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REVIEW ARTICLE

Cardiotoxicity induced by tyrosine kinase inhibitors

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Abstract

Background. Cardiotoxicity is a serious side effect of drugs used to treat cancer patients. Older chemotherapy drugs such as the anthracyclins and new targeted therapies, mainly trastuzumab, have been implicated in causing clinically significant cardiac dysfunction, which may be irreversible for many patients. The advent of a new category of drugs, the tyrosine kinase inhibitors has revolutionized the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and renal cancer, while their indications include a variety of other types of tumors. *Methods*. Assessment of the incidence and severity of cardiac toxicity caused by the tyrosine kinase inhibitors and discussion on the molecular mechanisms and mode of diagnosis based on recent clinical trials. Review of related literature. *Results*. Cardiac toxicity can be caused by the tyrosine kinase inhibitors imatinib mesylate, dasatinib, nilotinib, sunitinib, sorafenib and lapatinib, while gefitinib and erlotinib have not been related to toxic effect on the heart. Although targeted therapies are considered less toxic and better tolerated by patients compared with classic chemotherapy drugs, certain complications can be very serious and as these agents have been in use for a limited period of time, the exact profile of side effects will be better defined in the years to come. Cardiac toxicity may range from asymptomatic subclinical abnormalities such as electrocardiographic changes and left ventricular ejection fraction decline to life threatening events like congestive heart failure and acute coronary syndromes. For patients with severe side effects, discontinuation of treatment is warranted. *Conclusions*. Careful cardiac monitoring and assessment by a cardiologist throughout the course of treatment with those TKIs that exert cardiac toxic effect is of primary importance.

Abbreviations: Bcr-Abl, Fusion gene and corresponding protein in the Philadelphia chromosome, c-Kit, CD117, the stem cell factor receptor, PDGFR, Platelet Derived Growth Factor Receptor, Src, Sarcoma family of receptors, RET, REarranged during Transfection Gene, FLT3, FMS related tyrosine kinase 3, CSF1R, Colony Stimulating Factor 1 Receptor, VEGFR, Vascular Endothelial Growth Factor Receptor, RAF1, BRAF, Proto oncogenes serine threonine protein kinases, EGFR, Epidermal Growth Factor Receptor, ERB B2, ERythroBlastic leukemia viral oncogene homolog 2, CML, Chronic Myelogenous Leukemia, B-ALL, B-Acute Lymphoblastic Leukemia, GIST, GastroIntestinal Stromal Tumors, CMML, Chronic MyeloMonocytic Leukemia, CEL, Chronic Eosinophilic Leukemia, DFSP, DermatoFibroSarcoma Protuberans, RCC, Renal Cell Carcinoma, HCC, HepatoCellular Carcinoma, NSCLC, Non-Small Cell Lung Cancer, CHF, Congestive Heart Failure, LVEF, Left Ventricular Ejection Fraction, MI, Myocardial Infarction

Tyrosine kinases (TKs) are proteins whose activation leads to phosphorylation of key substrates within the cell. There are two groups of tyrosine kinases: transmembrane protein receptors, receptor protein kinases (RTKs) and intracellular signal transducers, non-receptor tyrosine kinases (NRTKs) [1]. When these proteins are mutated or overexpressed, their activation may lead to increased proliferation, angiogenesis and inhibition of apoptosis thus giving the cell the malignant phenotype.

Tyrosine kinase inhibitors (TKIs) are small molecules that interfere with the kinase activity. They have very high affinity to the Adenosine Triphosphate (ATP) binding pocket of the TKs and they act by inhibiting the transfer of a phosphate group from ATP to a tyrosine residue. TKIs inhibit TKs in cancerous and non-cancerous cells [2]. Their action on normal tissues explains their side effects; the most common side effects include diarrhea and rash. Although cardiac toxicity is less common, it

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is more serious and difficult to diagnose at early stages.

Cardiac toxic effects of TKIs range from asymptomatic QT prolongation to reduction in left ventricular ejection fraction (LVEF), symptomatic congestive heart failure (CHF), acute coronary syndromes and myocardial infarction (MI). Hypertension and sudden death have also been associated with treatment with these agents. Not all TKIs exert the same toxicity on the heart muscle, indicating that this is not a class toxic effect. The level of expression of certain TKs in the cardiomyocytes does not correlate with the toxicity induced by their corresponding inhibitors; rather the function of the specific TK when inhibited constitutes the determining factor. The rates of cardiotoxicity are not actually known since their detection is not included in most clinical trials. One common side effect, peripheral oedema, the incidence of which was as high as 66% [3], in one trial could, although unlikely, be an indicator of cardiac dysfunction; still difficult to prove, as measurements of left ventricular function were not undertaken. Symptoms like fatigue and dyspnoea could be attributed to heart failure as well as to the disease itself. Although the mode of action and toxicity profile with the use of these drugs is under clinical investigation, structural reengineering of their molecules is promising safety with preserved or even improved efficacy. One example of reengineered molecule is WBZ_4, a methylated variant of imatinib (see below).

Imatinib mesylate

Imatinib mesylate targets Bcr-Abl (the fusion protein encoded by the Philadelphia chromosome), c-Kit (the stem cell factor receptor) and PDGF (platelet-derived growth factor) α and β receptors. It is the drug of choice for the treatment of Chronic Myelogenous Leukemia (CML), while the same target, Bcr-Abl, makes it active in Ph+ B-Acute Lymphoblastic Leukemia (B-ALL). It also indicated as first line and in the adjuvant setting, in Gastrointestinal Stromal Tumors (GIST) by means of inhibition of c-kit receptor. Inhibition of PDGF receptors makes imatinib active in Chronic Myelomonocytic Leukemia (CMML), Chronic Eosinophilic Leukemia (CEL) and Dermatofibrosarcoma Protuberans (DFSP).

Known side effects of imatinib treatment include peripheral oedema, shortness of breath and fatigue. These symptoms may indicate a degree of left ventricular dysfunction, they may be attributed to the underlying disease but it is most likely that they constitute non-specific, non-cardiac side effects of the drug.

It has been reported that individuals treated with imatinib developed severe CHF due to myocyte contractile dysfunction [4]. All patients had their left ventricular ejection fraction (LVEF) calculated by radionuclide imaging before the onset of treatment and after they developed symptoms of heart failure. LVEF had dropped by 25±8% compared to its pretreatment value (Table I). The authors performed myocardial biopsies on two of ten patients who developed CHF and the biopsies showed prominent membrane whorls in the myocytes. This finding is characteristic of toxin-induced myopathies [5], as well as pleomorphic mitochondria with effaced cristae, scattered cytosolic lipid droplets and vacuoles and glycogen accumulation. Cultured cardiomyocytes showed activation of the endoplasmic reticulum stress response, collapse of the mitochondrial membrane potential, release of cytochrome c in the cytosol, reduction in cellular ATP and cell death. Although there was evidence of classical apoptosis with positive terminal deoxynucleotidyl transferase biotin-dUTP nickend labeling (TUNEL) staining [6], there were also morphological features of necrotic death. This may be partly explained by the fact

Table I. Comprehensive presentation of the tyrosine kinase inhibitors on clinical use, their targets, indications and type of cardiac toxicity.

Agent	Tyrosine kinase targets	Indications	Type of cardiac toxicity
Imatinib mesylate	Bcr-Abl, c-kit, PDGFR-α and β	CML, Ph+ALL, GIST, CMML, CEL, DFSP	CHF, LVEF depression
Dasatinib	Bcr-Abl, c-kit, PDGFR-α and β, Src Family	CML	QT prolongation, Peripheral oedema, pericardial effusion
Nilotinib	Bcr-Abl, c-kit, PDGFR-α and β	CML	QT prolongation
Sunitinib	VEGFR 1-3, RET, PDGFR-α and β, c-kit, FLT3, CSF1R	RCC, GIST	Hypertension, LVEF depression, CHF, MI
Sorafenib	VEGFR 2&3, c-kit, PDGFR β, FLT3, RAF1, BRAF	RCC, HCC	Acute coronary syndrome, MI, Hypertension
Lapatinib	EGFR, ERBB2	Breast Ca	Asymptomatic LVEF depression
Gefitinib	EGFR	NSCLC	
Erlotinib	EGFR	NSCLC, Ca pancreas	

that the ATP concentration dropped by ~65%; since apoptosis is a process that requires energy [7], when the ATP concentrations are very low, cell injury is followed by the necrotic death process rather than the apoptotic route. Imatinib treatment also led to a marked increase in the expression of protein kinase Cδ (PKCδ), a kinase with proapoptotic effect in the heart [8].

Some investigators question the existence of imatinib induced cardiac toxicity. In 55 patients with GIST under treatment with imatinib, assessments of serial plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) and cardiac troponin T (cTnT) in plasma were undertaken. NT-proBNP is a prohormone of BNP secreted by cardiomyocytes in response to ventricular dilation or local wall stress and is considered a sensitive marker to detect left ventricular systolic dysfunction. Only one patient with normal pre-treatment NT-proBNP showed an increase above normal after three months and clinically developed New York Heart Association (NYHA) class II heart failure five months after the patient commencement of the treatment. It should be noted that the patient had pre-existing asymptomatic mitral valve regurgitation. cTnT levels remained normal for all patients. The authors of the report suggest that only patients with a history of cardiac disease should have standard cardiac monitoring [9].

In a series of 103 patients with CML treated with imatinib [10] and 57 patients with CML not treated with imatinib, no statistical difference was observed between the two groups regarding cardiac symptoms and signs, BNP levels, and echocardiographic measurements. However, peripheral oedema was more frequent in the group that received imatinib. Four of these patients had a BNP level >100 pg/ml, one of them with depressed LVEF but overall there was no systematic deterioration of cardiac function. Another recent study disputed the possibility of cardiotoxicity from imatinib by measuring the BNP levels and finding no evidence of cardiotoxicity of imatinib therapy [11]. Similarly, in the largest study performed so far, in 946 patients with GIST, in all but two patients a possible cardiotoxic effect of imatinib could be fully excluded [12]. Cardiovascular assessment was based on physical examination and chest x-ray only, which by no means can be considered optimal for cardiovascular risk evaluation. In the IRIS trial [13] that compared interferon to imatinib in patients with CML, the overall incidence of grade 3 or 4 oedema was less than 1% with no difference between the two arms. No standard cardiac monitoring has been reported in this trial.

Although there are conflicting results from different studies regarding the cardiotoxicity of imatinib, it seems that observed pathologic changes do not necessarily translate into clinically significant cardiac toxicity. Clinical trials that will prospectively follow patients on imatinib will be able to identify those patients who are more susceptible to develop a cardiac toxic effect and take the appropriate measures to protect them. Also, long-term observation is needed, since most of these patients will have to be treated for months or years and in this case the toxicity profile may be different.

The role of ABL in cardiomyocytes is not clear. It mediates oxidant stress-induced death in fibroblasts but is protective in osteoclasts [14]. If it protects cardiomyocytes from oxidant stress, then its inhibition by imatinib explains its toxic effect. Recently, a modification to the molecule of imatinib to include an additional target, JNK, led to significant reduction of cardiotoxicity without any negative effect in the drug's potency [15]. This reengineered molecule, WBZ_4 is a methylated variant of imatinib. It has been tested on animal models and found to be as effective as imatinib without affecting the heart. It has been found that JNK activation may be responsible for the cardiac toxicity observed with imatinib and inhibition of the JNK pathway markedly reduces the collapse of the mitochondrial membrane potential and cell death [16].

Dasatinib and Nilotinib

Dasatinib is a TKI against Bcr-Abl, cKit, PDGFR-α and β and the Src family of kinases. It is 300-fold more potent than imatinib *in vitro* [17] and is currently indicated for treatment of CML and Ph+ ALL after imatinib failure. Although clinical trials report high rates of peripheral oedema [18], only a 2% incidence of congestive heart failure as well as arrhythmias (including tachycardia) has been associated with Dasatinib treatment (Table I). Isolated cases with asymptomatic QT prolongation and pericardial effusion have also been reported [19].

Nilotinib is an inhibitor of Bcr-Abl, c-Kit and PDGFRα and β receptors. It is 30-fold more potent than imatinib *in vitro*, has a favorable toxicity profile and studies have proven its activity when given as second line treatment in patients with CML initially treated with imatinib, while its efficacy in front line treatment of CML is currently under investigation [20]. Except for QT prolongation on ECG, no other cardiac event has been reported.

Sunitinib

Sunitinib is a multitargeted TKI against VEGFR (vascular endothelial growth factor receptors) 1-3, c-Kit, PDGFR α and β, RET (rearranged during

transfection), FLT3 (FMS related tyrosine kinase 3) and CSF1R (colony stimulating factor 1 receptor). It is the standard of care for first line treatment of renal cell cancer and it has also been approved as second line treatment for patients with GIST who failed treatment with imatinib. Concerns have been raised about the drug's cardiac safety since a considerable proportion of patients treated with sunitinib develop hypertension, left ventricular dysfunction and other cardiac events (Table I).

Early trials did not demonstrate any adverse cardiac events [21] however the follow up period was too short and more recent trials have shown that it may take more than 6 months for cardiac toxicity to develop. In a large phase III trial that compared sunitinib to interferon treatment in patients with previously untreated metastatic renal cell cancer [22], 10% of patients in the sunitinib arm had a LVEF decline. Cardiac safety in this study was assessed at regular intervals by multigated acquisition scanning. However, this was not associated with clinical sequelae and was reversible after a modification of the dose or discontinuation of treatment. In a prospective study of patients with metastatic, imatinib resistant GIST [23], 47% of the patients developed hypertension (systolic BP >150 mmHg and/or diastolic BP >100 mmHg), 20% had a LVEF reduction to less than 50%, 8% developed congestive heart failure (CHF) and two patients had myocardial infarction (MI), and which proved fatal for one patient. Cardiac surveillance included serial assessment of LVEF by radionuclide ventriculography before treatment and in each treatment cycle as well as blood pressure and troponin I measurements every week. The high incidence of cardiac adverse events in this study, as opposed to the previous studies mentioned, was attributed to the fact that the population under investigation was unselected and many of the patients either had a history of cardiac disease and hypertension or were treated with potentially cardiotoxic drugs in the past (imatinib and anthracyclins). The median time to a cardiovascular event was 30.5 weeks, a finding that denotes that even in patients with considerable risk factors it may take months after initiation of sunitinib therapy for cardiac toxicity to develop and that these patients need close, long-term follow-up observation by a cardiologist. Discontinuation or dose modification, even in patients with CHF, led to improvement of left ventricular function. Most of these patients were prescribed sunitinib again without recurrence of CHF but with episodic LVEF reductions. Endomyocardial biopsies were obtained from two patients that showed cardiomyocyte hypertrophy, swollen mitochondria with effaced cristae and membrane whorls while no inflammation, oedema or fibrosis was seen. In cultured cardiomyocytes, cytochrome C was released into the cytosol and activation of caspase-9 led to cell death via the necrotic and apoptotic route respectively. These microscopic findings were similar to the ones observed after treatment with imatinib (membrane whorls in the myocytes, pleomorphic mitochondria with effaced cristae) as previously described. Troponin I was also monitored and was found moderately increased in 18% of patients.

Sunitinib possibly exerts its cardiotoxicity through the inhibition of the PDGF receptors. It is well known that PDGFRs are expressed in cardiomyocytes and overexpression of PDGF can signal cardiomyocyte survival [24]. Inhibiting these receptors may promote apoptosis. Inhibition of VEGFRs may explain the high rates of hypertension (as discussed later with sorefenib).

In one retrospective study, only 2.7% of patients with metastatic renal cancer and imatinib resistant GIST, developed heart failure which occurred soon after initiation of sunitinib (mean onset 22 days after initiation). This was associated with decline in cardiac function and elevation in blood pressure, and was not completely reversible in most patients, even after termination of sunitinib therapy [25]. A similar study identified 15% of patients with symptomatic heart failure, which developed 22 to 435 days after initiation of sunitinib. Factors associated with increased risk were history of congestive heart failure, coronary artery disease and lower body mass index [26]. Researchers from the Netherlands have recently reported their experience with the use of sunitinib in 82 unselected patients (included all subtypes of renal cell cancer and patients with brain metastases) with advanced renal cancer. Nineteen (23%) patients developed hypertension and one patient experienced a transient ischaemic attack [27].

Cardiac toxicity induced by sunitinib is now a well recognised side effect leading to considerable morbidity. Conflicting results in different studies may reflect differences in the selection of patients but what has become clear is that physicians treating patients with sunitinib must be very careful, especially in those patients with preexisting risk factors for the development of cardiotoxicity like hypertension, history of cardiac disease or previous treatment with other cardiotoxic agents.

Sorafenib

Sorafenib is another multitargeted TKI against VEGFR 2&3, PDGFR β, c-Kit, FLT3, RAF1 and BRAF. Its current indications are the second line

treatment of renal cell cancer and hepatocellular carcinoma.

Sorafenib is known to induce acute coronary symptoms including myocardial infarction in 2.9% of patients [28]. In four phase I trials, related hypertension was observed in 5–11% of the treated patients [29] while in another study hypertension was reported in 17% of the patients [30] (Table I). Sorafenib is often given after sunitinib therapy which as mentioned earlier can be cardiotoxic. A retrospective analysis of 68 patients [31] treated with sorafenib following sunitinib treatment did not reveal increased cardiotoxicity rates. In contrast to the previous studies there is a report of three patients who developed adverse cardiac events: two of the patients experienced chest pain and ECG signs of myocardial ischemia (coronary T in precordial leads) without elevation of cardiac enzymes or LVEF depression, and the third patient experienced atrial fibrillation. ECG were performed in all patients before treatment, while ECG and LVEF measurements were undertaken after the development of symptoms. All adverse events were easily managed. The authors attributed the observed toxicity to the short interval between discontinuation of sunitinib and the administration of sorafenib that ranged between 12–22 days [32].

In an observational study from Austria, among 74 patients with metastatic renal cell carcinoma treated with either sorafenib or sunitinib, 33.8% experienced a cardiac event that was defined as the occurrence of increased enzymes if normal at baseline, symptomatic arrhythmia that required treatment, new left ventricular dysfunction, or acute coronary syndrome. Patients were assessed with ECG and the cardiac enzymes CK-MB and Troponin T while echocardiogram was performed in selected patients at baseline and in all those who experienced a cardiac event. All patients eventually recovered after appropriate cardiovascular management and were considered eligible for continuation of treatment with TKIs [33].

The safety and efficacy of this agent in patients with metastatic non-small cell lung cancer was evaluated in a phase II trial that recruited 54 patients. Grade 3 hypertension occurred in 4% of patients and myocardial infarction in one (2%) patient [34].

The inhibition of RAF1 possibly explains the toxicity observed with sorafenib. RAF1 is a member of the RAF family of intracellular signal transducing kinases. It inhibits two proapoptotic kinases, ASK1 and MST2 which are important in oxidant stress-induced injury [35]. Deletion of RAF1 gene in the heart led to a dilated, hypocontractile heart with increased cardiomyocyte apoptosis [36]. The protection provided by RAF1 may be important only in the presence of stress. The occurrence of hypertension, which imposes a pressure load on the heart, can be attributed to the inhibition of VEGF receptors. Indeed, the disruption of VEGF-VEGFR signaling through the inhibition of circulating VEGF by the monoclonal antibody bevacizumab, leads to hypertension in a considerable number of patients treated with this drug. It seems that reduction of capillary permeability causes increased pressure load, leading to hypertrophy of the heart and subsequently congestive heart failure [37]. Inhibition of PDGFRs may also add to its cardiac toxicity (as happens with sunitinib).

Rates of cardiotoxicity with sorafenib may not be very high but can be severe and life threatening in some patients. It is important to be able to identify these patients and current large trials are assessing this issue.

Lapatinib

Lapatinib is an orally administered quinazoline that targets EGFR and ERBB2. In a recent large randomized trial it has shown activity against metastatic breast cancer when combined with chemotherapy. In this study the only adverse cardiac event reported was a 2.5% asymptomatic decrease in LVEF (Table I). Evaluation of the LVEF by echocardiography or multiple gated acquisition (MUGA) scanning was performed before the onset of treatment and at the time of the efficacy assessments with the use of the same technique. A cardiac event was defined as a decline in the LVEF that was symptomatic, regardless of the degree of decline or was asymptomatic but with a relative decrease of 20% or more from baseline to a level below the institution's lower limit of the normal range. Lapatinib was discontinued in patients with symptomatic cardiac events (CTCAE grade 3 or 4); in asymptomatic patients it was withheld and could be resumed at a dose of 1 000 mg per day if the LVEF 2 to 3 weeks later was at or above the institution's lower limit of the normal range [38]. In another phase I study evaluating the safety and activity of this agent in heavily pretreated patients with metastatic carcinomas, no cardiac toxicity was observed [39]. It is not clear why the monoclonal antibody trastuzumab that targets the same receptor, ERBB2, has considerable rates of cardiotoxicity. This could be attributed to the different mode of action of the two molecules but further research is warranted to explain the differences observed.

Gefitinib and Erlotinib

Gefitib and Erlotinib are orally active Epidermal Growth Factor Receptor (EGFR) TKIs. They are

given as second line treatment in patients with non-small cell lung cancer (NSCLC) after platinum based chemotherapy. Female patients, of Asian origin with adenocarcinoma (especially the bronchioalveolar type) who are non-smokers respond better to these agents [40]. Usually responders harbor specific mutations in the EGFR gene. Erlotinib is also approved for the treatment of pancreatic cancer in combination with chemotherapy. No cardiac toxicity has been reported with the use of these two TKIs.

Conclusions

The exact incidence of cardiac toxicity induced by a new category of drugs, the tyrosine kinase inhibitors remains currently unclear. This is attributed to the lack of trials addressing this issue as an endpoint but also to confounding factors including history of heart disease and previous exposure to cardiotoxic drugs. We described some basic mechanisms of the injury they possibly exert on cardiomyocytes. As this issue is better elucidated, clinicians will know how safe it is to administer these agents, while reengineered molecules are promising more safety and efficacy. The early detection and application of treatment for left ventricular dysfunction is of key importance for the prevention of irreversible myocardial injury. Careful cardiac monitoring and assessment by a cardiologist throughout the course of treatment with those TKIs that exert cardiac toxic effect is of primary importance.

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