European Heart Journal (2013) **34**, 1102–1111
doi:10.1093/eurheartj/ehs181

REVIEW

Clinical update

Cancer drugs and the heart: importance and management

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Received 21 October 2011; revised 16 May 2012; accepted 23 May 2012; online publish-ahead-of-print 12 July 2012

Progress in the detection and treatment of cancer has led to an impressive reduction in both mortality and morbidity. Due to their mechanism of action, however, conventional chemotherapeutics and some of the newer anti-cancer signaling inhibitors carry a substantial risk of cardiovascular side effects that include cardiac dysfunction and heart failure, arterial hypertension, vasospastic and thromboembolic ischaemia, dysrhythmia, and QT prolongation. While some of these side effects are irreversible and cause progressive cardiovascular disease, others induce only temporary dysfunction with no apparent long-term sequelae for the patient. The challenge for the cardiovascular specialist is to balance the need for life-saving cancer treatment with the assessment of risk from cancer drug-associated cardiovascular side effects to prevent long-term damage. This review discusses concepts for timely diagnosis, intervention, and surveillance of cancer patients undergoing treatment, and provides approaches to clinical uncertainties.

Keywords Cardiovasacular side effects • Cancer treatment • Chemotherapy • Signalling inhibitors • Cardio-oncology

Introduction

New treatment modalities in oncology and haematology have improved the prognosis of patients with malignancies.[1] An important factor of this progress was the introduction of signalling inhibitors, which are now used either as monotherapy or in combination with conventional chemotherapy (*Table 1*). However, many of these new drugs also interact with cardiovascular signalling and have important side effects, particularly during times of increased cardiac stress. The cardiovascular system has limited variability in response to these iatrogenic effects, and the correct management may be crucial to ultimately improve longevity and quality of life for cancer patients. *Table 2* provides an overview of clinically relevant cardiovascular side effects associated with some more-commonly used anti-cancer agents.

The present review addresses cardiotoxicity in a different light, in that it does not attempt to provide a mere listing of frequent and infrequent adverse events but strives to provide the cardiologist with insight to appreciate the differences with which the heart can react, and how those differences affect our approach to these patients; more formal listings may be found in other sources.[2] We discuss concepts for timely diagnosis, intervention, and surveillance. Where necessary, and when strong data are not available, we provide approaches to clinical uncertainties, and in that regard, this review represents a perspective that is continually evolving as new data are presented. The vital balance of accepting temporary cardiovascular side effects so as not to impede a patient's ability to benefit from cancer treatment is a fundamental component of a new discipline now often referred to as Cardio-Oncology or Onco-Cardiology.

Non-reversible or reversible: a cardinal distinction

Historically, non-reversible cardiovascular side effects that eventually led to progressive cardiac disease were the consequence of some oncologic therapies; a prime example being anthracycline-induced cardiotoxicity leading to progressive systolic heart failure.[3] With the introduction of new cancer drugs, such as signalling inhibitors, a new phenomenon has been observed; cardiac dysfunction that resolves for most patients over time. In an effort to classify cardiotoxicity of cancer drugs, Ewer *et al.*[4] proposed a system to identify drugs that have the potential to cause irreversible damage (Type I) vs. drugs that predominantly induce reversible dysfunction (Type II) (*Figure 1*). However, this classification system does have limitations; for example, trastuzumab, a Type II drug, can

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Table 1 Systemic cancer drugs with important cardiovascular side effects; selected indications

	Class/drug	Selected indications	Important CV side effects
Cytostatic chemotherapeutics	Anthracyclines/analogues		
	Doxorubicin	Lymphoma	Cardiac dysfunction/heart failure
	Daunorubicin	Leukaemia	
	Epirubicin	Breast cancer	
		Ovarian cancer	
		Sarcoma	
	Mitoxantrone	Leukaemia	
		Multiple sclerosis	
	Pyrimidine analogues		
	Fluorouracil (5-FU)	Colorectal cancer	Coronary spasms/ischaemia
	Capecitabine	Breast cancer	
	Alkylating agents		
	Cyclophosphamide	Breast cancer	Myocardiatis (rare)
	Cisplatin	Genitourinary cancer	Thrombosis
	Antimicrotubule agents		
	Paclitaxel	Breast cancer	Bradycardia
		Colorectal cancer	
Signalling inhibitors	Anti-HER2		
	Trastuzumab	Breast cancer	Cardiac dysfunction
	Lapatinib	Gastric cancer	
	Angiogenesis inhibitors/anti-VEGF		
	Bevacizumab	Gastrointestinal cancer	Hypertension
	Sunitinib	Renal cell carcinoma	Endovascular damage
	Sorafenib	Hepatocellular carcinoma	
	BCR-ABL inhibitors		
	Imatinib	Leukaemia	Oedema, cardiac dysfunction (rare)
	Dasatinib	Gastric cancer	QTc prolongation
	Nilotinib		

Table 2 Summary of cardiovascular side effects of selected cancer therapeutics

Cardiac response	Drug	Frequency	Mechanism	Reversibility
Contractile dysfunction/heart failure	Anthracyclines	Cumulative dose-related	Myocyte death	Minimal
	Cyclophosphamide	Rare	Myocarditis	Partial
	Cisplatin	Rare	Unknown	Unknown
	Trastuzumab	Variable[a]	Contractile protein dysfunction	High
	Lapatinib			Reported
	Bevacizumab	Low	Hypertension?	Reported
	Sunitinib	Low	Mitochondrial dysfunction	Partial
	Sorafenib	Rare		Unknown
	Imatinib	Rare	Mitochondrial dysfunction	High
Arterial hypertension	*All angiogenesis inhibitors*	Moderate, dose-dependent	Endothelial dysfunction	Unknown
Myocardial ischaemia	Pyrimidine analogues	Moderate	Direct vasospasm	High, unless infarction
Thomboembolism	Cisplatin	Moderate	Endothelial dysfunction	Variable
	All angiogenesis inhibitors	Moderate	Endothelial dysfunction	Variable
Arrhythmia/QT prolongation	Arsenic trioxide	Moderate	HERG K+ blockage	High
	Lapatinib	Rare	HERG K+ blockage	Unknown
	Sunitinb	Rare	HERG K+ blockage	Unknown
	Nolitinib	Rare	HERG K+ blockage	Unknown
	Dasatinib	Rare	HERG K+ blockage	Unknown

[a]Frequently in combination with anthracyclines.

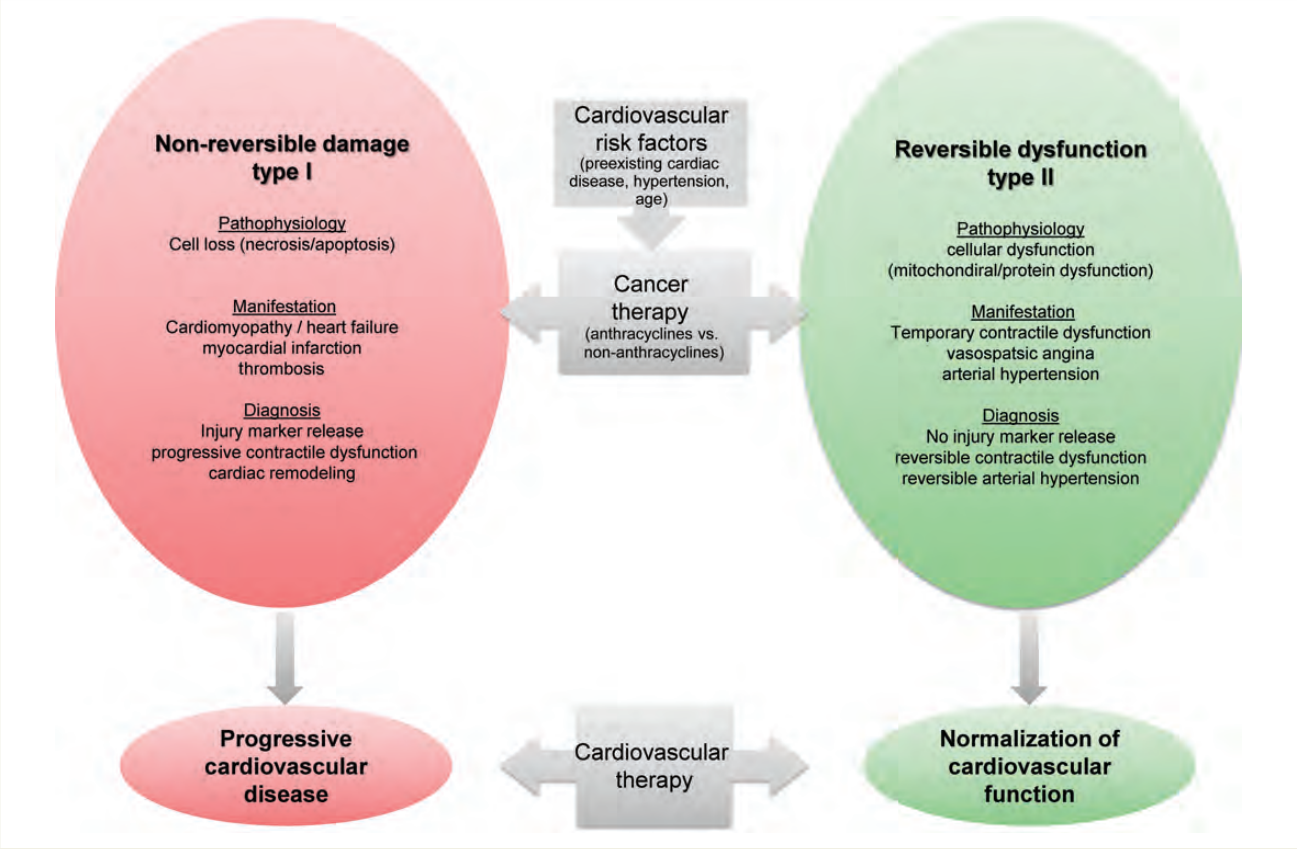

Figure 1 Depiction of the fundamental differences between non-reversible damage (type I) and reversible dysfunction (type II). Non-reversible damage is associated with cell loss, resulting in an injury that is cumulative dose-related and irreversible at the cellular level. Reversible dysfunction may result in disarray of the contractile elements, a phenomenon that has a much greater likelihood to undergo functional recovery. Risk factors and other cancer therapy may influence the expression of both forms of injury, while cardiovascular therapy may delay or prevent the ultimate expression of functional cardiac dysfunction.

trigger irreversible cardiac damage in patients with severe pre-existing cardiac disease, or potentiate anthracycline Type I cardiotoxicity.[5] For cardiovascular side effects from other modern cancer therapeutics, such as angiogenesis inhibitors-induced arterial hypertension and nephrotoxicity, the reversibility remains unknown.

Cardiac dysfunction and heart failure

Cardiac dysfunction and heart failure are among the most serious cardiovascular side effects of systemic cancer treatment. Conventional chemotherapeutics, such as anthracyclines, antimetabolites, and cyclophosphamide, can induce permanent myocardial cell injury—albeit by diverse mechanisms—and by cardiac remodelling.[6] Signalling inhibitors currently in use, like human epidermal growth factor receptor 2 (HER2/erbB2) and angiogenesis inhibitors, predominantly affect cardiac metabolism and contractile proteins, leading to transient contractile dysfunction. Understanding the mechanistic pathophysiology of cancer drug-associated cardiac dysfunction is important to predict, treat, and prevent these side effects, although it can be challenging to identify the proper mechanism in individual patients.

Anthracyclines and agents with cumulative dose-related cardiotoxicity (Type I agents)

Anthracyclines and the non-anthracycline analogue mitoxantrone (*Table 1*) are among the most effective antitumor agents; however, their use is compromised by cardiotoxicity, which has been the subject of considerable attention over the past 35 years.[7] Data from endomyocardial biopsy and troponin I measurements suggest that myocyte injury may occur during or early after anthracycline exposure. However, due to substantial cardiac reserves and the activation of compensatory mechanisms, clinical manifestation may not become apparent until months to years after the initial chemotherapy exposure (*Figure 2*).[8,9]

Clinically, early cardiac side effects are typically reversible and self-limiting and include dysrhythmia, repolarization changes in the electrocardiogram, pericarditis, and less frequently myocarditis (*Table 3*). It remains uncertain whether patients who experience these early cardiac side effects are also more likely to develop

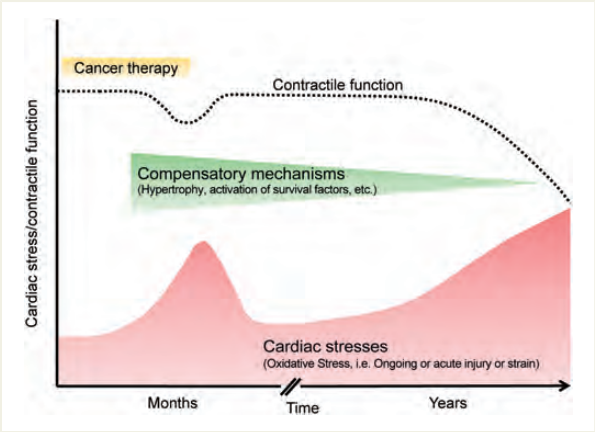

Figure 2 Graphic representation of the temporal relation between the administration of a cardiotoxic agent (e.g. anthracyclines) and the development of contractile dysfunction. Exposure to chemotherapeutic agents can induce myocardial oxidative stress and provoke dose-dependent cardiac cell loss. Activation of cardiac compensatory mechanisms including survival factors, may delay cardiac dysfunction typically for years. However, exhaustion of these mechanisms and additional stress factors, such as hypertension and coronary artery disease eventually lead to progression of disease and cardiac dysfunction.

Table 3 Key facts: anthracycline-induced cardiotoxicity

Anthracycline cardiotoxicity
Injury may result in myocyte death; irreversible
Risk factors
Cumulative dose
Pre-existing heart disease
Age (young children and >65 years)
Mediastinal radiation
Combination chemotherapy
Systolic heart failure
Typically months to years after exposure
Individual variation (genetic predisposition)
Cardioprotective strategies
Altered anthracycline structure (Epirubicin)
Altered delivery systems (liposomal preparations)
Schedule modification (24–96 h continuous infusion instead of bolus)
Cardioprotective agents (dexrazoxane)
Cardiac medications (only single-centre experience)
Angiotensin-converting enzyme inhibitors

late anthracycline cardiotoxicity, a condition that leads to cardiomyopathy and systolic heart failure. Patients treated with anthracyclines are five times more likely to develop chronic heart failure or reduced left ventricular ejection fraction (LVEF) compared with those treated with a non-anthracycline-containing chemotherapy.[10] The incidence of anthracycline-induced cardiotoxicity is dose-dependent. Patients with no other risk factors usually tolerate cumulative doses of doxorubicin of up to 300 mg/m^2 (equivalent to 550 mg/m^2 of epirubicin) quite well, with a rate of heart failure of less than 2%.[11] Above this dosage, the rates of cardiotoxicity rise exponentially. However, there is significant inter-individual heterogeneity; patients over 65 years of age and children may develop toxicity at lower cumulative dosages.[11,12] Other factors that seem to influence sensitivity to anthracycline-induced cardiotoxicity include genetic predisposition, arterial hypertension, previous or concurrent mediastinal radiation therapy, and combination with alkylating or antimicrotubule chemotherapeutics; many other risk factors have been studied, and from a practical standpoint we may assume that any insult that has previously damaged (i.e. depleted reserves) or any factor that makes the heart more susceptible to ongoing or future damage should be considered a potential risk factor for anthracycline cardiotoxicity. It should be noted, however, that those risk factors that have been studied have had a relatively short follow-up period and long-term investigations are needed to better assess the true impact of risk factors for anthracycline cardiotoxicity.[3]

The mechanism of anthracycline-induced cardiotoxicity is complex and not fully understood. The drug must enter myocytes to cause damage. Once inside the cell, anthracyclines form reactive oxygen species through iron-complex formation and cause mitochondrial dysfunction with consecutive changes in calcium homeostasis and contractile function. This also explains why one of the first manifestations of anthracycline cardiotoxicity is diastolic dysfunction—a finding with unknown prognostic significance.[13] Further increase in myocardial anthracycline concentration induces myocyte cell death either by apoptosis or necrosis, a critical factor for long-term cardiovascular prognosis. Quantitative methods of assessing myocardial injury, such as right ventricular biopsies or cardiac biomarkers, can therefore have a prognostic value.[8,14]

Several methods were investigated to reduce anthracycline cardiotoxicity, including pharmacokinetic modification by liposomal encapsulation, alteration of chemical structure leading to drugs such as epirubicin, altering drug-infusion regimens to decrease peak plasma levels, and attenuation of iron chelation through pretreatment with dexrazoxane.[15–18] Most of these methods have been associated with a reduction in cardiovascular events in anthracycline-treated patients; however, except for the use of epirubicin, most of these strategies are not in common practice in the clinical setting. Other approaches to mitigate the cardiotoxic impact of anthracyclines employ potentially cardioprotective medications, such as angiotensin-converting enzyme (ACE) inhibitors.[19] Although promising data have been published recently, convincing evidence from large randomized and prospective trials is still needed.

Other agents with myocyte destruction

Any cancer drug that may lead to myocyte injury or destruction can induce irreversible cardiotoxicity. For example mitoxantrone, an anthracycline analogue, can result in cardiotoxicity that is not clinically different from the cardiac damage caused by true anthracyclines.[20] Cyclophosphamide can cause haemorrhagic cell necrosis that is more common with larger single doses, and may lead to

severe heart failure or death. However, with the lower cycle doses presently used, these toxicities are seen infrequently.[21] Cisplatin has also been associated with late-onset cardiac dysfunction, although the cardiovascular side effects appear less severe than those of anthracyclines.[22] Finally, myocardial ischaemia induced by pyrimidine analogues infrequently leads to myocardial infarction with all long-term cardiovascular sequelae.

Myocardial dysfunction from agents not associated with cumulative dose-related cardiotoxicity (Type II agents)

A number of recently introduced cancer drugs cause cardiac dysfunction. Among them are the 'targeted drugs' against HER2/erbB2- and vascular endothelial growth factor (VEGF) signalling pathways (*Table 1*).[23]

Anti-HER2/erbB2 cancer drugs

Trastuzumab, a monoclonal antibody against the HER2/erbB2 receptor, in combination with chemotherapy substantially improves overall survival of women with HER2-overexpressed breast cancer and prolongs lives of patients with advanced gastric cancer.[24,25] It was the first type II agent to be studied broadly with regard to cardiotoxicity, as the pivotal trial of trastuzumab and anthracyclines found severe (NYHA III–IV) heart failure in 16% of patients. This incidence was much higher than that associated with anthracycline treatment alone.[26] One common finding was that the concomitant use of trastuzumab with anthracycline greatly increased the risk of cardiotoxicity. Consequently, in all adjuvant breast cancer trials, trastuzumab was only used after anthracyclines or with anthracycline-free chemotherapy (*Table 4*). This lowered the incidence of severe heart failure to 0–3.9% and the rate of (asymptomatic) cardiac dysfunction to 7–34%. Importantly, patients in these trials were carefully selected and were required to have a normal cardiac function (i.e. LVEF > 50–55%) and no significant pre-existing cardiac disease. The stringent criteria for trastuzumab discontinuation were employed and the withdrawal rate for cardiac dysfunction was as high as 16%.[27] Further analysis of the time interval between the administration of the anthracycline and the start of trastuzumab suggested that a strong correlation in the concomitant administration was associated with the highest reported incidence of cardiotoxicity, while an interval of 3 months had an incidence that was almost as low as was the incidence for those who had not been treated with prior anthracyclines.[28] This observation supported the concept that trastuzumab may well act as a modulator of anthracycline toxicity when administered during a period of myocyte vulnerability following anthracycline exposure (*Figure 2*).

Table 4 Key facts: Type II drug-induced cardiotoxicity

Anti-HER2 and VEGF cardiotoxicity
Contractile dysfunction related to contractile element and mitochondrial dysfunction
Mostly reversible
Risk factors
Anthracycline-related (when used with anthracyclines, all anthracycline risk factors apply)
Lower pre-trastuzumab LV ejection fraction
Higher age
Pre-existing heart disease
Prevention
Decreased anthracycline burden
Increased time between anthracycline and trastuzumab?

Based on the observations in these trials, the following risk factors for trastuzumab-associated cardiotoxicity were identified: prior treatment with anthracycline chemotherapy; a borderline lower limit of normal LVEF; prior treatment with anti-hypertensive medication (for the lack of better definition this likely means pre-existing arterial hypertension); advanced age; and a poorly understood result found in one trial, a body mass index >25 kg/m^2.

One common finding in these trials was that cardiac dysfunction and heart failure occurred predominantly during the trastuzumab treatment and was frequently reversible.[29] However, only data from about 5 years of the patient follow-up in the most prominent trastuzumab trials are available, and longer-term surveillance is needed. The cardiotoxicity of other anti-HER2 therapies, such as the small molecule tyrosine kinase (TKI) inhibitor lapatinib, look promising, however, but are still under investigation.[30]

Angiogenesis inhibitors (anti-vascular endothelial growth factor) cancer drugs

Angiogenesis inhibitors that target VEGF with either antibodies against VEGF (bevacizumab) or small molecule TKIs (sunitinib, sorafenib) prolong the lives of patients with a variety of solid tumours, including metastatic colorectal, renal cell, hepatocelluar cancer, and in GI stromal tumours.[31,32] Vascular endothelial growth factor signalling also plays a role in myocardial and vascular homeostasis; therefore, it is not surprising that these drugs can affect endothelial cells, myocyte function, and metabolism.[33]

Bevacizumab was associated with cardiac dysfunction and heart failure in up to 3.8% of patients, particularly when used together with or after anthracyclines.[34] Two recent meta-analysis, including almost 7000 patients treated with sunitinib and 900 patients treated with sorafenib, found a rate 4.1% for sunitinib-induced heart failure and 1% for sorafenib-associated cardiac dysfunction.[35,36] However, most of these data are from retrospective analyses; only few trials have evaluated cardiac function and heart failure prospectively. Therefore, none of the data provided regarding these agents should be considered definitive, and on-going studies will investigate these effects in further detail.

The pathophysiology of anti-VEGF-induced cardiac dysfunction and heart failure remains poorly understood. Sunitinib can induce myocyte apoptosis in preclinical models: although, similar to trastuzumab, cardiac biopsies from patients treated with this agent show no major myocardial injury.[23] Furthermore, all of these agents can induce arterial hypertension, which may lead to secondary heart failure in vulnerable patients.

These newer therapies should not yet be considered to have a class effect on the heart; they have different mechanisms of oncologic efficacy, affect different metabolic pathways, have varying half-lives, and are used in very different populations with differing

underlying predispositions for cardiac events. The mechanisms of action vary between agents, as do their intended direct effects on signalling within cells. Furthermore, yet to be studied indirect effects may play a role in causing a variety of side effects and toxicities to be seen in patients.[23]

BCR-ABL inhibitors

Imatinib and dasatinib are a small molecule TKIs used for the treatment of chronic myelogenous leucemia (CML) and gastrointestinal stromal tumours. Initial reports described severe heart failure in 10 CML patients treated with imatinib, but these findings could not be confirmed in a large follow-up study.[37,38] Isolated events of heart failure were also reported in CML patients treated with dasatinib.[39] Both compounds can also induce peripheral oedema, pleural and pericardial effusion unrelated to heart failure—a condition that has to be considered in the differential diagnosis.

Cardiovascular side effects beyond cardiac dysfunction

Arterial hypertension

Cancer drug-induced arterial hypertension is now recognized as an entity primarily associated with the use of angiogenesis inhibitors.[40] On a dose-dependent basis, these drugs can worsen pre-existing hypertension, or can cause *de novo* hypertension to develop. It is difficult to determine the true incidence of anti-VEGF-induced hypertension since various methods of blood pressure measurement and definitions of hypertension have been used in trials. A recent meta-analysis of studies with bevacizumab reported an incidence of more than 23% for any grade hypertension, with almost 8% of patients experiencing severe hypertension.[41] The incidence of arterial hypertension associated with sunitinib and sorafenib appear similar, and patients with pre-existing hypertension or renal cell cancer have a higher risk.[42,43]

Hypertension can occur at any time during treatment: acute complications include heart failure, proteinuria with renal thrombotic microangiopathy, intracerebral haemorrhage, and, infrequently, reversible posterior leukoencephalopathy.[40] It is unclear if patients will encounter hypertension-induced long-term consequences, such as cardiac and renal remodelling. For most patients, the condition improves when angiogenesis inhibitor treatment is held or stopped altogether, but in some instances profound hypertension may persist and become life-threatening. Interestingly, in the case of sunitinib, a correlation has been demonstrated between oncologic efficacy and hypertension, suggesting that blood pressure increases may be a marker for efficacy rather than, or in addition to, a simple cardiac adverse event. Treatment of sunitinib-associated hypertension has not been shown to impair oncologic response, but further studies are needed. Such interactions further support the need for careful monitoring and clinical correlations between efficacy and adversity, and the need for a broad onco-cardiologic perspective (*Table 5*).

The mechanism of angiogenesis inhibitor-induced hypertension is not completely understood, but may be directly linked to the inhibition of VEGF-2 signalling.[44] Vascular endothelial growth factor signalling is important for proper endothelial function and nitric oxide synthesis; inhibition impairs vasodilation.[45] Other effects of VEGF inhibition may include induction of endothelial cell death and rarefaction of resistance vessels.[40] Hypertension involves mechanisms similar to those of tumour destruction, and therefore may also be a marker for efficacy of angiogenesis inhibitors.[46]

Table 5 Key facts: cancer drug-induced arterial hypertension

Arterial hypertension
Primarily with angiogenesis inhibitors
Mechanism: endothelial dysfunction
Risk factors
Pre-existing hypertension
Consequences
Acute heart failure, generally reversible
Proteinuria, renal failure
Intracerebral haemorrhages
Reversible posterior leuckoencephalopathy
Prevention
Optimal treatment of per-existing high blood pressure
Treatment
No trial-based evidence
Use common antihypertensives
Caution with non-dihydropyridine calcium channel blockers

Vasospastic and thromboembolic ischaemia associated with anti-cancer treatment

Among agents associated with coronary artery spasm, the pyrimidine analogues 5-fluorouracil (5-FU) and its oral pre-drug capecitabine are the most common.[47–49] Underlying coronary artery disease has been associated with an increased incidence of coronary artery spasm, although there are patients with normal coronaries that have had spasms while being treated with these drugs. Rhythm disturbances accompanying ischaemic events have been reported as well. Ischaemia most typically occurs after the second or third administration of these antimetabolites. Nitroglycerin and calcium-channel blockers are often effective for the treatment and prevention of ischaemia. In rare instances, progression to myocardial infarction has been reported.

Thromboembolic events

Patients with malignancies are in a hypercoagulable state and conventional chemotherapeutics, signalling inhibitors, and endocrine cancer therapies can further increase a patient's risk of experiencing a venous or arterial thromboembolic event (VTE and ATE, respectively).[50] For example, cisplatin was found to cause VTE in up to 18% of patients; a direct endothelial-toxic effect and changes in the coagulation system are likely responsible for this side effect.[51] Patients treated with bevacizumab also experienced a higher rate of thromboembolic events compared with patients treated with chemotherapy alone; elderly patients with cardiovascular risk factors were shown to have the highest rates of all.[52,53] Similar

risks for ATEs have been reported for sunitinib and sorafenib.[54] Increased incidences of thromboembolic events have also been found with hormonal therapy, such as tamoxifen, which is now an integral part of many breast cancer regimens.[55]

Prophylactic anticoagulation is only recommended in high-risk cancer patients who are hospitalized or undergo surgery and in selected patients with multiple myeloma.[56] Several trials are currently investigating the potential role of prophylactic low molecular heparin. There are no clear guidelines for the prevention of ATEs in the setting of cancer therapy; only evidence-based guidelines used for patients without cancer should be used until studies are conducted. It is unknown whether cancer patients have an altered risk of coronary thrombosis after stenting.

Dysrhythmia and QT prolongation

Rhythm disturbances associated with anti-cancer treatment are typically transient and not especially troubling. They occur most commonly as a consequence of metabolic changes and generally resolve after electrolyte homeostasis is re-established. Anthracyclines, for example, are associated with supraventricular arrhythmias and ventricular ectopy during and shortly after administration, a condition that usually resolves without sequelae after heart rate control. Similarly, taxanes can induce sinus bradycardia during treatment, but this is seldom severe and intervention is rarely warranted. Some rhythm disturbances are associated with structural changes within the heart, as may be seen with tumour invasion or as a manifestation of chronic anthracycline cardiomyopathy.

QT prolongation is associated with a number of anti-cancer drugs and may constitute a significant problem. Many cancer patients have multiple comorbidities, including diarrhea- and vomiting-induced electrolyte disturbances, and concomitant medications such as psychotropic medications and anti-emetics that may further prolong the QT interval. Among specific anti-cancer treatments, arsenic trioxide, typically used to treat leucemia, has received considerable attention in this regard since it may prolong the QT interval in up to 40% of treated patients and has a significant risk of Torsades de Pontes.[57] Several of the newer signalling inhibitors also prolong the QT interval, although Torsades is a relatively infrequent event. Vandetanib, an orally available multiple target TKI for the treatment of thyroid cancer, has been associated with a moderate risk of QT prolongation.[58] Nilotinib and dasatinib can also prolong the QT interval, although symptomatic manifestations were recorded in only a few patients.[59] In patients treated with lapatinib or sunitinib, QT prolongation was rarely observed.

Diagnostic considerations

While cardiovascular side effects such as arterial hypertension, myocardial ischaemia, dysrhythmia, and thrombosis can be readily diagnosed, the assessment of cardiac dysfunction and its prognosis is more challenging. Most currently used methods assessing cardiac function cannot differentiate between irreversible (Type I) and reversible (Type II) cardiotoxicity, and may mislead physicians to stop potentially lifesaving cancer therapy unnecessarily.

Historically, patients with anthracycline-induced cardiotoxicity were evaluated with right-ventricular endomyocardial biopsies; morphologic changes correlated with the cumulative dose applied and (to a limited extent) with the onset of heart failure.[60,61] However, correlation of biopsy scores with non-invasively assessed LVEFs was poor.[9] More recently, the predictive value of serial LVEF evaluation by either echocardiography or multiple gated acquisition (MUGA) scans in adult cancer patients was assessed in several studies. While some investigators found an early drop in LVEF to be predictive for later onset of heart failure, others did not.[11,62,63]

Despite these limitations, non-invasive imaging is now commonly used in cancer patients for initial screening and detection of cardiac dysfunction during cancer therapy.[64] Although these methods of evaluating patients for cardiotoxicity are useful, and should be applied for any patient at risk for cardiac dysfunction, they have limited accuracy for risk stratification. Newer echocardiographic modalities, such as tissue Doppler and strain techniques, were shown to detect anthracycline-induced cardiac dysfunction earlier than conventional echocardiography, but it is not known if these methods have a higher specificity to detect Type I cardiotoxicity.[65] Other imaging methodologies that can assess myocardial tissue structure may prove superior to echocardiography and MUGA; initial data with cardiac magnetic resonance look promising.[66]

The limitations of cardiac imaging to risk stratify cancer patients with cardiac dysfunction may be resolved by the use of cardiac biomarkers. These biomarkers should readily identify myocardial and endothelial injury; these would be particularly useful if they predict cardiovascular outcome for patients.

Early data assessing brain natriuretic peptide (BNP) in patients treated with anthracyclines showed that most patients experience a transient increase in this biomarker and the predictive value for long-term cardiotoxicity may be limited when used alone.[67,68] Troponins I and T have been shown to be predictive markers for late anthracycline cardiotoxicity in children.[69] Furthermore, Cardinale and colleagues successfully used troponin to identify anthracycline-treated patients who would benefit from treatment with an ACE inhibitor.[70] Despite these promising results, the assessment of cardiac biomarkers is not being done routinely in patients undergoing potentially cardiotoxic cancer treatment and there is a need for large, multicentre trials to evaluate the role of biomarkers in this population.

Key clinical points

Cancer drugs inducing cardiac dysfunction and heart failure

Because of the side effects, and the availability of alternative, less cardiotoxic regimens, treatment with anthracycline has declined over the last decade; also, the exceedingly high cumulative doses used previously are employed much less frequently now. Notwithstanding these considerations, anthracyclines are still widely used, and it is likely that these agents will remain part of our therapeutic

armamentarium for some time to come. Evidence-based algorithms for pre-treatment evaluation and surveillance of adult patients during and following cancer treatment do not exist; they are unlikely to evolve, in view of the diversity of both treated populations and variety of regimens employed. Additionally, prospective long-term studies focusing on late cardiotoxicity are few. Despite these limitations, we present our approach based on data derived from experience with our particular patient population.

Prior to anthracycline treatment, we obtain a comprehensive medical history and complete a physical examination, supplemented by an electrocardiogram, baseline measurement of LVEF, and cardiac biomarkers troponin and BNP. This information helps stratify patients at low, intermediate, or high risk for cardiotoxicity, each of which should be treated differently. Patients without significant cardiac history who are under age 65, and have normal LVEF and cardiac biomarkers should be considered low risk. Such patients will usually tolerate up to six cycles of an anthracycline-containing regimen without unacceptable cardiac risk. If any exams prior to chemotherapy are indicative of pre-existing or active cardiovascular disease, the patients would be considered either intermediate or high risk for cardiotoxicity. In these cases, a dialogue with the treating oncologist in an attempt to balance oncologic benefit with anticipated cardiovascular risk is warranted. A less cardiotoxic regimen might be particularly important if treatment with a signalling inhibitor is planned after chemotherapy.

We re-assess cardiac function of all patients after four cycles of chemotherapy to identify asymptomatic patients who are experiencing increased cardiac damage; if LVEF has decreased by either 15 percentage points, or 10 percentage points to a value below 50 and a repeat assessment after 3 weeks confirms the finding; or if troponin or BNP are elevated, we discuss alternative chemotherapeutic regimens with the oncologist, as continuing treatment with an anthracycline carries increased risk for cardiotoxicity. The parameters suggested here represent a balance between over-inclusiveness that may result in increased monitoring and under-inclusiveness that may miss potentially important early signs of cardiac damage. They proved reasonable in many recent cancer trials testing potentially cardiotoxic drugs, but are not yet universally accepted. Additionally, considerable variation exists in the measurement of LVEF in that factors unrelated to the cancer drug may have a significant impact on cardiac function. As discussed earlier, newer imaging modalities may be more helpful in detecting early signs of cardiotoxicity, but these methods have not yet been shown to predict long-term prognosis of patients. Regardless of the technique employed, elevated concern at the time of the cardiac re-assessment moves such initially low-risk patients into the intermediate risk group (*Figure 3* for specific recommendations).

Treatment of anthracycline-induced cardiac dysfunction warrants aggressive intervention with standard modalities consistent with treatments for other forms of heart failure. When the underlying malignancy is well controlled and life-expectancy does not preclude aggressive interventions, even the use of devices and in extreme instances, cardiac transplantation may be considered.[71] No clear consensus regarding the duration of the follow-up for asymptomatic patients exists. Nevertheless, studies of patients undertaken years after their treatment with anthracycline-based regimens have shown cardiac abnormalities; additionally, patients may develop frank heart failure that may be due to intercurrent stress or injury, making some level of follow-up mandatory. A reasonable schedule might include a measurement of systolic function at 6 months after conclusion of treatment, annually for 2 or 3 years thereafter, and then at 3–5-year intervals for life. Any cardiovascular occurrences during the follow-up warrant more stringent surveillance. High-risk patients, e.g. those with underlying cardiovascular disease, or those who have received $>300\ mg/m^2$ of doxorubicin or equivalent, may be monitored more frequently, although data to support an outcome advantage resulting from such monitoring has not been reported.

Optimal surveillance for patients treated with Type II agents is not well established. Patients who have received both anthracyclines and newer signalling inhibitors who develop cardiac failure should be treated and monitored as suggested above. Those who develop cardiac dysfunction during or following treatment with type II agents in the absence of anthracyclines can be observed if they remain asymptomatic and LVEF remains >40% (*Figure 3*). Persistently low or further declines in LVEF or development of symptoms should trigger discussion of risk and benefit with the treating oncologist, as well as consideration for pharmacologic cardiac treatment. Duration of cardiac therapy has not been studied sufficiently to warrant guidance; some patients have been successfully discontinued 6 months following the recovery of LVEF into the normal range, with no subsequent dysfunction. Most patients tolerate anti-cancer therapy after treatment for the cardiac dysfunction, but isolated instances of recurrent symptomatic dysfunction that require cessation of anti-cancer therapy have been reported. Reintroduction of anti-cancer therapy is a priority, when possible, even if cardiac therapy must be continued throughout.

Cancer drugs inducing arterial hypertension

Careful monitoring and treatment of blood pressure throughout therapy with angiogenesis inhibitors is important. There are no evidence-based therapeutic guidelines available for patients experiencing elevated blood pressures; we have successfully used ACE inhibitors, beta-blockers, and dihydropyridine calcium channel blockers. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) should only be used with caution, since they are cytochrome P450 3A4 inhibitors and can interact with the metabolism of several cancer drugs. Some have advised that diuretics should not be used as first-line therapy since small molecule VEGF TKIs sometimes lead to severe diarrhea and potential dehydration. In general, angiogenesis-inhibitor induced hypertension is manageable, and we only stop treatment with VEGF inhibitors for severe hypertension (*Figure 3*), or if the patient experiences additional hypertension-related complications. We agree with recently published recommendations of the US National Cancer Institute to maintain patients' blood pressure at lower than 140/90 mmHg.[40]

		Hypertension			Cardiac Dysfunction			Heart Failure	
		Grade I[a] 140-159/ 90-99mmHg	**Grade II** 160-179/ 100-109mmHg	**Grade III** ≥ 180/ ≥ 110mmHg	**Mild** LVEF ↓ >15%, LVEF > 50%	**Moderate** LVEF 50-40%	**Severe** LVEF <40%	**Mild** NYHA II	**Severe** NYHA III-IV
Chemotherapy	**Anthracycline-containing CT**	· treat hypertension · continue CT			· continue CT	· confirm LVEF after 3 weeks · hold CT · consider therapy for LVD	· confirm LVEF after 3 weeks · stop CT, discuss alternatives · treat LVD	· confirm LVEF after 3 weeks · hold CT · treat HF	· confirm LVEF after 3 weeks · stop CT, discuss alternatives · treat HF
	Non-anthracycline-containing CT				· continue CT	· confirm LVEF after 3 weeks · continue CT · consider therapy for LVD	· confirm LVEF after 3 weeks · stop CT, discuss alternatives · consider therapy for LVD	· confirm LVEF after 3 weeks · continue CT · treat HF	· confirm LVEF after 3 weeks · stop CT, discuss alternatives · treat HF
Signaling Inhibitors	**Anti-HER2** · post anthracyclines	· treat hypertension · continue CT			· confirm LVEF after 3 weeks · continue CT	· confirm LVEF after 3 weeks · continue CT · consider therapy for LVD	· confirm LVEF after 3 weeks · hold CT · treat LVD	· confirm LVEF after 3 weeks · hold CT · treat HF	· confirm LVEF after 3 weeks · stop CT, discuss alternatives · treat HF
	· post non-anthracyclines				· rare			· confirm LVEF after 3 weeks · hold CT if LVEF is <40% · treat HF	· confirm LVEF after 3 weeks · stop CT · treat HF
	Angiogenesis Inhibitors	· treat HTN · continue CT	· treat HTN · consider holding CT	· treat HTN aggressively · stop CT, discuss alternatives	· check for HTN · Continue CT	· check for HTN · discuss CT if bevacizumab or sunitinb · consider therapy for LVD	· check for HTN · stop CT, discuss alternatives · treat LVD	· check for HTN · hold CT · treat HF	· check for HTN · stop CT, discuss alternatives · treat HF

Figure 3 Therapeutic considerations for patients under active cancer treatment with cardiovascular side effects. [a]Hypertension grade according to European Society of Hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Classification; CT, cancer therapy; LVD, left ventricular dysfunction; HF, heart failure; HTN, hypertension.

Summary and conclusions

The recognition of cardiac problems related to the treatment of cancer is complex. The heterogeneity of the population makes comparison between and among groups difficult. Studies on sufficiently large populations are frequently not available, and the number of new agents used in the treatment of some diseases makes evaluation of large cohorts impossible. Some reported results are therefore fragmented, and prospective data on long-term survival, treatment strategies, and monitoring represents all too often expert opinion rather than firm and established data-derived certainty. Identifying patients who are at increased risk for cardiovascular problems associated with the cancer treatment, or who develop side effects following treatment is a major component of an evolving area often referred to cardio-oncology. Working together with oncologists, cardiologists can offer vital support to those who are the primarily clinicians treating cancer patients so that therapy can be optimized; the goal should be to maximize meaningful survival. Judicious scrutiny of the needs of these complex patients requires careful balance: excessive concern regarding potentially reversible cardiac issues may compromise the administration of highly beneficial anti-cancer therapies, while under-appreciation of cardiac risk may result in life-long cardiac concerns for a patient who has been cured of their cancer. Knowledge of the cardiac effects of anti-cancer agents balanced with knowledge regarding the natural history of the malignancy and the likelihood of tumour response offers such patients the greatest chance for long-term disease-free survival.

Through observation of side effects caused by newly developed cancer therapeutics, some cardiovascular signalling pathways have become more clearly understood. It is postulated that the Neuregulin/erbB2/HER2 signalling pathway, the target of several anti-cancer therapies, plays an important role in cardiovascular homeostasis, and studies are being conducted to evaluate the stimulation of this pathway to treat heart failure patients.[72]

Signalling inhibitors, chemotherapeutics, and combinations thereof are the subject of intense research and ongoing clinical trials in oncology. New cancer therapeutics will continue to target signalling cascades that may also be important for the survival and homeostasis of cardiovascular tissue.[73] Cardiovascular side effects from these agents should be expected because of their direct effect on signalling or the potential of additional non-targeted inhibitory effects.[23]

Acknowledgements

We thank Patrick Lobdell for excellent editorial help. Part of this manuscript was written during a sabbatical of T.M.S. at Mayo Clinic, Jacksonville, FL, with Dr Edith A. Perez.

Funding

This work was supported by the Swiss National Science Foundation grant 3231-054985.98/1 and 32-55136.98 to T.M.S.

Conflict of interest: T.M.S.: Consultant or Advisory Role: Hoffman La Roche (Uncompensated), Glaxo Smith Kline (Uncompensated), Speakers Bureau: Ratiopharm, Funding: Hoffman La Roche. M.S.E. owns no direct equity interest in any health care entity. He is a consultant to GlaxoSmithKline, Roche Laboratories, Helsinn, and Boehringer-Ingelheim Laboratories with regard to new drug development. He has been a paid member of Data Safety Monitoring and Cardiac Advisory Boards.

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