2.7%) who developed significant cardiomyopathy, necessitating treatment in 5 patients (9). In RCC, a prospective cohort study of 86 patients treated with sunitinib and sorafenib observed that 33.8% of patients developed significant cardiotoxicity (6). At our institution, a review of the first 48 RCC and GIST patients treated with sunitinib found that 7 patients (15%) developed symptomatic heart failure (10). A meta-analysis found that of 6,935 patients treated with sunitinib for RCC and non-RCC cancers, 4.1% of patients developed heart failure (relative risk [RR]: 1.81, compared to those not treated with sunitinib) and 1.5% of patients developed high-grade heart failure (RR: 3.3) (8). The variability in these reported incidences may reflect differences in defining toxicities (with

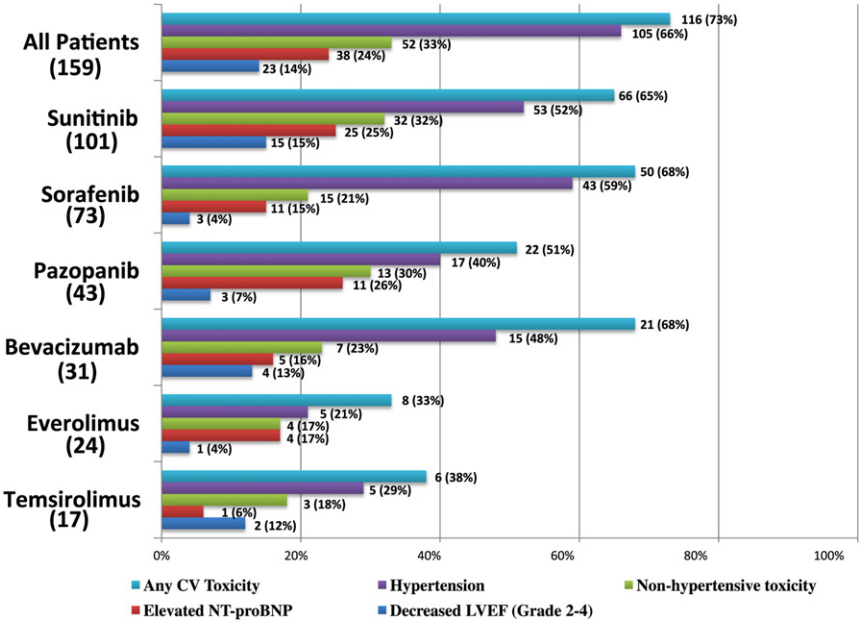

Figure 1 Incidence of Cardiovascular Toxicity by Type

The incidence of cardiovascular toxicity varied by type of toxicity and by chemotherapy agent received. Many patients received multiple therapies in succession and are included only once in "All Patients." CV = cardiovascular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal B-type natriuretic peptide.

Table 4 Cardiac Medications Before/During Cancer Therapy

	Beta-blockers	ACEI/ARB	CCB	Diuretics
Pre-treatment	22%	26%	14%	19%
Initiation or dose increase with treatment	24%	25%	47%	14%

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker.

some overlap present even within CTCAE itself) (Table 1) (19,20). Until our analysis, the incidence of asymptomatic cardiovascular toxicity has not been reported.

In addition to its widely recognized association with hypertension, bevacizumab has been increasingly associated with nonhypertensive cardiotoxicity as well. A recent meta-analysis of 3,784 patients with breast cancer treated with bevacizumab found a 1.6% incidence of high-grade heart failure compared with placebo, with an RR value of 4.74 (21). That analysis did not identify the incidence of asymptomatic toxicity.

The biochemical mechanism of cardiotoxicity caused by targeted therapies is not completely understood but is likely partially related to the therapies' inhibition of the VEGF pathway, the platelet-derived growth factor receptor pathway, and the KIT pathway (3,11,22,23). Proposed mechanisms include impairment of myocyte contractility, decreased mitochondrial function, and dysregulation of vascular endothelial signaling (3,11,23). With broader inhibition of tyrosine kinases, patients are increasingly prone to encounter off-target side-effects (23). This concept may explain why sunitinib, a very potent agent with activity against a broad array of tyrosine kinases, appears to have more significant cardiovascular adverse events (excluding hypertension) than sorafenib, which antagonizes fewer tyrosine kinases, and bevacizumab, which predominantly blocks only the VEGF ligand (24,25).

Development of hypertension during treatment with targeted therapies has been associated with response to therapy. A retrospective analysis of patients with RCC treated with sunitinib demonstrated that patients who developed hypertension during treatment had better response rates and progression-free survival than patients who did not develop hypertension (26). To our knowledge, the relationship between the development of nonhypertensive cardiovascular toxicity and response to treatment has not yet been studied and will be the subject of further investigation of our data.

In our analysis, we found a strikingly high number of patients with cardiovascular toxicity, 73% overall, but still 33% when the widely recognized side effect of hypertension was excluded. Although sunitinib has been the TKI most associated with toxicity, we found a similar incidence of adverse events with bevacizumab, sorafenib, and pazopanib.

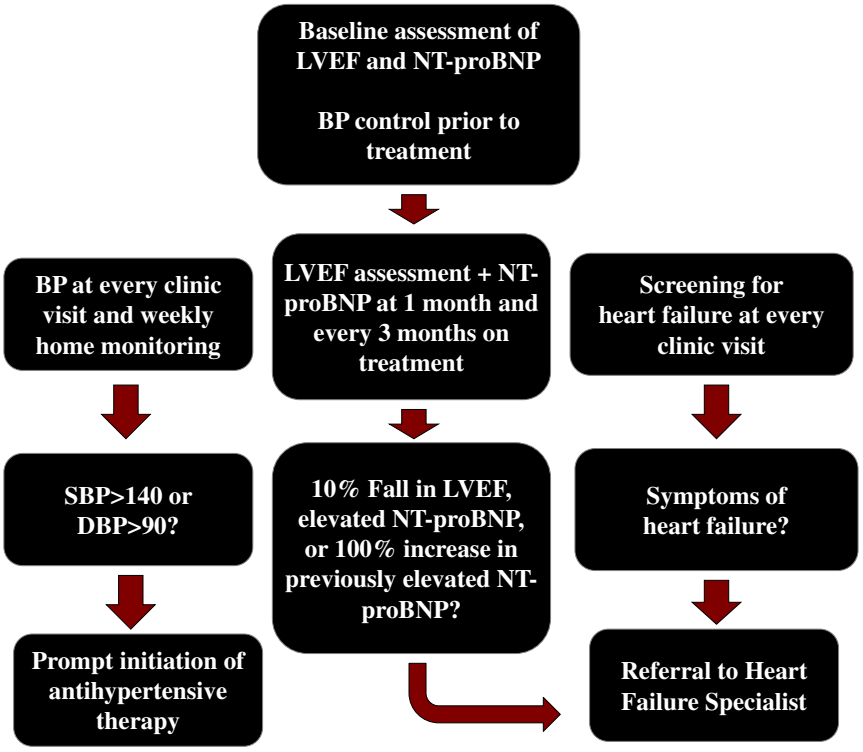

Figure 2 The Stanford Monitoring Algorithm for Targeted Therapies

Cardiovascular monitoring algorithm for patients with renal cell carcinoma receiving targeted chemotherapy. BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Figure 1.

Our data reflect the frequency and characteristics of cardiotoxicity among real-world patients receiving TKIs and other targeted therapies. Although the incidence of symptomatic heart failure was similar to that of the recent meta-analysis, we found a very high rate of asymptomatic cardiotoxicity, which often allowed for a timely referral to a heart failure specialist. According to current guidelines, asymptomatic left ventricular dysfunction is considered stage B heart failure and is an indication to begin medical therapy with beta blockers and inhibitors of the renin-angiotensin system (27,28). In our study, asymptomatic cardiotoxicity, as defined by an elevated NT-proBNP level and/or a decrease in systolic function as estimated by LVEF, was identified in 43 patients (27%). Given their asymptomatic status, these patients would likely not have been identified without screening.

Data suggest that a monitoring algorithm could be an important tool to identify patients with early toxicity, much like that used for the anti-Her2 therapeutic agent trastuzumab, for which LVEF assessment every 3 months is considered standard of care (27,29). We have discontinued troponin monitoring from our routine protocol due to the low incidence of troponin elevation in our patients uncovered by this analysis.

Study limitations. Our data are potentially limited by incompleteness. While our clinicians do have a monitoring algorithm in place, it has not been subject to the rigors of an established surveillance protocol; as such, some patients did not have NT-proBNP levels monitored or echocardiography tests during treatment. The net result of the lack of universal screening may therefore be an even higher incidence of toxicity than we reported. Similarly, detection of symptomatic heart failure was based on the documentation of symptoms in clinic notes. Before cardiac toxicity associated with these agents was recognized, many providers did not ask specifically about heart failure symptoms. Symptomatic patients may have gone undetected, particularly given the fact that heart failure symptoms are often nonspecific and can be confused with noncardiac chemotherapy side effects or symptoms from the malignancy itself (28). Additionally, while asymptomatic elevation of NT-proBNP levels is defined as grade 1 heart failure by CTCAE guidelines, the clinical significance of this finding is unclear (20). This patient cohort may have been more likely to experience adverse cardiac events than a cohort with lower rates of pre-existing hypertension.

Future investigations will be directed at evaluating the reversibility of targeted therapy-induced cardiotoxicity and characterizing the temporal relationship between treatment and development of toxicity. In addition, comparative analysis of the potential association with development of cardiotoxicity and improved tumor response/outcome may provide important prognostic information.

Conclusions

In summary, we found a strikingly high rate of cardiovascular toxicity among patients treated with targeted cancer therapies, much of which was clinically silent. Accordingly, we propose guidelines (Fig. 2) for monitoring therapy in this population to potentially improve detection and guide treatment.

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Key Words: chemotherapy ■ heart failure ■ hypertension ■ tyrosine kinase inhibitor.