Cardiotoxicity of the new cancer therapeutics – mechanisms of, and approaches to, the problem

Thomas Force[1] and Risto Kerkelä

[1] Center for Translational Medicine, Jefferson Medical College, 1025 Walnut Street, 316 College Building, Philadelphia, Pennsylvania 19107, USA

Cardiotoxicity of some targeted therapeutics, including monoclonal antibodies and small-molecule inhibitors, is a reality. Herein we will examine why it occurs, focusing on molecular mechanisms to better understand the issue. We will also examine how big the problem is and, more importantly, how big it may become in the future. We will review models for detecting cardiotoxicity in the preclinical phase. We will also focus on two key areas that drive cardiotoxicity: multitargeting and the inherent lack of selectivity of ATP-competitive antagonists. Finally, we will examine the issue of reversibility and discuss possible approaches to keeping patients on therapy.

Introduction

Dysregulation of tyrosine kinases (TKs) drives the progression of many cancers [1]. Targeted therapeutics in cancer, which inhibit activity of the dysregulated TKs, have revolutionized the treatment of some cancers and hold the promise of doing the same for many more. These agents are of two classes, monoclonal antibodies (mAbs), generally targeting growth factor receptors or their growth factor ligands, and small-molecule inhibitors of tyrosine and, in some cases, serine/threonine kinases, hereinafter referred to as tyrosine kinase inhibitors (TKIs; Fig. 1). mAbs generally act by binding to the extracellular domain of the receptors, and can block ligand binding to the receptor, dimerization and activation of the receptor, and/or induce the downregulation of expression of the receptor. There are three types of TKIs (see below) but the vast majority either approved or in the development are Type I, which are ATP-competitive inhibitors (i.e. they compete with ATP for binding to the kinase).

At present, there are 21 mAbs and 8 TKIs that are being approved by the U.S. Food and Drug Administration (Table 1) [2,3]. Three new drug application (NDA) filings for kinase inhibitors are expected in 2008 and an additional three in 2010 [2,3]. There are, however, approximately 175 mAbs and 150 TKIs in the clinical trials with many more in the preclinical development. Taken together, there are ~600 agents somewhere in between discovery and market, with ~80% of drug development being in cancer.

Corresponding author: Force, T. (thomas.force@jefferson.edu)

The first question to address is whether there is an important cardiotoxicity with these agents. Unfortunately, this requires a good deal of speculation because, with few exceptions (i.e. trastuzumab, lapatinib and sunitinib), prospective evaluations of cardiac function have not been done for any of these agents. This forces a reliance on retrospective reviews of case report forms which are notoriously unreliable [4]. For example, in one study, dyspnea, one of the cardinal symptoms of congestive heart failure (CHF), was recorded only 23% the time it was reported by patients [4]. Furthermore, the diagnosis of CHF in cancer patients can be difficult because the triadic symptom suggesting CHF (i.e. fatigue, dyspnea on exertion and peripheral edema) is commonly seen in cancer patients because of etiologies unrelated to CHF such as anemia, and therefore one might not think of CHF as a possible etiology. One possible example of the current limitations of approaches to detect CHF, even in patients who are closely monitored in clinical trials, is with the multitargeted TKI, sunitinib. Two large trials of this agent were reported in 2006 and 2007, and neither of them detected significant CHF [5,6]; however, in a unique study that employed a close partnership of oncology and cardiology with monitoring of left ventricular function at a single institution, 8% of patients were found to develop moderately severe to severe CHF and others developed deteriorations in left ventricular ejection fraction of >15 EF% [7]. Thus, the answer to the first question is clearly 'yes', but it is crucial to stress that this is not a class effect of TKIs. For example, mAbs and TKIs targeting the epidermal growth factor (EGF) receptor seem to have little, if

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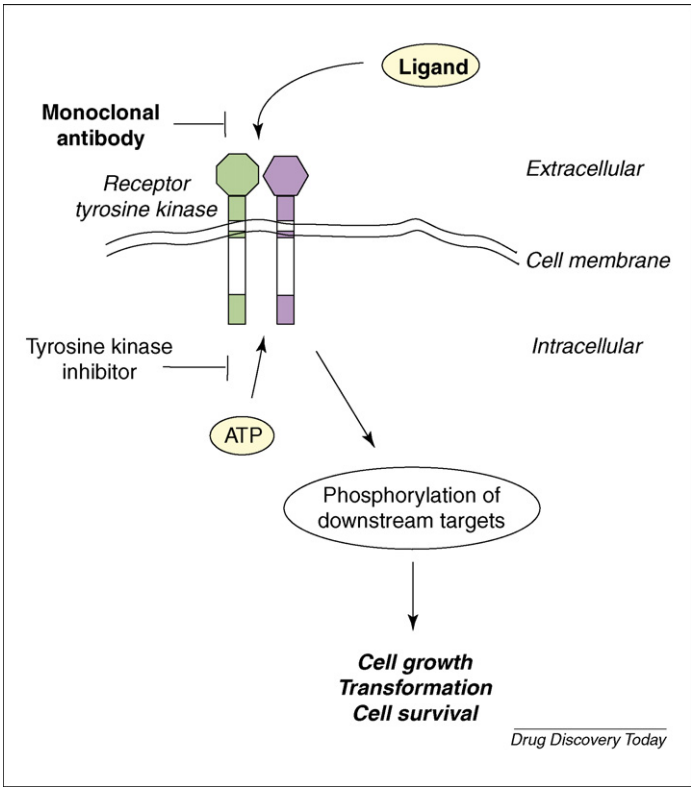

FIGURE 1

Mechanisms of inhibition of receptor tyrosine kinase activity by monoclonal antibodies (mAbs) versus small-molecule tyrosine kinase inhibitors (TKIs). Ligand binding to receptor tyrosine kinases (RTKs) leads to receptor dimerization and activation of the intracellular tyrosine kinase domain of the receptor. Substrates are then phosphorylated, leading to cellular responses. mAbs interfere with ligand binding to receptor and/or receptor dimerization, blocking activation of the RTKs [17]. TKIs do not prevent ligand binding or dimerization, but by preventing ATP from binding to the kinase domain (which is necessary for the kinase to phosphorylate substrates), they block activation of receptors and phosphorylation of substrates.

any, cardiotoxicity. Surprisingly, given the documented cardiotoxicity of trastuzumab, lapatinib has been reported to have minimal cardiotoxicity [8,9].

Herein we will ask several questions about these agents, including (i) why is there cardiotoxicity? (ii) how big a problem might it be? (iii) are there ways to screen for it in the preclinical models? and (iv) what happens after FDA approval? The major message is that a close partnership between manufacturers, the oncology and cardiology communities, and possibly regulatory agencies, will be crucial going forward, with the goal being to be able to maintain patients on these sometimes life-saving therapies even in the setting of some cardiotoxicity.

Why is there cardiotoxicity?

This issue breaks down into two classes of effects – so-called 'on target' effects and 'off target' effects.

On target toxicity

For on target toxicity, the same factor that promotes cancer cell survival, and is therefore a valid TKI target, performs a similar function in cardiomyocytes [10,11]. In these instances, cardiotoxicity will be unavoidable until (a) targeted delivery specifically to cancer cells becomes possible or (b) a downstream pathway mediating cardiotoxicity but not crucial to cancer cell death is identified and is itself inhibited. Two examples are trastuzumab and imatinib.

Trastuzumab leads to cardiac dysfunction in 4–7% of patients when used alone and up to 27% with concurrent administration of anthracyclines [12–14]. Trasztuzumab blocks activation of the human epidermal growth factor receptor 2 (Her2, known as ErbB2 in the mouse). Her2 is amplified in ~25% of breast cancers [13,15] and trastuzumab prolongs survival in these patients [16–18]. However, Her2 and its ligand, neuregulin, via somewhat obscure mechanisms, provide important signals that are necessary for the maintenance of cardiomyocyte 'health' (Fig. 1). Targeted deletion of ErbB2 in the mouse heart leads to a spontaneous dilated cardiomyopathy with advancing age [19,20]. When these mice are exposed to a pressure load (mimicking severe hypertension), the hearts rapidly fail. Furthermore, these mice are markedly sensitized to anthracycline therapy, providing an explanation for the observed toxicity when the combination was used in patients. All these findings in the ErbB2 knockout mouse make it difficult to understand how lapatinib can be free of cardiotoxicity, although their different mechanisms of actions and/or the antibody-dependent cell cytotoxicity seen with mAbs but not with TKIs may provide an explanation [11]. Recently, it was reported that lapatinib, in contrast to trastuzumab, led to the activation of the AMP-activated protein kinase (AMPK) in cardiomyocytes [21]. This is a response that is generally cytoprotective in the setting of cellular stress, and may account for any differences in cardiotoxicity of the two agents.

The second agent we will discuss is imatinib. No prospective evaluations of left ventricular ejection fraction (LVEF) have been done with this agent. We are fully aware of the retrospective reviews that have been published reporting a minimal incidence of heart failure (e.g. see Ref. [22]). We [23] and others [24] have, however, found clear-cut evidence of cardiotoxicity in mouse models (a disconnect that will be discussed further below), and we will use this as an example of how identification of the crucial target, inhibition of which mediates cardiotoxicity, can help influence drug design.

In studies of mouse models, we found that imatinib induced a modest, though consistent and statistically significant, decline in LV function [23]. More striking was a loss of myocardial mass, consistent with cell loss. In cardiomyocytes in culture, we found that imatinib, via induction of the endoplasmic reticulum stress response, led to the cell death with features of both apoptotic and necrotic cell death. Imatinib is one of the more selective TKIs. It inhibits activity of the causal fusion protein Bcr-Abl in chronic myeloid leukemia cells. Imatinib also inhibits c-Kit (the receptor for stem cell factor) and platelet-derived growth factor receptors-α and -β (PDGFR-α and -β), targets in gastrointestinal stromal tumors (GISTs) see Table 1. Adult cardiomyocytes do not express c-Kit, but do express PDGFRs and Abl (the normal TK expressed in all cells of the body). We took advantage of spontaneously occurring mutations in the Abl domain of Bcr-Abl that make Abl resistant to imatinib [25]. When we expressed this mutant (AblT315I) in cardiomyocytes it largely rescued the cardiotoxicity. These studies identified Abl as the target of imatinib, inhibition of which led to the cardiotoxicity.

TABLE 1

Kinase inhibitor cancer therapeutics

Drug	Class	TK target(s)	Malignancies	Cardiomyopathy/(rate)/other
Imatinib (Gleevec)	TKI	ABL1/2, PDGFRα/β, KIT	CML, Ph^+ B-ALL, CMML, HES, GIST	Y/(low)[a]
Dasatinib (Sprycel)	TKI	ABL1/2, PDGFRα/β, KIT, SRC family	CML	Y/(low to mod)[a]/QT prolongation
Nilotinib (Tasigna)	TKI	ABL1/2, PDGFRα/β, KIT	CML	Unknown/QT prolongation
Sunitinib (Sutent)	TKI	VEGFR1/2/3, KIT, PDGFRα/β, RET, CSF-1R, FLT3	RCC, GIST	Y/(mod)/hypertension, hypothyroidism
Lapatinib (Tykerb)	TKI	EGFR (ErbB1), HER2 (ErbB2)	$HER2^+$ breast cancer	N
Sorafenib (Nexavar)	TKI	c-/B-Raf, VEGFR2/3, PDGFRα/β, KIT, FLT3	RCC, melanoma	Y/(low?)[a]/ACS/hypertension
Gefitinib (Iressa)	TKI	EGFR (ErbB1)	NSCLC	N[a]
Erlotinib (Tarceva)	TKI	EGFR (ErbB1)	NSCLC, pancreatic cancer	N[a]
Temsirolimus (Torisel)	Novel	mTOR (drug binds to FKBP12 and complex inhibits mTOR)	RCC	N[a]
Trastuzumab (Herceptin)	mAb	HER2 (ErbB2)	$HER2^+$ breast cancer	Y/(mod)
Bevacizumab (Avastin)	mAb	VEGF-A	Colorectal cancer, NSCLC	Y/(low to mod)[a]/arterial thrombosis
Cetuximab (Erbitux)	mAb	EGFR (ErbB1)	Colorectal cancer, squamous cell carcinoma of head/neck	N[a]

mAb, humanized monoclonal antibody; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; ALL, acute lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; HES, hypereosinophilic syndrome; GIST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer. Please see text for additional abbreviations.

[a] Effect on LV function has not been determined and therefore these estimates are speculative only.

In theory, these findings could be used to improve drug design. Proof-of-principal of this approach was recently provided by Fernandez *et al.* [24] who redesigned imatinib so that it no longer inhibited Abl but retained activity against c-Kit and PDGFRs. This new compound, WBZ4, was as effective as imatinib in treating mouse models of GIST, but did not, in contrast to imatinib, induce a decline in LV function (Fig. 2). Furthermore, our studies had suggested that the pathway downstream of Abl, inhibition of which mediated cardiomyocyte death, was the c-Jun N-terminal kinase (JNK) pathway. Therefore, Fernandez *et al.* also redesigned WBZ4 to inhibit JNKs. Again, since the compound was as effective as imatinib in GIST models, clearly JNKs were mediating toxicity but were not necessary for tumor cell killing. We propose that this is the kind of rational drug design that is needed, going forward, to achieve efficacy in cancers without inducing cardiotoxicity.

Off target toxicity

Off target effects are inherently related to non-selectivity, either by design (as with the multitargeted TKIs) or by virtue of the predominance of Type I inhibitors in the marketplace and in development. In this scenario, inhibition of a target not intended to be inhibited by the TKI is responsible for the cardiotoxicity. This cardiotoxicity is, therefore, potentially avoidable by improving selectivity and/or redesigning the drug so that it specifically no longer inhibits the crucial factor, assuming the factor does not play a key part in cancer progression. One possible example of this is sunitinib. Sunitinib was developed to inhibit factors important in cancer cell survival/proliferation and in tumor angiogenesis, and it is very effective in treating highly vascularized cancers such as renal cell carcinoma. The drug inhibits vascular endothelial

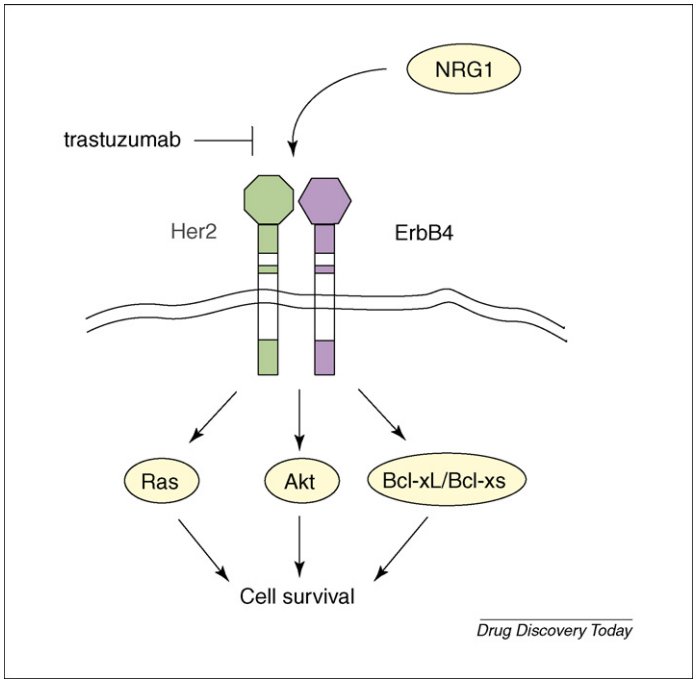

FIGURE 2

Her2 signaling in cardiomyocytes. In cardiomyocytes exposed to Nrg1, ERBB2/ERBB4 heterodimers form, activating two key survival pathways in the heart, ERK and Akt. Trastuzumab blocks this activation and, via multiple mechanisms including alterations in levels of Bcl-X family members, leads to decreased cardiomyocyte survival. Not shown is the possible antibody-dependent cell cytotoxicity (an immune response) that may also contribute.

growth factor receptors (VEGFRs), PDGFRs, c-Kit, Fms-like tyrosine kinase-3 (Flt3), and rearranged during transfection (Ret, mutated in multiple endocrine neoplasia syndromes) [1]. Of these kinases, only PDGFRs are expressed in adult cardiomyocytes, and it is our best guess that inhibition of PDGFRs would not lead to the cardiotoxicity seen in patients, animal models and cultured cardiomyocytes that we see with sunitinib. More recently, novel approaches to screening drugs for the activity against large numbers of kinases (>200) have been developed, and use of this approach identified several kinases that would probably be inhibited by sunitinib *in vivo*, and that are known to play important parts in cell survival including members of the RSK family of serine/threonine kinases [26] (Fig. 3). Interestingly, several proapoptotic kinases were also predicted to be inhibited, including Mst1, DRAK1 and the GCK family members, TNIK and GCKR [26]. It is conceivable that redesigning sunitinib so that it no longer inhibits these targets could enhance cytotoxicity of the drug toward cancer cells.

It seems fairly obvious that off target toxicities will be much more frequent with multitargeted agents; however, if one of these agents can be used in several different cancers, the return on investment will be much greater than if the drug can be used in only one or two cancers. Thus, market forces may drive the development of multitargeted agents forward.

In addition to multitargeting, the preponderance of development of Type I inhibitors (e.g. sunitinib) is problematic. These target the ATP-binding pocket of the kinase, and compete with ATP for binding to that pocket. However, this region of kinases is highly conserved across the 500+ protein kinases in the human genome, making selectivity nearly impossible. Equally worrisome, there are approximately 2000 other purine-binding proteins that could also be the targets of ATP-competitive inhibitors, including two documented ones for imatinib – the oxidoreductase NQO2 and the transmembrane transporter, breast-cancer-related protein (BCRP) [27–29]. Thus, from purely an 'avoidance of cardiotoxicity' perspective, focus should probably shift more toward Type II inhibitors (e.g. imatinib and nilotinib), which also bind to the ATP pocket but in addition bind an adjacent region that is open when the kinase is inactive [30–32]. These agents, thus, bind to kinases in the inactive conformation and lock them into an inactive state, making them generally more potent and more selective (though not always, as with sorafenib). Type III inhibitors (e.g. the archetypal extracellular signal-regulated kinase (ERK) pathway inhibitors PD98059 and U0126) bind to sites remote from the ATP pocket, including the substrate recognition region and other regions that are much more divergent across the kinome. Consequently, these agents should possess greater selectivity, although they are more difficult to make and will probably be able to be used in fewer types of cancers. These are issues that the biotechnology and pharmaceutical industry must address.

One final concern is the recently proposed use of the combination therapy for CML, as opposed to the sequential strategy employing imatinib first, and then as resistance emerges, progressing to dasatinib [33]. Again, this makes perfect sense from the perspective of optimal therapy of the malignancy, but combining agents, particularly less selective ones like dasatinib [29], may have consequences on the heart.

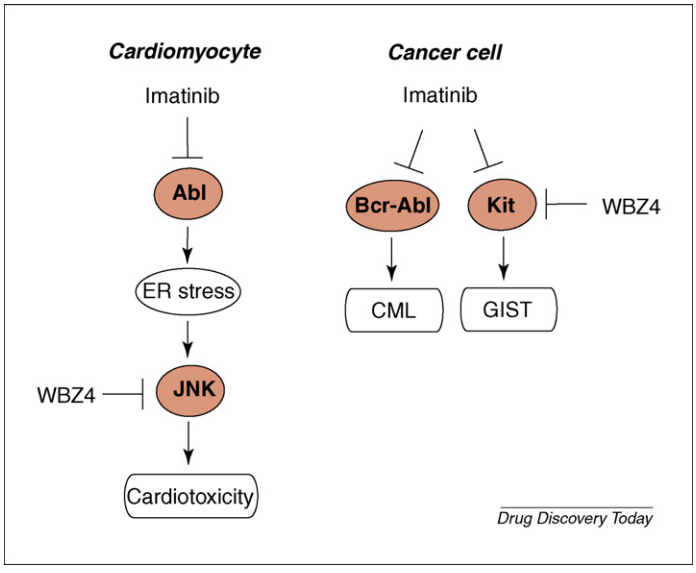

FIGURE 3

Redesign of imatinib based on identification of the mechanisms of cardiotoxicity. Imatinib inhibits activity of Bcr-Abl, the causal fusion protein in chronic myeloid leukemia (CML), and also targets PDGFRs (not shown) and c-Kit for the treatment of GIST. In cardiomyocytes imatinib-mediated inhibition of Abl leads to cell death via induction of the endoplasmic reticulum stress response and subsequent JNK activation. WBZ4 is an imatinib derivative that no longer inhibits Abl, does inhibit c-Kit and PDGFRs. To further protect from cardiotoxicity WBZ4 was also designed to inhibit JNK [24].

What is the magnitude of the problem?

As noted, we really do not know much about the cardiotoxicity of agents that are FDA-approved much less than those in the development. By looking at agents, however, and knowing the biological roles in the heart played by the targets of many of these agents, there certainly is cause for concern (Table 2). For example, Raf family members are a popular target in cancer because they are upstream of the prosurvival extracellular signal-regulated kinase (ERK) family, also known as MAP kinase. Sorafenib is a multitargeted TKI that also inhibits Raf family members. Till date, little cardiotoxicity has been reported with this agent. However, studies in mice deleted for the Raf-1 gene or expressing dominant inhibitory mutants of Raf-1 suggest a key role for this kinase in settings in which the heart is facing a significant pressure load, as with severe hypertension [34,35]. Given that sorafenib (and in fact all of the agents targeting VEGF/VEGFR including sunitinib and bevacizumab) induce significant hypertension in a high percentage of patients, Raf inhibition raises concerns. Furthermore, VEGF/VEGFR signaling is also important for the adaptive response of the heart to blood pressure stress and, in the setting of inhibition of VEGF/VEGFR signaling, pressure stress leads to heart failure [36–38].

Additional targets of potential concern can also be identified by reviewing the literature concerning such things as the phenotypes of mice deleted for a gene encoding a particular target. The obvious caveat is that the cardiovascular effects observed with the partial inhibition of kinase activity one sees with a drug may not be nearly as marked as homozygous deletion of the gene encoding that target. That said, Table 2 contains some targets of potential concern based on the phenotypes seen with gene deletion or other manipulations of those targets and the drugs that inhibit the targets.

TABLE 2

Experimental models suggesting possible cardiotoxicity of TK inhibition

TK targets	Agents	Model	Cardiac phenotype of model	Refs
Her2	*Trastuzumab* Lapatinib	ErbB2 KO	Dilated CMP; heart failure with pressure load; ↑ anthracycline sensitivity	[19,20]
VEGF **VEGFRs**	Sunitinib Sorafenib Bevacizumab	VEGF trap p53 KO sunitinib	Pathologic remodeling in response to pressure overload	[36–38]
c-Kit	Imatinib Sunitinib Sorafenib	W/W^v mouse (Kit deficient)	Adverse remodeling post-MI; reduced re-stenosis post-injury; because of reduced homing to sites of injury of bone marrow stem cells	[46,47]
Raf-1/B-Raf	Sorafenib	Raf-1 KO/DN	LV dilatation and CHF with pressure load	[34,35]
PDGFRs	Imatinib Sunitinib Sorafenib	Administration of PDGF	Protection from ischemic injury	[50,51]
JAK2	Lestaurtinib	STAT3 KO	STAT3 (JAK2 target) maintains capillary density of heart and increases resistance to anthracycline toxicity	[48,49]
Abl/Arg	Imatinib Dasatinib Nilotinib	Administration of imatinib or WBZ4	ER stress and cardiomyocyte death. ↓ LVEF	[23,24]

mAb, humanized monoclonal antibody; KO, knockout mouse model; DN, dominant negative mouse model; ER, endoplasmic reticulum; MI, myocardial infarction; CMP, cardiomyopathy; STAT3, signal transducer and activator of transcription 3. See text for other abbreviations. mAbs are italicized.

Finally, it seems clear that with the huge effort in the development of these agents, and the number of them likely to appear on the market over the next five years, whatever the problem is now it will probably pale by comparison in the future if this issue is not addressed.

Are there effective ways to screen for cardiotoxicity during the preclinical development?

The clear issue here is the predictive accuracy of an abnormality seen with one particular preclinical model to predict that an agent will have associated clinical cardiotoxicity. As noted, we and Fernandez *et al*. identified significant deteriorations in LVEF with imatinib by echo and MRI [23,24]. By contrast, several retrospective reviews report that CHF is rare. This raises the question as to how well will findings *in vitro* or in mouse models reflect the clinical situation. This question can only be answered when LV function is measured in the clinical trials, and, as noted, till date that has only been done for trastuzumab, sunitinib and lapatinib. That said, at least for trastuzumab and sunitinib the models appear to 'track' quite well with the clinical scenario [7,19,20].

In vitro models

Obviously these models examine direct toxicity to cardiomyocytes in the absence of effects on the vasculature.

Cell lines

It is our opinion that cardiomyocyte cell lines will probably not work given that cultured cells utilize glucose for energy generation (i.e. anaerobic metabolism). By contrast, the mitochondrial electron transport chain is by far the dominant source of energy in cardiomyocytes. Given that mitochondria appear to be a prime target of TKIs, we believe primary cells are required.

Primary cells

These can either be neonatal rat ventricular myocytes (NRVMs) or adult RVMs (ARVMs). We have used NRVMs successfully, and this approach certainly seems effective at detecting toxicity, but there are concerns over it being too sensitive. As noted, cardiotoxicity mediated by the effects of agents on the vasculature will not be identified.

Rodent models and techniques to screen for cardiotoxicity

Echocardiography or other means of measuring LVEF

It is our sense that this approach lacks sensitivity, based largely on our studies with sunitinib [7]. Despite marked derangements in mitochondrial structure, LV function was normal in mice treated for five weeks with the drug. Possible reasons for this include: (i) rodents can readily recruit compensatory mechanisms (enhanced sympathetic tone, etc.) that elderly patients with cardiovascular comorbidities may not be able to recruit; (ii) treatment duration was insufficient (for investigators in academic institutions this is a problem of cost since drugs often have to be purchased from pharmacies at retail price, and cage charges and manpower requirements can be significant; (iii) even in patients, LVEF is an insensitive measure of the contractile status of the heart (see below).

Stressor plus TKI

With this approach, mice are fed drug for a period of time and then a stressor, typically one that increases the pressure load faced by the LV, is added. We used this approach to expose a proapoptotic effect of sunitinib in mice [7]. These mice, however, did not experience a decline in LVEF even with a pressure load.

Use of a more sensitive means to detect LV dysfunction

We and many others have employed catheterization with a high frequency pressure transducer and a graded infusion of isoproterenol to expose a defect in contractile function. This can expose abnormalities not seen in standard resting studies.

Isolated working heart prep or Langendorf prep

This approach removes the heart and studies it in the absence of systemic catecholamines that might artificially enhance LV

function. This approach, therefore, eliminates systemic effects and reduces effects of compensatory mechanisms. It is not clear if this approach is better than any of the above since no one, to our knowledge, has examined this issue directly.

Transmission electron microscopy of hearts

This is, in our opinion, the most sensitive way to detect cardiotoxicity *in vivo*. This is a morphologic endpoint and whether EM abnormalities in mice will be predictive of cardiotoxicity, much less LV dysfunction, in patients is not at all clear.

Clinical approaches to detecting cardiotoxicity

Optimal methods for the detection of cardiotoxicity in patients are even more unclear, with the primary issues being lack of sensitivity and, in the case of standard transthoracic echocardiography, poor reproducibility. Even with the more reproducible technique of nuclear LVEF determination the clear sense that measurement of LVEF, the current 'gold standard' for detecting cardiotoxicity in patients, is insensitive has led to the use of various biomarkers to detect injury (e.g. troponin I and T, myoglobin and creatine kinase) or heart failure (B-type natriuretic peptide or BNP). However, the sensitivity and specificity of these are just beginning to be explored. In addition, more reproducible methods of examining LV function and/or ones potentially more sensitive for detecting injury are also being explored. These include magnetic resonance imaging and cardiac magnetic resonance tagging, contrast echocardiography, 3D echocardiography, and tissue Doppler strain and strain rate. Indeed, some of these have been found to be more sensitive than traditional approaches at detecting 'subclinical' abnormalities in other disease states but remain to be tested in this patient population.

Eventually we believe that an understanding of the role of genetic and epigenetic factors will allow one to predict who is, and who is probably not, at risk for developing cardiotoxicity. This has been examined in patients taking anthracyclines [39,40] but, to our knowledge, has not been extended, as yet, to patients taking TKIs. It seems probably that polymorphisms in TK targets of TKIs, in factors modulating activity of the entire pathway upstream and downstream of the TK, as well as interacting pathways, will play a part. However, we believe genome-wide association scanning, which does not rely on the 'best guess' approaches, will be the optimal approach to identify candidate modulators of cardiotoxicity of TKIs, although at present cost and restricted availability of technology limit its application to a few centers.

In summary, it seems unprobably that any single technique in the preclinical models will be adequate to predict, with acceptable sensitivity and specificity, which agents will have associated cardiotoxicity in patients. Added to this is the suboptimal definition of cardiotoxicity in patients which at this point relies on LVEF determination. At the preclinical stage, it is probably that a combination of studies in NRVMs (high sensitivity for detecting direct toxicity to cardiomyocytes but unclear specificity) and in mouse models with both transmission EM and a functional readout that includes an additional stressor that induces hypertension and/or isolated working heart preps may be necessary.

Issues following FDA approval

The typical patient enrolled in trials before FDA approval does not have significant cardiovascular comorbidities [41–43]. Yet, post-FDA approval, many patients with comorbidities, including CAD and LV dysfunction, will be treated. Thus, rates of CHF can be expected to be higher than in the highly selected population of patients that is enrolled in Phases I–III clinical trials. This makes post-approval monitoring for cardiotoxicity important. We believe that it is fair to say the post-marketing adverse event reporting is probably not adequate, and this issue needs to be addressed.

The issue of reversibility

It seems that the course of patients who present with mAb- or TKI-induced CHF is different from that of patients with anthracyline-induced CHF or patients with more usual etiologies for CHF [44] (but also see Ref. [45]). Many respond well to withdrawal of the drug, with or without additional therapy directed at the heart failure *per se* (angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists and/or β-blockers). Indeed, many patients treated with trastuzumab [44] and, although a small series, a high percentage of patients with sunitinib-associated CHF [7] had substantial improvement in LVEF and some were able to resume treatment. That said, the natural history of this is not known and obviously patients will need to be followed carefully.

Concluding remarks

We have tried to outline concerns, real and theoretical, over the issue of cardiotoxicity of the new cancer therapeutics. We obviously believe that significant challenges face oncology and cardiology with the wave of new mAbs and TKIs that will be coming to market over the next several years. In some instances cardiotoxicity will be avoidable, for instance by redesigning the agent to avoid specific targets that are irrelevant to the treatment of the cancer. In other instances this will not be possible, and effective strategies to deal with the cardiotoxicity must be sought. It is the clear goal that patients will be able to continue on therapy, and we believe this can best be achieved by a cooperative approach between the two disciplines that rigorously addresses this issue.

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