Cardiovascular toxicity of molecularly targeted agents

Elizabeth L. Strevel[a,b], Lillian L. Siu[b]

[a]*The Credit Valley Hospital, Department of Medical Oncology, Mississauga, Canada*
[b]*The Princess Margaret Hospital, Division of Medical Oncology/Hematology, Toronto, Canada*

Introduction

Over the last decade, molecularly targeted drugs have become established in oncology therapeutics and clinical research. While initially marketed as "cancer specific" agents with superior toxicity profiles to conventional anti-proliferative and DNA-damaging chemotherapy, it has become increasingly apparent that these drugs have numerous serious "on-target" and "off-target" adverse effects [1]. Cardiovascular events are one such toxicity, with wide-reaching and profound therapeutic implications. As we continue to strive for and achieve superior patient outcomes in terms of cancer-specific survival, the relevance of competing causes of patient morbidity and mortality such as cardiovascular toxicity rises [2]. The objectives of this review are to discuss hypertension, ventricular dysfunction and QT_c prolongation as toxicities directly related to the administration of molecularly targeted agents in cancer patients, with the goal of enhancing the oncologist's approach to and management of these increasingly common side effects.

Hypertension

Prior to the development of angiogenesis inhibitors, oncologists rarely dealt with treatment-related hypertension [3]. This is no longer the case as angiogenesis inhibitors have been approved for the treatment of many common malignancies such as breast, lung and colon cancers, and are in widespread use. While targeting angiogenesis through the vascular endothelial growth factor (VEGF) and/or its receptor (VEGFR) pathway has proven to be an effective strategy for anticancer management, oncologists need to become adept at assessing and managing hypertension, a serious, common adverse event associated with the use of anti-VEGF agents.

Mechanisms of hypertension

Angiogenesis is the growth of new blood vessels from pre-existing larger vessels, and was first proposed as an anti-cancer therapeutic strategy by Folkman in 1971 [4]. Of the various biochemical mechanisms to impede angiogenesis, targeting the VEGF pathway has clinically been the most successful. Classes of anti-VEGF pharmacologic agents include monoclonal antibodies that bind the VEGF ligand (i.e. bevacizumab), decoy VEGF receptors (i.e. aflibercept), and small-molecule tyrosine kinase inhibitors of VEGFR (i.e. sorafenib, sunitinib). Vascular disrupting agents (VDAs), while they do not directly target VEGF, are considered as anti-angiogenic in mechanism as they disrupt the established abnormal vasculature that feeds tumors by targeting their dysmorphic endothelial cells. Tumor endothelium is primarily reliant on a tubulin cytoskeletal network to maintain functional integrity. There are two types of VDAs. First, biological or ligand-directed VDAs use antibodies, peptides or growth factors to target toxins or procoagulants to the tumour endothelium. In contrast, small molecule VDAs work either as tubulin-binding agents or through induction of local cytokine production [5]. Angiogenesis inhibitors that modulate VEGF or VEGFR have all displayed hypertensive toxicity. Those that do not impact VEGF or VEGFR (e.g. matrix metalloproteinase inhibitors) are not associated with this adverse effect, with the exception of VDAs. Table 1 summarises agents that have been approved for clinical use, as well as agents in later phases of clinical development that modulate VEGF. Blood pressure elevation is a reported toxicity in clinical trials of these drugs, highlighting the class-specificity of this toxicity.

The VEGF pathway is primarily active in proliferating endothelial cells. Initially, it was thought that vascular endothelium was largely quiescent in normal adults, with the exception of wound healing and the menstrual cycle [6,7]. This belief created the expectation that anti-angiogenics would produce minimal non-tumor-related toxicity. However, clinical experience has altered this expectation. Oncologists and scientists alike have subsequently learned the

Table 1
Anti-VEGF agents reporting significant hypertension in clinical trials

Agent	HTN incidence (%)		Reference
	Total	Grade ⩾3	
FDA approved			
Bevacizumab	22	11	[8]
Sorafenib	17	4	[9]
Sunitinib	24	8	[10]
Non-FDA approved			
Alfibercept	46	18	[11]
Axitinib	39	11	[12]
Brivanib	36	n/a	[13]
Cediranib	72	33	[14]
KRN951	93	n/a	[15]
Motesanib	56	25	[16]
Pazopanib	37	8	[17]
Vendetanib	21	2	[18]

VEGF – vascular endothelial growth factor; HTN – hypertension; FDA – Food and Drug Association (United States).

importance of the VEGF pathway in endothelial cell homeostasis [19]. Anti-VEGF activity in perivascular endothelial cells is the root of hypertensive toxicity from anti-angiogenic pharmaceuticals.

Interestingly, there is a growing belief that hypertension may act as a valuable biomarker of efficacy with anti-VEGF agents [20]. A retrospective review of patients receiving bevacizumab in combination with 5-fluorouracil and irinotecan in the first-line setting for metastatic colon cancer indicated that patients developing drug-related hypertension had higher rates of partial remission, progression-free survival, and overall survival [21]. Diastolic blood pressure rise was also associated with improved overall survival in a retrospective review of six phase II studies with axitinib [12]. Evidence for hypertension as a biomarker for sorafenib has also been presented [22]. Blood pressure elevation as a predictive marker of anti-VEGF activity remains to be explored prospectively, but may indicate that this mechanism-based side effect correlates with the anti-cancer intent of VEGF-directed therapy [23].

Scientifically, VEGF impact on blood pressure has been extensively studied. Blood pressure is regulated by cardiac output, renal control of blood volume, baroreceptors, and hormonal influences. VEGF normally causes release of nitric oxide and prostacyclin from endothelial cells, leading to vasculature dilatation and increased endothelial permeability, which decreases systemic blood pressure [24]. This process is achieved through downstream effectors of the VEGF receptor, via PI3K (phosphatyidylinositol 3-kinase) and MAPK (mitogen-activated protein kinase) signalling control of nitric oxide synthetase. Lack of nitric oxide and prostacyclin as a result of VEGF inhibition produces vasoconstriction and decreased vascular permeability, increasing intra-luminal pressure and therein systemic arterial blood pressure [25]. VEGF inhibition also up-regulates baroreceptor function, increasing vascular tone [26]. Another important mediator of hypertension, peripheral vascular resistance, is ramped up through VEGF inhibitors as a direct result of the "desired" anti-angiogenic effect - reduced density of auxiliary capillaries and arterioles [27, 28]. All in all, VEGF's impact on blood pressure is highly physiologically complex, and remains an area of ongoing investigation. Nonetheless, multiple described mechanisms account for the observance of this previously "unexpected" toxicity.

Is hypertension clinically important for the medical oncologist?

A number of reputed organisations have established vigorous criteria for the definition of hypertension [29–32]. These criteria generally involve either a single gross elevation in blood pressure which is symptomatic (hypertensive urgency/emergency), or serial measurement of abnormal elevations of either systolic or diastolic blood pressure (Table 2). While the relationship between blood pressure levels and cardiovascular risk is continuous and direct, an individual's likelihood of a cardiovascular event is also known to be modified by the presence of other established risk factors (i.e. age, gender, dyslipidaemia, family history of premature cardiovascular disease) [33]. Sequelae of unmitigated hypertension can be life-threatening and disabling, including stroke, encephalopathy, coronary artery disease, heart failure, and peripheral vascular disease.

Many important characteristics differentiate oncology patients from the general population for which established guidelines on hypertension apply. Patients with clinically significant malignancies or drug-induced hypertension were excluded from the research studies that comprise the evidence pool for a population-based approach to blood pressure regulation [34]. To date, no adequately designed prospective or retrospective trials have been reported evaluating the unique facets of hypertension control in cancer patients receiving anti-VEGF therapies. This has been identified as an area of investigative

Table 2
WHO/ISH definition and classification of blood pressure levels

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High-normal	130–139	85–89
Hypertension:		
Grade 1 (mild)	140–159	90–99
Grade 2 (moderate)	150–179	100–109
Grade 3 (severe)	⩾180	⩾10
Isolated systolic hypertension	⩾140	<90

WHO – World Health Organisation; ISH – International Society of Hypertension.

need [23]. Nevertheless, it stands to reason that existing recommendations for hypertension management are a reasonable minimal standard to apply to cancer patients at risk of drug-induced hypertension. While some may argue that the benefits of hypertension control are less relevant in cancer patients with diminished life expectancy, clinical experience does not support this rationale. First, preventable serious adverse events have been reported in patients with unmanaged hypertension receiving anti-VEGF therapies [35–37]. Second, abnormal baseline cardiovascular risk profiles are common in cancer patients, and addition of an anti-VEGF agent increases the likelihood of an adverse hypertensive event [38]. Third, it has been shown that management of co-morbidities such as hypertension has direct impact on cancer patient prognosis, even in the incurable setting [39]. It is likely that improved control of hypertension may improve our efforts to positively impact overall survival, especially when these agents are to be incorporated in the adjuvant setting or as maintenance therapy in the minimal tumour burden setting.

Evaluation of hypertension

Before considering treatment with an anti-VEGF agent, it is essential that a careful baseline assessment of cardiovascular risk is performed. It is important to note that patients with significant cardiovascular disease within 6 to 12 months of anti-VEGF treatment initiation were generally excluded from the published studies of bevacizumab, sorafenib, sunitinib, and other anti-angiogenic agents. Before starting an anti-VEGF agent, a formal pre-treatment risk assessment should be performed including repeated blood pressure measurements as per recommended technique [40]. Comprehensive history and physical, as well as directed laboratory, investigations are also mandatory for cardiovascular risk stratification, as endorsed by the European Society of Hypertension and the European Society of Cardiology (Table 3) [41].

All patients with documented hypertension and/or elevated cardiovascular risk require risk factor modification, hypertension control and close surveillance while on anti-VEGF treatment. Individualised risk-benefit analysis is recommended for patients who are at very high pre-treatment risk as per Table 3 or who would have been excluded from the anti-angiogenic clinical trials on the basis of their cardiovascular status.

Current target blood pressure goals for cancer patients being considered for and receiving anti-angiogenics are consistent with generally accepted population guidelines – maintaining blood pressure <140/90mmHg [31]. Targets should be modified to lower levels as per public health recommendations in patients with multiple pre-existing risk factors. For example, target blood pressure is generally <130/80mmHg in diabetic and chronic renal dysfunction populations [31]. In order to reach baseline target blood pressures, anti-hypertensive interventions may need to be started with demonstration of blood pressure stabilisation before anti-VEGF treatment.

Once on therapy, it is imperative that regular and comprehensive blood pressure monitoring occurs, with initiation of anti-hypertensive agents if blood pressure crosses accepted thresholds. The magnitude of blood pressure elevation in response to anti-angiogenics can be dramatic and rapid, occurring even within the first week of treatment [28,35,42]. Currently, it is not known how to differentiate which patients are most likely to experience significant or early elevations in blood pressure on anti-VEGF agents. Clinical practice guidelines recommend blood pressure monitoring weekly during the first cycle of therapy,

Table 3
Hypertension risk stratification for likelihood of adverse outcome [41]

Systolic BP ⩾160mmHg or diastolic BP ⩾100 mmHg

Diabetes Mellitus

Established CV disease including any history of:
- ischaemic stroke, cerebral haemorrhage, or transient ischaemic attack
- myocardial infarction, angina, coronary revascularisation, or heart failure
- peripheral artery disease
- retinal haemorrhages or exudates, papil oedema

Established or sub-clinical renal disease including:
- microalbuminuria or proteinuria (>30 mg/24h)
- serum creatinine in men >1.5 mg/dl, women >1.4 mg/dl
- calculated/estimated glomerular filtration rate <60ml/min/1.73m^2

Sub-clinical organ damage previously documented by:
- ECG or echocardiogram revealing left ventricular hypertrophy
- carotid ultrasound study revealing wall thickening or plaque

3 or more of the following CV risk factors:
- age (men >55 years, women >65 years)
- cigarette smoking
- dyslipidaemia as measured by:
  - total cholesterol >190 mg/dl or:
  - low-density lipoprotein cholesterol >130 mg/dl or:
  - high-density lipoprotein cholesterol (men <40mg/dl; women <46mg/dl) or:
  - triglycerides >150 mg/dl
- fasting plasma glucose >100 mg/dl
- family history of premature CV disease (1st degree male relative age <55 years or 1st degree female relative <65 years)
- abdominal obesity male waist circumference >40 inches*; female >35*

BP – blood pressure, CV – cardiovascular, ECG – electrocardiogram.
* = in persons of East Asian ancestry for male waist circumference >35 inches, for women >31.
High risk – Individuals who meet any of the above bold-faced criteria.
Very high risk – Individuals who meet more than one of above bold-faced criteria.

and then at least every 2 to 3 weeks for the duration of anti-VEGF drug exposure [43].

Management of hypertension

Evidence for non-pharmacologic interventions in onco-therapeutics is lacking. However, as per general population guidelines, patients should be counselled to avoid excessive alcohol consumption and excessive salt intake [44]. Avoidance of other aggravating drugs such as non-steroidal anti-inflammatory drugs, steroids, erythropoietin agonists and sympathomimetics is also recommended when clinically feasible.

Pharmacologic management of hypertension in the cancer patient receiving anti-VEGF treatment requires a tailored approach. To date, there is no evidence that supports superior efficacy of one antihypertensive agent over another in this population. In the absence of evidence, treatment recommendations should be made on the basis of the potential risks and benefits associated with each unique drug and patient. For example, agents which impact renal clearance such as angiotensin converting enzyme inhibitors (ACE inhibitors) are not recommended with concurrent use of agents that depend on renal clearance (i.e. cisplatin, pemetrexed). However, ACE inhibitors may be a prudent choice for patients with impaired left ventricular systolic dysfunction, who would stand to have secondary gain from the use of this class of agent [45,46]. Table 4 outlines general considerations for the selection of anti-hypertensive agents. Blood pressure that is not readily controlled with initial anti-hypertensive manoeuvres should be assessed by a local hypertension specialist.

Another strategy to control blood pressure is modification of the anti-VEGF agent dose or schedule. Anti-VEGF induced hypertension therapy is mechanism-based and reversible. Depending on the type of anti-VEGF agent used and the individual patient's pharmacokinetic and pharmacodynamic status, this may be a reasonable approach for difficult to control hypertension. For patients receiving daily-dosed tyrosine kinase inhibitors of VEGF such as sunitinib or sorafenib, temporarily withholding or reducing the drug can be rapidly effective if hypertension is symptomatic or refractory to standard anti-hypertensive interventions [47]. Anti-VEGF agents with longer

Table 4
Considerations for individualising anti-hypertensive therapy

Class of drug	Cancer-specific cautions	Basis for preferred selection	General cautions and contraindications
Angiotensin converting enzyme inhibitors	– Renal clearance – Hyperkalaemia	– Left ventricular systolic dysfunction – Diabetic nephropathy	– Renal impairment – Peripheral vascular disease
Angiotensin II receptor blockers	– Renal clearance – Hyperkalaemia	– Intolerance of ACE inhibitors – Left ventricular systolic dysfunction – Diabetic nephropathy	– Renal impairment – Peripheral vascular disease
Beta blockers	– Fatigue	– Angina – History of myocardial infarction	– Bradycardia / heart block – Asthma/COPD – Decompensated heart failure
Calcium channel blockers	– Lower extremity swelling	– Isolated systolic hypertension	– Bradycardia / heart block – Decompensated heart failure – Post-myocardial infarction
Thiazide diuretics	– Gout – Hypercalcaemia – Hypokalaemia	– Elderly patients – Isolated systolic hypertension – Inexpensive	– Documented sulfa allergy

COPD – chronic obstructive pulmonary disease.

half-lives such as bevacizumab and aflibercept do not respond as quickly to withdrawal or dose reduction. Administration of these long-acting agents when blood pressure is extremely high (i.e. systolic >160mmHg and diastolic >100mmHg) is strongly discouraged. Aggressive anti-hypertensive efforts should be employed and sustained stability of blood pressure should be demonstrated before long acting anti-VEGF agents are re-introduced. In all cases where blood pressure is difficult to control, a hypertensive expert should be involved.

Lastly, blood pressure needs to be monitored closely when anti-VEGF therapy is discontinued. As the hypertension is drug exposure related and reversible, a patient may experience hypotension and associated sequelae if blood pressure is not closely observed.

Hypertension summary

Blood pressure elevation is directly related to the administration of anti-VEGF agents and their subsequent interference on VEGF and vascular endothelial cells. Unregulated, this toxicity has the potential for serious adverse events. Before starting on anti-VEGF agents, patients should undergo cardiovascular risk stratification and possible blood pressure modification. Blood pressure needs to be closely monitored after initiation of anti-VEGF therapy, with increased frequency of assessments during the first cycle of treatment. While on anti-angiogenic therapy, blood pressure management needs to be aggressive, and tailored to the individual patient's situation. By vigorously assessing and controlling hypertension, patient outcomes and tolerance of anti-VEGF therapy will be improved.

Ventricular dysfunction

Concerns regarding the long-term impact of anti-cancer therapies on myocardial tissues have long been raised. Myocardial cells have limited regenerative capacity, which renders the heart susceptible to transient as well as permanent drug effects [48]. Anthracylines exhibit dominantly irreversible ventricular dysfunction as their dose-limiting and dose-dependent toxicity, and are the classic example from conventional chemotherapy [49]. However, these agents are usually used for relatively short periods of time rather than on a chronic basis. Molecularly targeted agents have altered the landscape of ventricular dysfunction in oncology, particularly given their chronicity of use, unpredictability given the lack of a dose-toxicity relationship, possibility of cardiac recovery, and likelihood of tolerance with drug re-challenge [50]. As cancer survivorship improves, the long-term consequences of off-target side effects such as ventricular dysfunction become increasingly relevant [51].

Mechanisms of ventricular dysfunction

Drug-induced ventricular dysfunction can occur via several distinct mechanisms. Type I cardiotoxicity, as caused by anthracyclines, results in structural abnormalities of the cardiac ultrastructure and subsequent cell death. In contrast, myocyte injury induced by

molecularly targeted agents (particularly trastuzumab) is systematically distinct, and known as type II cardiotoxicity. Type II cardiotoxicity is caused by failure of myofibril contractile elements to exert coordinated activity, but cell death is not a dominant feature. Myocardial cell sustainability despite damage in type II impairment is central to the unique behaviour of molecularly targeted agent induced ventricular dysfunction.

Trastuzumab is the prototypical molecularly targeted agent associated with cardiotoxicity. Ventricular dysfunction due to trastuzumab centres on the role of ErbB2 (human epidermal growth factor type 2 / Her2) in normal myocyte function. ErbB2 is relatively scarce in cardiomyocytes, however, its role is essential [52, 53]. Embryonic animal models indicate ErbB2 is critical for cardiac development and protection from cardiotoxins [54]. Knock-out mice deficient in ErbB2 develop dilated cardiomyopathy [53]. Mechanistically, apoptotic and metabolic pathways have been causally implicated. Rat models indicate that binding to ErB2 activates BCL-XS, which induces mitochondrial apoptosis. Mitochondria are essential for myocyte vitality, as they generate adenosine triphosphate (ATP), the "fuel" for muscle contractility and survival [55]. Decreased mitochondria reduces ATP production, which impedes cardiac muscle contraction. Erb2 inhibition also adversely impacts depolarisation. ErbB2 receptors are primarily located in the T-tubule system, which are invaginations of the myocyte cell membrane that allow for transmission of cardiac action potentials. Impaired ErbB2 function in the T-tubule system may result in diminished contractility secondary to lack of impulse transmission.

Interestingly, less cardiotoxicity is seen with tyrosine kinase inhibition of ErbB2, such as lapatinib, than monoclonal antibodies to ErbB2 such as trastuzumab [56]. It is possible that antibody-dependent, cell-mediated cytotoxicity is a substantial contributor to impaired ErbB2 function in myocytes, although this hypothesis remains theoretical and has not been scientifically substantiated.

Molecularly targeted agents associated with ventricular dysfunction

Trastuzumab

Trastuzumab, an approved agent relevant for the adjuvant and metastatic treatment of Her2 positive breast cancer, is the most recognised of the molecularly targeted agents for causing left ventricular dysfunction. Interestingly, while preclinical evidence at this point supports direct myocyte injury in the context of ErbB2 antagonism, cardiomyopathy was an unexpected toxicity that did not emerge in preclinical data or early phase clinical trials with trastuzumab. Ventricular dysfunction only became a serious concern once trastuzumab entered phase III clinical trials [57]. In an initial metastatic breast cancer trial, trastuzumab administered in combination with anthracycline-based combination chemotherapy demonstrated a surprising 27% cardiotoxicity rate, versus 13% with chemotherapy alone [58]. Subsequently, a Cardiac Review and Evaluation Committee was formed which retrospectively analysed the clinical trial experience with trastuzumab. The committee ultimately concluded that the greatest risk of trastuzumab-associated cardiac dysfunction occurred in patients receiving concurrent anthracyclines, and that cardiac monitoring and screening should be employed in all subsequent clinical trials and therapeutic use with trastuzumab [59]. Meta-analysis of the adjuvant breast cancer trastuzumab trials indicates that grade 3 or 4 cardiac toxicity occurred in 4.5% of patients receiving trastuzumab versus 1.8% in women who did not receive the drug [60]. This is notable, as all of the adjuvant trials employed cardiac screening and monitoring designs, with early discontinuation of trastuzumab if abnormal left ventricular ejection fractions or symptoms of congestive heart failure emerged.

Analyses have ensued to identify patients at risk for trastuzumab-induced cardiac dysfunction. Currently, the strongest links appear to be older age, as well as concurrent administration chemotherapy or exposure to previous anthracyclines [59]. Data regarding other potential risk factors remain under ongoing investigation. Proposed cardiovascular risk factors include baseline left ventricular dysfunction, coronary artery disease, uncontrolled hypertension, valvular heart disease, and cardiac arrhythmia. Non-cardiovascular risk factors may include chest wall radiation, diabetes and obesity [61]. The lack of adequate predictors as well as the absence of a cumulative dose-toxicity relationship render trastuzumab-induced cardiac dysfunction highly unpredictable, and all patients receiving the drug should be considered "at-risk" and undergo appropriate screening and monitoring.

The natural history of cardiomyopathy secondary to trastuzumab usage is favourable. With rare exception, full or at least partial cardiac recovery is expected after trastuzumab withdrawal, with or without institution of heart failure medications [62]. The timing for ventricular recovery is variable, ranging from 1.5 months to 1.5 years, depending on the data set [63, 64]. Re-challenge with trastuzumab after ventricular

Table 5
New York Heart Association functional classification system

Functional Class	Definition
I	No symptoms from ordinary activities; no limitation of physical activity
II	Symptoms with ordinary exertion; patients have slight, mild limitation of physical activity
III	Symptoms at less than ordinary exertion; patients have marked limitation of physical activity
IV	Symptoms at rest (any physical activity brings on discomfort); patients should be at complete rest

recovery is well documented, and most patients do not experience repeat cardiac injury with drug re-introduction [63]. Standard heart failure medications have been efficacious for both symptomatic and therapeutic relief.

Cardiotoxicity associated with other molecularly targeted agents

Lapatinib is a small molecule dual tyrosine kinase inhibitor of ErbB1 and ErbB2, used in the palliative treatment of Her2-positive breast cancer. Based upon clinical experience with trastuzumab, lapatinib was expected to induce ventricular dysfunction as it impairs ErbB2. However, a pooled analysis of 44 clinical trials with lapatinib reported low levels of cardiac toxicity of 1.5–2.2%. When ventricular dysfunction was experienced, the decrease in left ventricular ejection fraction was rarely severe, almost always reversible, and almost always asymptomatic [65]. Lapatinib is likely less cardiotoxic than trastuzumab, although head-to-head comparison data is lacking.

Sunitinib is a small molecule multi-targeted tyrosine kinase inhibitor that is garnering an increasingly concerning relationship with cardiac dysfunction. Sunitinib impedes receptors of VEGF, stem-cell-factor (KIT), platelet-derived growth factor (PDGF), colony-stimulating-factor 1 receptor, FLT3 and RET. Sunitinib is approved for treatment of advanced renal-cell cancer and refractory gastrointestinal stromal tumour (GIST). As ErbB2 is not a target of sunitinib, the exact mechanism of sunitinib-induced cardiotoxicity remains uncertain. Multiple observational reports have indicated clinically significant heart failure rates ranging from 2.7% to 11% [35,66]. According to sunitinib's product monograph, of the patients who were treated for metastatic renal cell carcinoma or GIST that had a documented drop in left ventricular systolic function, 41% recovered without intervention, 23% required intervention but normalised, 27% did not regain normal ventricular function and 9% died [67]. Based upon these findings, it has been recommended that left-ventricular ejection monitoring be incorporated into standard practice for patients receiving sunitinib [68].

Treatment-related ventricular dysfunction has also been described with a number of other targeted agents. For some, congestive heart failure is an end organ manifestation of the agent's other vascular toxicities (i.e. bevacizumab). In other instances, such as imatinib, establishment of a true drug-related cardiotoxic relationship is more challenging. Imatinib is a tyrosine kinase receptor inhibitor of c-KIT, PDGF and BCR-ABL, indicated for the treatment of chronic myeloid leukaemia and GIST. In a review of ten patients receiving imatinib who suffered severe congestive heart failure, myocardial biopsies suggest the ABL protein played an important role in maintaining the function of cardiac muscle cells, and its inhibition through imatinib predisposed to cardiac dysfunction [69]. However, clinical reports of significant cardiotoxicity remain low, and a clear-cut relationship between imatinib and ventricular dysfunction has yet to be defined.

An oncologist's approach to ventricular dysfunction

A careful assessment of cardiac history, risk factors, and physical examination create the framework for an oncologist to analyse the risks and benefits of treatment with a molecularly targeted agent associated with ventricular dysfunction. It is important to note that patients were excluded from the NSABP B-31 and NCCTG N9831 adjuvant trastuzumab trials if they reported history of active angina, arrhythmia, symptomatic valvular heart disease, poorly controlled hypertension, or history of congestive heart failure or myocardial infarction [70]. In clinical practice, these criteria have not translated to absolute contraindications to trastuzumab administration, but they should serve as "red flags" of caution.

Prior to initiation of treatment, all patients need to undergo baseline assessment of their left ventricular ejection fraction. Only patients with normal cardiac function and no symptoms of congestive heart failure as quantified by the New York Heart Association

(NYHA) classification system (Table 5) should be treated with a potentially ventricular-toxic agent [71]. Once on therapy, regular monitoring with physical examination as well as radiological measurement of left ventricular ejection fraction should ensue. Also, with any symptoms or signs suggestive of heart failure, functional cardiac assessment should occur. Guidelines detailing this process for trastuzumab have been endorsed by Memorial Sloan Kettering Cancer Centre, as well as by the British Society of Echocardiography [72,73]. It is reasonable to extend these guidelines to other molecularly targeted agents associated with impaired ventricular function.

When significant cardiac dysfunction is demonstrated, molecularly targeted therapy should be interrupted and aggressive management of heart failure should be implemented. Numerous guidelines exist on the management of heart failure, although no specific strategy has been identified for therapy in the context of molecularly targeted drug-induced cardiomyopathy. It is prudent for the oncologist to involve an expert in cardiology to help guide management. In the absence of directed evidence, it is rational to consult general population guidelines for the management of systolic dysfunction [74–76]. Initial strategies include efforts in lifestyle interventions, co-morbidity assessment, and adjunct pharmacotherapy. Lifestyle modifications include salt and fluid restriction, weight management, and alcohol reduction. One should also be careful to rule out non-drug related causes of cardiac dysfunction, such as ischaemic heart disease, valvular dysfunction, and hypertension, and treat accordingly. When a patient's symptoms are stable, upfront pharmacologic management for systolic dysfunction includes use of an ACE inhibitor in combination with a beta-blocker (although initiation times should be staggered) [77]. Loop diuretics are indicated for acute symptomatic management, but do not place a role in reversibility and cardiac remodelling. Other medications such as digoxin, spironolactone and nitrates are reserved for NYHA III to IV dysfunction, and likely should be administered in consultation with a cardiologist.

Serial reassessment of cardiac status is needed once dysfunction is demonstrated. At this point, it does not appear that long-term cardiovascular status is substantially altered by treatment-related ventricular dysfunction, and in fact many patients retreated with trastuzumab are able to safely tolerate its re-introduction [63]. However, follow-up is immature, and it remains to be seen whether drug-induced cardiac dysfunction with molecularly targeted agents portends to increased risk of future adverse events or a significant co-morbidity burden for patients.

Ventricular dysfunction summary

Ventricular dysfunction associated with molecularly targeted agents occurs via a unique mechanism, and has not been adequately explored in existing preclinical models. Trastuzumab-related cardiomyopathy is unique in its lack of relationship to cumulative dose, lack of identifiable predictive factors, reversibility, and likelihood of tolerance upon therapeutic re-challenge. Other implicated agents include lapatinib, sunitinib and imatinib, although the evidence base and depth of clinical experience are less robust. Before initiating therapy with an anti-cancer agent that has a significant likelihood of cardiotoxicity, careful clinical risk assessment should occur in conjunction with documentation of normal baseline left ventricular ejection fraction. When drug-induced systolic dysfunction does occur, the suspect agent should be discontinued and vigorous management of heart failure should ensue as per standard population guidelines. The long-term implications of drug-induced cardiotoxicity are currently unknown; however, it is promising that most individuals readily respond to strategies of cardiac recovery, and often return to their baseline level of function.

QT prolongation

QT prolongation is a rare, but serious, drug-induced cardiotoxicity. Before the molecularly targeted era, QT prolongation and its adverse sequelae of ventricular tachyarrhythmias registered on oncologists' radars as an infrequent toxicity associated with use of arsenic trioxide, the drug of first choice for acute promyelocytic leukaemia [78]. As arsenic trioxide has a known efficacious role, its arrhythmogenic risk has been tolerated. However, for most oncologists, usage of arsenic trioxide is low, and thus QT toxicity is rarely a concern. Recently, QT effects have emerged as an issue of importance for oncology drug developers, as several novel agents being tested in early phase trials have been associated with this adverse outcome, infrequently resulting in ventricular arrhythmia and sudden death [79]. Furthermore, prolongation of the QT interval by non-cardiac drugs is an important cause of delays, non-approvals, and post-marketing withdrawal by the US Food and Drug Administration (FDA) [80]. While the day-to-day clinical relevance of QT toxicity remains to be determined, one must weigh-in on this adverse effect when considering

the cardiovascular toxicity of molecularly targeted agents.

Background and mechanisms of QT prolongation

The QT interval on the electrocardiogram (ECG) is a measure of ventricular depolarisation and repolarisation, corresponding to the duration of the ventricular action potential. On the ECG, the QT interval is measured from the beginning of the QRS complex to the end of the T wave in the lead without prominent U waves (Fig. 1). The interval is known to have biologic variation, most importantly with gender and heart rate. Formulae exist to account for these biologic confounders, and "corrected" QT (QT_c) measurements of 450ms for men and 460ms for women are generally accepted as the upper limit of normal. A number of factors, particularly electrolyte imbalances, predispose to prolonged QT_c duration (Table 6) [81,82]. Ventricular arrhythmias, particularly torsade de pointes (TdP), correlate with a QT_c interval of more than 500ms [83–85].

Mechanistically, drug-induced QT interval prolongation is directly caused by a drug's three-dimensional molecular structure interacting with myocardial repolarisation ion channels (human ether-a-go-go-related gene potassium ion channels, HERG K+). Drug-HERG K+ interaction results in impeded electrical flow and delayed impulse conduction [86,87]. In silico computer simulation systems modelling a drug's three-dimensional molecular structure and subsequent ability to interact with the HERG K+ channel shed more insight into the technicalities of this process, and promise more efficient screening [86]. It is important to note that indirect mechanisms also predispose to QT prolongation events. These include baseline abnormal cardiovascular status, concomitant medication usage, and electrolyte imbalances – all of which are very common in oncology populations. In almost all reported cases of QT-related serious arrhythmias or sudden deaths with targeted oncology agents, indirect confounders predisposing to QT risk were identified. Very likely a drug needs to both directly impede HERG K+ as well as indirectly facilitate an unstable environment for QT toxicity to occur.

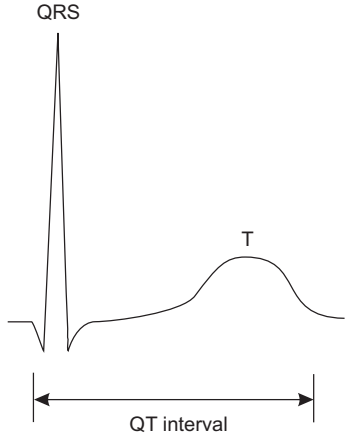

Fig. 1. The QT interval on the electrocardiogram. QRS – QRS complex; T – T-wave.

Molecularly targeted agents associated with QT interval prolongation

Molecularly targeted agents have displayed a wide range of QT toxicity in their clinical development, ranging from asymptomatic ECG findings to sudden cardiac death [79,88]. Implicated classes of agents include histone deacetylase (HDAC) inhibitors, small-molecule tyrosine kinase inhibitors, SRC/ABL kinase inhibitors, farnesyl protein transferase inhibitors, protein kinase C inhibitors, and vascular disruption agents (Table 7). The majority of implicated agents remain investigational, and the relevance of their QT-effects remains uncertain.

The most compelling pattern of QT toxicity has been demonstrated with the HDAC inhibitors, although it remains to be seen if this is a class-effect. The shared hydroxamate chemistry of panobinostat, LAQ824, and belinostat has been theorised to cause their aberrant QT effects, and a dose-dependent QT interval increase has been demonstrated with these agents [89–94]. However, romidepsin, a cyclic peptide which does not contain the hydroxamate moiety, also induces QT prolongation and has displayed the greatest number of reported sudden cardiac deaths of the HDAC inhibitors in clinical development [95,96]. In contrast, the benzamide HDAC inhibitor CI-994 has not displayed QT toxicity, although this agent remains highly investigational [97]. There is need for better understanding of the molecular, chemical, and conformational factors that underlie the direct mechanisms of QT prolongation.

QT assessment for drug developers

A number of preclinical screens for evaluation of a new drug's potential to induce QT prolongation exist: *in vitro* cell line assays of myocardial electrical repolarisation channels, *in vitro* measurement of cardiac action potential duration, and *in vivo* models of cardiac electrophysiology and haemodynamics [98]. It is important that drug developers consider the preclinical pattern of a drug's QT-effects, and that

Table 6
Factors with the potential for QT prolongation

Genetic causes		
Congenital long QT syndrome (LQT1, LQT2, LQT3)		
Acquired causes		
Cardiac structural causes	Low left ventricular ejection fraction Left ventricular hypertrophy Cardiac ischaemia Atrioventricular nodal blockade Sinus node dysfunction Mitral Valve Prolapse	
Metabolic	Electrolytes	Hypokalaemia, Hypomagnesaemia, Hypocalcaemia
	Altered Oral Intake	Starvation, Anorexia Nervosa, Liquid protein diets
	Hypothyroidism	
Drug induced	Anti-Arrhythmics	Quinidine, Procainamide, Amiodarone, Disopyramide, Dofetilide, Sematilide, Ibutilide, Berpridil, Mibefradil, Sotolol
	Psychotropics	Amitryptyline, Desipramine, Venlafaxine, Doxepin, Haloperidol, Risperidone, Olanzapine, Pimozide, Ziprasidone, Chlorpromazine, Mesoridazine, Quetiapine, Very high dose methadone
	Anti-microbials	Clarithromycin, Erythromycin, Telithromycin, Azithromycin, Gatifloxacin, Moxifloxacin, Sparfloxacin, Levofloxacin, Pentamidine, spriamycin, chloroquine, halofantrine mefloquine
	Anti-histamines	Terfenadine, Astemizole
	Other	Domperidone, cisapride, doperidol, Felbamate, Foscarnet, Fosphenytoin, indapamide, Moexipril/hydrochlorothiazide, Octreotide, Ondansetron, Quinine, Tacrolimus, Tamoxifen, Vasopressin, Arsenic trioxide
Other	HIV infection	
	Connective tissue disease with Anti-R_o/SSA antibody	
	Hypothermia	
	Intracranial disease	

HIV – human immunodeficiency virus.

this history heightens or dispels concerns for the plausibility of clinically significant toxicity.

General guidelines exist for QT assessment early in a drug's clinical development, for which determination of drug influence on the QT interval over an entire dose range is quantified [99]. This guideline was not developed specifically for early phase oncology trials, and its relevance as well as feasibility in cancer patients has been drawn into question [87]. Subsequently, "thorough QT studies" are not routinely incorporated into therapeutic cancer trials, although modified study designs involving ECG and haemodynamic monitoring are frequently required for drug candidates identified as "at risk" for QT toxicity. However, to date, no validated oncology specific clinical guidelines for QT assessment exist.

QT interval prolongation summary

QT interval prolongation is a serious adverse drug reaction due to its potential to degenerate into malignant ventricular arrhythmia such as TdP and sudden cardiac death. As QT concerns are currently most relevant for early phase drug investigators and have yet to impact standard practice, the following recommendations can be made. First, drugs that demonstrate preclinical QT effects should undergo comprehensive QT assessment in early phase clinical trials. Second, identification of cardiac risk factors and minimisation of QT-influencing medications should be performed in all patients. Third, electrolytes should be closely monitored and aggressively corrected while on "at-risk" therapy. Fourth, drugs that display QT aberrancy in early phase trials should undergo more intensive and expanded cardiac monitoring in subsequent phase II and III development. Finally, if QT interval prolongation is observed, the study drug in question should be withheld and close cardiac monitoring should ensue, with a low threshold to involve experts in cardiology. While the perceived risks of QT toxicity remain serious but rare, it is

Table 7
Summary of clinical QT interval toxicity of molecularly targeted agents

Class	Drug	QT Cardiac effects
HDAC inhibitors	Romidepsin	– QT prolongation (mean 14 ms) – arrhythmia: SVT, VT, sinus pause – sudden cardiac death
	Panobinostat	– Dose related increase in QT interval – arrhythmia: TdP (IV formulation only)
	LAQ824	– Dose related increase in QT interval – arrhythmia: atrial fibrillation
	Belinostat	– arrhythmia: SVT, atrial fibrillation
Tyrosine kinase inhibitors	Sunitinib	– Asymptomatic QT prolongation
	Vandetanib	– Asymptomatic QT prolongation
	ZL674	– Asymptomatic QT prolongation
Src/Abl kinase inhibitor	Dasatinib	– Asymptomatic QT prolongation
Vascular disruption agent	CA4P	– Asymptomatic QT prolongation – Arrhythmia: tachycardia, bradycardia, syncope
Farnesyl protein transferase inhibitors	L-778123	– Asymptomatic QT prolongation – Arrhythmia: atrial fibrillation, syncope
	Lonafarnib	– Asymptomatic QT prolongation – Arrhythmia: syncope
Protein kinase C inhibitors	Enzastaurin	– Asymptomatic QT prolongation

HDAC – histone deacetylase; SVT – supraventricular tachycardia; VT – ventricular tachycardia; TdP – Torsades de Pointes.

worthwhile for oncologists to remain committed to ongoing evaluation of this cardiovascular toxicity.

Conclusions

Novel adverse cardiovascular toxicities will become increasingly common in modern oncology, and cannot be overlooked. As patients with cancer continue to have superior outcomes due to successful anti-neoplastic strategies, a shift in paradigm from short-term to long-term patient care must occur. Hypertension and ventricular dysfunction are examples of established toxicities with serious long-term consequences. Drug-induced QT prolongation has been observed with a number of novel agents, and may emerge as a serious concern. Commitment to ongoing preclinical and clinical assessment of cardiovascular concerns in oncology is necessary to provide a tailored approach for the unique needs of this population.

Conflict of interest statement

None declared.

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