Chapter 15
Cardiotoxicity

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Abstract Although outcomes in cancer patients have dramatically improved with the development of novel cancer chemotherapies and combination treatment, these developments are nonetheless associated with emerging concerns over drug-induced cardiotoxicity. Moreover, recent incorporation of targeted therapies into therapeutic regimens has widened the cardiotoxic spectrum. Knowledge of these side effects and the main risk factors associated with cardiotoxicity in cancer patients is essential for adequate monitoring and early treatment of such events in these patients. This concern is reflected in drug development with an emphasis on improved characterization of potential cardiotoxicity of new compounds during the early phases of development and designing safer drugs. This chapter summarizes the major cardiotoxic effects and pathophysiology of a large number of antineoplastic treatments currently in use. Current recommendations for early treatment and future development are also described.

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Introduction

Oncologists are becoming increasingly concerned about the presence of cardiotoxicity associated with many antineoplastic agents currently used to effectively treat patients, particularly in light of the observation that such chronic adverse events may worsen the long-term outcomes of survivors [1–4]. It is especially important given that the general population is aging and that cancer and cardiovascular diseases are common in this elderly population. In addition, novel mechanisms of cardiotoxicity associated with classic cytotoxics and new targeted therapies have been described. There is thus a need for cooperation between cardiologists and oncologists to improve prevention and management of cancer-associated cardiovascular events. Various authors have recently proposed the need for a novel discipline that has been referred to as cardio-oncology or onco-cardiology [5].

Cardiotoxicity is defined by the National Cancer Institute (NCI) as "toxicity that affects the heart" [5], which not only includes direct effects on the heart but also hemodynamic flow alterations or thrombotic events associated with cancer treatment. The most common complications related to anticancer treatment include dilated cardiomyopathy due to myocardial necrosis, rhythm disturbances, and angina or myocardial infarction secondary to vasoocclusion or vasospasm. Several drugs act via a combination of the underlying mechanisms that result in these conditions, but typically one is predominant in the clinical landscape for each drug [5–7].

The incidence of both cancer and heart disease increase with age. Additionally, the presence of an underlying heart condition increases the risk of cardiotoxicity of any kind [8], leaving the elderly population more prone to developing cardiotoxicity.

Table 15.1 Drug-induced ventricular dysfunction classification

	Type I	Type II
Reversibility	No	Yes
Cumulative dose-related	Yes	No
Ultrastructural changes	Vacuoles, sarcomere disruption, necrosis	Not relevant
Drugs	Doxorubicin	Trastuzumab
	Mitoxantrone	Sunitinib
	Cyclophosphamide	Lapatinib
		Imatinib
		Bortezomib

Cardiomyopathy: Left Ventricular Dysfunction

Anthracycline-related cardiomyopathy is the paradigm of chemotherapy-induced cardiotoxicity, but in recent years, other agents have also been shown to induce cardiomyopathy, such as trastuzumab and the tyrosine kinase inhibitors sunitinib, lapatinib, and imatinib.

A classification of cardiomyopathy developed in association with an anticancer treatment has been proposed, based on its reversibility and observed pathological features (Table 15.1) [9], Type I agents, such anthracyclines, mitoxantrone, or cyclophosphamide, induce irreversible myocardial damage, which correlates with the cumulative dose. On the other hand, type II agents, such as trastuzumab or tyrosine kinase inhibitors, induce potentially reversible cardiomyopathy without ultrastructural myocyte damage. Based on the transient nature of this cardiotoxicity, the anticancer agent may be resumed after recovery from toxicity, assuming an acceptable risk.

Anthracyclines

Anthracyclines, the cornerstone treatment of breast cancer, sarcoma, and hematological malignancies, can potentially induce cardiotoxicity as either an early event after administration or as a chronic side effect [6–8, 10].

Acute/subacute cardiovascular complications include those occurring within the first 2 weeks after dosing. They consist of electrocardiographic abnormalities, supraventricular or ventricular arrhythmias [11], or a pericarditis-myocarditis syndrome [12]. Chronic cardiotoxicity is manifested as clinical heart failure or subclinical decline in myocardial function. For some patients, this toxicity constitutes an early event (within the first year) after chemotherapy completion, while others experience it as a delayed effect manifesting more than 1 year after treatment completion [13].

The main mechanism associated with anthracycline-related cardiotoxicity is oxidative stress, which generates free radicals that induce cellular membrane damage due to lipid peroxidation [5]. Other proposed mechanisms include mitochondrial DNA mutations, calcium imbalance, direct DNA damage, and deregulation of cardiac transcription factors. Endomyocardial biopsies show several specific features under electron microscopy such as vacuole formation, disarray of the contractile elements, and myocyte necrosis [14–16]. Furthermore, these findings have been shown to correlate with cumulative dose, which is considered by some to be the main risk factor associated with anthracycline-induced cardiomyopathy [10]. For instance, cumulative doxorubicin doses of 400–450 mg/m^2 result in a 5 % likelihood of congestive heart failure [17]. An additional risk factor identified is the rate of infusion, with lower infusion rates appearing to be less harmful [17, 18].

Various studies have observed anthracycline toxicity at lower cumulative doses than expected in specific susceptible patient populations, based on the following risk factors: planned cumulative doxorubicin dose >300 mg/m^2 [8, 19], prior cardiac irradiation [20], previous heart disease [21], hypertension [21], coronary artery disease [21], and age greater than 65 years [17]. Patients can be stratified according

to these risk factors in low-risk (no risk factors), moderate-risk (one to two risk factors), and high-risk (more than two risk factors) categories [8]. Evaluation of these risk factors, adequate correction of reversible risk factors prior to anthracycline treatment, and subsequent close monitoring of high-risk patients are paramount.

One approach to reducing anthracycline cardiotoxicity involves the development of new compounds and formulations. Epirubicin and liposomal formulations are good examples. Epirubicin is a semisynthetic epimer of doxorubicin that induces less cardiotoxicity than doxorubicin at equivalent myelosuppressive doses, allowing administration of approximately one-third more equivalent treatment cycles [22–25]. Liposomal formulations confer substantial cardioprotection, as they induce changes in the drug distribution pattern, achieving lower concentrations in the heart and higher concentrations in the tumor. Thus, pegylated liposomal doxorubicin allows administration of twice as many cycles compared to the native compound [26, 27]. Moreover, high distribution to peripheral tissues has widened its oncological spectrum, leading to approval for use in ovarian cancer, multiple myeloma, and AIDS-related Kaposi's sarcoma, in addition to breast cancer. Pegylated liposomal doxorubicin is thus a possible chemotherapeutic alternative in patients requiring anthracycline treatment when a cardiac-sparing agent is sought.

Mitoxantrone

Structurally related to anthracyclines, mitoxantrone induces similar ultrastructural changes in myocytes. Its potential to induce cardiotoxicity is linked to its cumulative dose or of any other type I agents [28].

Cyclophosphamide

This alkylating agent produces myocardial hemorrhagic necrosis, especially with high-dose regimens. Distinct from anthracyclines and mitoxantrone, cyclophosphamide-induced cardiotoxicity is

less dependent on the cumulative dose and more closely related to the dose administered in an individual cycle [29, 30].

Trastuzumab

This humanized monoclonal antibody against HER2 tyrosine kinase receptor is effective in patients with HER2-positive breast cancers (20–25 % of all breast cancers). Trastuzumab induces left ventricular dysfunction, which mimics the stunning or hibernation phenomenon described in myocardial ischemia [9]. Extensive data supporting the underlying mechanism for this toxicity have been published; HER2 is also expressed in the heart, and preclinical studies suggest that perturbation of downstream pathways affects cardiomyocyte survival and adaptation to stress. According to trastuzumab adjuvant trials [31–33], associated cardiotoxicity is not dependent on cumulative dose, is reversible, and does not result in endomyocardial ultrastructural changes [9].

A number of risk factors have been associated with higher incidence of trastuzumab-induced cardiotoxicity: age greater than 50 years, borderline left ventricular ejection fraction (LVEF) prior to trastuzumab treatment, history of cardiovascular disease, cardiovascular risk factors (diabetes, dyslipidemia, or body mass index greater than 30), the sequence in which chemotherapy is administered, and prior anthracycline treatment (cumulative dose greater than 300 mg/m^2) [6, 34–38]. In a metastatic setting, the incidence of LVEF decrease or asymptomatic heart failure with single-agent trastuzumab was 7 %, increasing to 13 % when administered concurrently with paclitaxel and to 27 % when administered sequentially with anthracyclines [38]. The synergistic toxicity seen with trastuzumab and anthracyclines, which was also observed in adjuvant trials, may be related to two aspects of the regimen. Firstly, anthracyclines induce loss of cardiomyocytes, and thus, by the time trastuzumab is administered, several remodeling processes are underway. This favors anti-HER2 treatment-induced toxicity [39]. Secondly, HER2 appears to be required for cell repair in the heart. Trastuzumab administration might

inhibit downstream pathways, leading ultimately to increased damage and myocyte death [36, 40, 41].

It is important to note that a higher incidence of heart failure was observed in trials in which trastuzumab was administered concurrently with, or shortly after, anthracycline treatment [38]. Results of the Breast Cancer International Research Group study (BCIRG-006) are of particular interest. This study assessed the efficacy and safety of trastuzumab combined with a non-anthracycline regimen (paclitaxel, cyclophosphamide, and trastuzumab) compared to sequential administration of trastuzumab in an anthracycline-containing group (four cycles of doxorubicin and cyclophosphamide, followed by four cycles of docetaxel and trastuzumab) and in comparison to an anthracycline-containing regimen without trastuzumab [32]. In this trial, the risk of developing New York Heart Association (NYHA) class III or IV heart failure was significantly lower in the non-anthracycline arm (0.38 %) versus the anthracycline-containing arm (1.96 %).

Lapatinib

Lapatinib is an oral dual inhibitor of the epidermal growth factor receptor and of HER2. Pooled data from 44 studies suggest that 1.6 % of patients treated with lapatinib developed clinical failure or experienced an absolute LVEF decrease of ≥20 % [42]. In most cases cardiac events were reversible. The mechanism of toxicity is related to impaired myocyte response following injury secondary to inhibition of HER2 downstream pathways [36, 40, 41]. The reasons why the rates of cardiotoxicity induced by trastuzumab and lapatinib, both targeting HER2, are so different remain controversial.

Sunitinib

Sunitinib is an oral inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1–3, platelet-derived growth factor receptors (PDGFRs)-(alpha)α and (beta)β, KIT, fms-related

tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSFIR), and rearranged during transfection (RET). Chu et al. retrospectively analyzed the cardiotoxicity of this agent in 75 patients with gastrointestinal stromal tumors enrolled in phase I and II trials using sunitinib. The incidence of LVEF decrease >10 % was 28 %, while the incidence of heart failure was 8 % [43]. LVEF significantly improved after sunitinib discontinuation, and no cumulative dose relationship was observed.

It is thought that the underlying mechanism is a so-called "off-target" effect mediated by ribosomal S6 kinase inhibition, which causes ATP depletion and activates the intrinsic apoptotic pathway [36]. In contrast to trastuzumab-induced cardiomyopathy, some changes in myocardial biopsies, such as alterations in mitochondria, have been observed [43]. An additional potential mechanism is that sunitinib induces hypertension, but also impairs heart adaptation to pressure overload through VEGFR inhibition, as is the case for other antiangiogenic treatments [36]. It is still unknown whether angiotensin-converting enzyme inhibitors or beta-blockers, now commonly used to treat sunitinib-induced hypertension, have a role in preventing sunitinib-induced left ventricular dysfunction [8].

Imatinib

This is a small molecule tyrosine kinase inhibitor of ABL, ABL-related gene (ARG), PDGFRs-(alpha)α and (beta)β, and KIT. Peripheral edema has been described along with a 0.6 % incidence of heart failure, usually in older patients with prior cardiovascular disease [44]. This toxicity is considered to be secondary to endoplasmic reticulum stress response activation, and it is mediated by PKR-like ER kinase (PERK) [45].

Bortezomib

This proteasome inhibitor is associated with a 5 % incidence of heart failure [46]. It is believed that proteasome inhibition causes endoplasmic reticulum stress, leading ultimately to myocyte dysfunction [6, 47].

Coronary Artery Disease

Systemic anticancer treatments have been shown to induce coronary events, mainly via two different mechanisms: coronary artery vasospasm and arterial thrombotic events. 5-Fluorouracil is the most commonly used drug associated with the first mechanism, while antiangiogenic drugs are the archetype of the second. Additionally, other antineoplastic agents commonly linked to cardiac ischemia include purine analogues, topoisomerase inhibitors such as etoposide, and antitumor antibiotics.

Fluoropyrimidines

Treatment with 5-fluorouracil and capecitabine may lead to cardiac ischemia, myocardial infarction, and malignant ventricular arrhythmia through coronary vasospasm. The incidence of 5-fluorouracil-induced angina varies widely between studies, from as little as 1 % to up to 68 % [6, 48–51], with a mean onset of 72 h after treatment initiation [52]. The incidence of capecitabine-induced toxicity ranges from 3 to 9 % [6, 49], and its onset is typically in the range of 3 h to 4 days after treatment initiation. In a study of over 600 patients treated with 5-fluorouracil, 4 % developed clinical symptoms, electrographic changes, or both [6, 53]. In most cases, patients had a prior coronary condition. Treatment with nitrates and calcium-channel blockers has successfully prevented new episodes of ischemia in these patients [51]. 5-fluouroracil-induced toxicity appears to be dose- and rate-dependent, with continuous infusion and high doses (>800 mg/m^2) associated with higher rates of toxicity [52].

Antiangiogenic Therapies

One of the proposed mechanisms for antiangiogenic drug-induced arterial thrombosis is mediated by inhibition of the vascular endothelial growth factor (VEGF), which may impair endothelial cell regeneration after incidental trauma,

leading to subendothelial collagen exposure followed by activation of tissue factors that ultimately induce arterial thrombosis. Interference with platelet aggregation has also been described as playing a role. A third mechanism associated with sorafenib-induced ischemia has been proposed, with RAF inhibition activating two proapoptotic kinases involved in oxidant stress-induced injury in cardiomyocytes, making them more prone to ischemic damage [54].

The incidence of angina and myocardial infarction with bevacizumab, a monoclonal antibody against VEGF, varies in the literature from 0.6 to 1.5 % [55, 56]. This toxicity has not been shown to be dose-dependent, and the median time to a coronary event is 3 months. Proposed risk factors include age over 65 years and previous history of arterial thrombotic event [55].

Regarding antiangiogenic multi-targeted kinase inhibitors, in an observational study of 86 patients with metastatic renal cell carcinoma treated with sunitinib or sorafenib, 33.8 % experienced a cardiovascular event, most of which were related to myocardial damage of varying degrees. Approximately half of the cases (16.2 % of the total population) were asymptomatic and had cardiac enzyme elevations or electrocardiogram (ECG) changes. The remaining cases (17.6 % of the total population) experienced mild to life-threatening clinical symptoms. Seven patients (9.4 %) required intermediate or intensive care admission. As is discussed later, a high proportion of the patients in this study had at least one coronary artery disease risk factor [57].

Cardiac Arrythmias

Cancer patients are prone to arrhythmic events, secondary to systemic treatment as well as to other conditions and concomitant medications [58–60]. Fortunately, most arrhythmogenic events are not clinically significant rhythm alterations; in some cases, however, life-threatening arrhythmias can occur. Their early identification and treatment as well as correction of the associated risk factors are essential [59, 60].

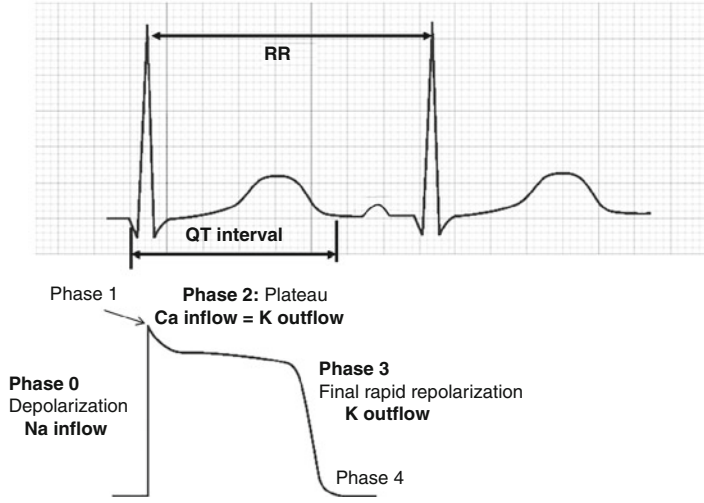

FIGURE 15.1 QT interval and its correlation with ventricular action potential. QT interval is measured from the beginning of the QRS complex to the end of the T wave; RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. The lower part of the figure shows the correlation between QT interval and ventricular action potential: phase 0 or depolarization is mainly caused by sodium influx into the cells; while in phase 2 or plateau there is equilibrium between calcium influx and potassium efflux. Phase 3 or rapid final repolarization is caused by a potassium efflux

QT Interval and Prolonged QTc Interval-Associated Arrhythmias

QTc Interval Prolongation: Definition and Physiopathology

The QT interval is measured from the beginning of the QRS complex to the end of the T wave [61, 62] (Fig. 15.1) and represents ventricular activation and recovery (depolarization and repolarization) on an ECG. Depolarization is a result of sodium and calcium influx into the cardiomyocyte. Conversely, when potassium efflux exceeds sodium and calcium influx,

Table 15.2 QTc interval correction formulas

References	Formula
Fridericia [66, 67]	$QT_F = QT / RR^{1/3}$
Bazett [66, 68, 69]	$QTc = QT / RR^{1/2}$
Framingham (Sagie) [70]	$QT_{LC} = QT + 0.154(1 - RR)$

Abbreviation: *RR* interval from the onset of one QRS complex to the onset of the next QRS complex

repolarization occurs [61]. Any drug affecting these channels, especially hERG potassium channels involved in potassium efflux during repolarization [63], can potentially cause changes in the QT interval [64, 65]. Additionally, electrolytic disturbances may also interfere in the normal process of depolarization and repolarization [58, 59].

The QT interval is prolonged with slower heart rates and shortened with faster rates. To avoid the variability associated with heart rate, several formulas have been developed that mathematically correct the QT interval, known as the QTc interval (Table 15.2) [7, 58, 59, 61, 71]. This is the most common measurement used to evaluate the arrhythmogenic potential of a drug secondary to repolarization interference. There is currently no agreement regarding which is the most appropriate method. Automatic measurements usually provide QTc intervals adjusted according to the Bazett formula. This formula is known to overestimate QTc interval at high heart rates, while the Fridericia formula seems to be more accurate in this setting [72, 73].

An international consensus regarding what can be considered as normal versus prolonged QTc intervals is also currently lacking. Generally, QTc intervals ≤430 for males and ≤450 ms for females are considered normal, while QTc intervals >450 ms in men and >470 ms in women are considered prolonged [58, 59]. These different values reflect the physiological variation of the QTc interval between genders [74]. Based on experience in patients with congenital long-QT

Table 15.3 Drugs inducing QTc interval prolongation

Drug class	Known drugs
Serotonin agonists/ antagonists	Cisapride, ketanserin, zimeldine
Antibiotics	Clarithromycin, erythromycin, gatifloxacin, sparfloxacin, pentamidine
Antifungal	Ketoconazole, miconazole, itraconazole
Antipsychotics	Phenothiazine, droperidol, haloperidol, pimozide, ziprasidone, olanzapine, risperidone
Antidepressants	Amitriptyline, clomipramine, desipramine, imipramine, sertraline, venlafaxine
Vasodilators	Bepridil, perhexiline
Antiarrhythmic drugs	IA: Procainamide, quinidine, amaline, disopyramide
	IC: Flecainide, propafenone
	III: Amiodarone, sotalol, dofetilide, ibutilide
Other	Methadone

syndrome, it is considered that the risk of ventricular arrhythmias, particularly Torsade des Pointes, is increased when the QTc interval exceeds 500 ms [73]; however, there is no threshold below which the QTc interval prolongation is considered free of proarrhythmic risk [58].

While several anticancer agents that induce QTc interval prolongation have been identified, a review of the literature shows other conditions with the potential to cause prolongation are commonly associated with cancer patients. This includes concomitant medications (Table 15.3), other comorbidities, and electrolytic disturbances (Table 15.4) [59,71,73,75]. Identification and correction of any reversible risk factors present in a patient are paramount to limiting additional toxicity when prescribing drugs with the potential to prolong the QTc interval.

Table 15.4 Drug-induced QTc interval prolongation risk factors

Parameter	Risk factor
Gender	Female
Related to drug administration	High drug concentration
	Rapid rate of intravenous infusion with a QT-prolonging drug
Electrolyte disturbances	Hypocalcemia
	Hypokalemia
	Hypomagnesemia
Previous cardiovascular disease	Myocardial ischemia
	Cardiac hypertrophy
	Congestive heart failure
	Bradycardia
	Atrioventricular block
	Myocarditis
Baseline ECG alteration	Subclinical long-QT syndrome
	Baseline QT prolongation
Endocrine disorders	Hyperaldosteronism
	Hypothyroidism
	Hyperparathyroidism
Neurologic disorders	Stroke
	Subarachnoid hemorrhage
	Intracranial trauma
Other diseases	Diabetes
	Cirrhosis

After the post-marketing withdrawal of several chemically unrelated drugs in the early 1990s due to their arrhythmogenic risk secondary to QTc interval prolongation [76], evaluation of drug-induced QTc interval changes became a

clinical issue for both anticancer agents and other medications. The International Conference Harmonization Guideline for the clinical evaluation of QT interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH E14) was published in 2005 [66]. This guideline requires every new drug to undergo clinical assessment for its repolarization effects before entering phase II trials. Nonetheless, such guidelines have limitations when evaluating anticancer agents because in most cases, studies cannot be performed in healthy volunteers; thus, studies including placebo are likely to be unethical [58, 73, 77].

Furthermore, the risk-benefit balance must be taken into account when evaluating anticancer drugs. Thus, while drugs such as terfenadine were removed from the market for inducing a mean QTc interval prolongation of 6 ms, approval has been maintained for others with similar or longer intervals. Examples include the antiemetic granisetron, which induces a 5 ms mean QTc interval prolongation [73], and drugs such nilotinib or romidepsin, approved on the basis of their efficacy, despite inducing mean QTc interval prolongations of 10 ms [78] and 14 ms [79], respectively.

Anticancer Agents Associated with QTc Interval Prolongation

Both classic chemotherapeutic agents and targeted therapies have been shown to induce QTc interval prolongation [80]. These are summarized in the following sections and in Table 15.5.

Chemotherapeutic Agents

Anthracyclines have been associated with prolonged QTc intervals and an increased arrhythmogenic risk [83, 105, 106]. Even years after having received chemotherapy, women receiving anthracycline pretreatment for breast cancer have been observed to have longer baseline QTc and significant differences in QTc interval prolongation after isoflurane anesthesia [107].

Table 15.5 Anticancer agent-induced QTc interval prolongation

Drug	Effect measured[a]	Percentage of patients/ interval duration	Reference
Chemotherapeutic agents			
Arsenic trioxide	QTc interval prolongation (any grade)	38.4 %	Barbey et al. [81]
	QTc interval prolongation ≥500 ms	26.5 %	Barbey et al. [81]
	Ventricular tachycardia	4 of 14 patients	Ohnishi et al. [82]
Anthracyclines	QTc prolongation after first dose	11.5 %	Pudil et al. [83]
	QTc prolongation 6 months after chemo	34.6 %	Pudil et al. [83]
Histone deacetylase inhibitors			
Romidepsin	Mean QTc prolongation	14 ms	Piekarz et al. [79]
	QTc prolongation 480 ms (grade 2)	10 %	Bates et al. [73]

Vorinostat	QTc prolongation grade 2	1–3 %	Munster et al. [84]
	QTc prolongation grade 3	0.8–4 %	
	QTc prolongation >60 ms enlargement from baseline	2 %	
Panobinostat			
IV, daily × 7 days every 3 weeks	DLT due to QTc interval prolongation >500 ms	4 of 6 patients	Giles et al. [85]
	Grade 2 QTc interval prolongation	1 of 2 patients	
IV, day 1, 3, and 5 every 3 weeks	QTc interval prolongation >500 ms	1 of 44 patients	Sharma et al. [86]
Dose 20 mg			Zhang et al. [87]
	QTc interval prolongation 480–500 ms	2 of 44 patients	

(continued)

Table 15.5 (continued)

Drug	Effect measured[a]	Percentage of patients/ interval duration	Reference
LAQ824	Mean QTc prolongation	14 ms	De Bono et al. [88]
Plitidepsin	Mean QT prolongation	2.51 ms	Soto-Matos et al. [89]
Multi-targeted tyrosine kinase inhibitors			
Vandetanib			
Single agent			Tamura et al. [90]
Single-agent dose 100 mg	QTc interval prolongation (any grade)	23 %	
Single-agent dose 200 mg	QTc interval prolongation (any grade)	50 %	
	Grade 3	5 %	
Single-agent dose 300 mg	QTc interval prolongation (any grade)	47 %	
	Grade 3	5 %	

Combination with docetaxel NSCLC			Heymach et al. [91]
Control arm (docetaxel)	Median QTc interval prolongation after 6 weeks of treatment	2 ms	
Vandetanib 100 mg + docetaxel	Median QTc interval prolongation after 6 weeks treatment	14 ms	
	QTc interval prolongation grade 3 or more	5 %	
Vandetanib 300 mg + docetaxel	Median QTc interval prolongation after 6 week of treatment	26 ms	
	QTc interval prolongation grade 3 or more	11 %	
Sunitinib	Torsade de pointes	<0.1 %	Food and Drug Administration [92]

(continued)

Table 15.5 (continued)

Drug	Effect measured[a]	Percentage of patients/ interval duration	Reference
Nilotinib	QTc interval prolongation >30 ms	33–40.8 %	Hazarika et al. [93]
	QTc interval prolongation >60 ms	1.9–2.5 %	
Dasatinib	Mean QTc interval changes	7.0–13.4 ms	Food and Drug Administration [94]
	QTc interval prolongation <30 ms	54 %	Johnson et al. [95]
	QTc interval prolongation 30–60 ms	36 %	
	QTc interval prolongation >60 ms	11 %	
	QTc interval prolongation 450–500 ms	21 %	
	QTc interval prolongation >500 ms	1 %	
Other agents			
Lonafarnib	QTc interval prolongation grade 3	1 out 15 patients	Hanrahan et al. [96]

Combretastatin A4 phosphate	QTc interval prolongation grades 1–2	5 %	Dowlati et al. [97]
Enzastaurin			
Single agent			
800 mg daily	QTc interval prolongation grade 3	1 out of 9	Kreisl et al. [98]
250 mg twice daily	QTc interval prolongation grade 3	1 out of 5	
Multiple doses	QTc interval prolongation grades 1–2	23 %	
350 mg twice daily	QTc interval prolongation grade 2	1 out of 7	Rademaker-Lakhai et al. [99]
500–525 mg daily	QTc interval prolongation grade 2		Kreisl et al. [100]
500 mg daily	QTc interval prolongation >50 ms	5 %	Oh et al. [101]

(continued)

Table 15.5 (continued)

Drug	Effect measured[a]	Percentage of patients/ interval duration	Reference
Multiple doses (healthy volunteers)	QTc interval prolongation >450 ms	1 out of 25	Welch et al. [102]
	QTc interval prolongation >30 ms	5 out of 25	
Combination with capecitabine			
Enzastaurin 350 mg	QTc interval prolongation >500 ms	1 out of 7	Camidge et al. [103]
Multiple doses	QTc interval prolongation grades 1–2	23 %	
Goserelin-bicalutamide	QTc interval prolongation 30–60 ms	46 %	Garnick [104]
	QTc interval prolongation >60 ms	8 %	
Leuprolide-bicalutamide	QTc interval prolongation 30–60 ms	26 %	Garnick [104]
	QTc interval prolongation >60 ms	6 %	

Abbreviation: *DLT* dose-limiting toxicity
[a]Graded according to NCI-CTCAE, version 3

The chemotherapeutic agent most closely associated with QTc interval prolongation is probably arsenic trioxide. Its potential to induce QTc interval prolongation was first described in an acute promyelocytic leukemia study in which 16 of the 40 enrolled patients experienced QTc interval prolongation >500 ms, accompanied in one case by a single, asymptomatic, brief, self-limited episode of Torsade de Pointes [108]. Pooled analysis of 99 patients enrolled in phase I and II trials with arsenic trioxide showed that 38 patients experienced QT interval prolongation, 26 of whom experienced QT interval prolongation >500 ms. Arsenic trioxide-induced QTc interval prolongation is reversible before the following cycle, dose-dependent, and also more likely to occur in females, in patients with hypokalemia, or those with an underlying heart disease [81].

Other chemotherapeutic agents associated with QTc interval prolongation are amsacrine [80], 5-fluorouracil, generally in the context of a coronary event [109, 110], and cyclophosphamide [111]. The magnitude of QTc interval prolongation associated with cyclophosphamide appears to correlate with further risk of heart failure.

Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) inhibitors are a group of compounds that modulate histone acetylation, which ultimately induces epigenetic changes in transcription. Several chemically unrelated HDAC inhibitors induce QTc interval prolongation. The first HDAC inhibitor that showed arrhythmogenic potential was romidepsin, also known as depsipeptide. A phase II study of romidepsin in metastatic neuroendocrine tumors was prematurely terminated because two patients experienced ventricular tachycardia and a sudden death was described in a third patient [112]. Pooled analysis of NCI-sponsored clinical trials including more than 500 patients showed a 10 % incidence of QTc interval >480 ms [73]. Moreover, mean QTc interval prolongation in the cardiac substudy of a phase II trial of romidepsin in T-cell lymphoma was 14 ms [79]. Romidepsin, now approved for T-cell lymphoma, merits further development

that takes into account QTc data; Food and Drug Administration (FDA) approval includes several recommendations regarding QTc interval monitoring and management of its potential prolongation [113].

Vorinostat, a phenylbutyrate-derived HDAC, led to a QTc interval >470 ms in 1 of 74 patients enrolled in a phase II study in refractory T-cell lymphoma [114]. The incidence of grade 2 QTc interval prolongation according to CTCAE v3.0 was 1–3 %, and that of grade 3 was 0.8–4 % [84]. A dedicated phase I cardiac study in advanced solid tumors showed that a single overdose of vorinostat did not significantly increase QTc interval [84]. FDA approval includes a specific recommendation for electrolyte monitoring prior to vorinostat administration to diminish the risk of QTc interval prolongation and arrhythmia [115].

Another chemically unrelated molecule, panobinostat, showed dose- and schedule-related QTc interval prolongation, with a much higher incidence of grade 3 QTc interval prolongation observed following daily intravenous administration compared to the intermittent schedule [85–87].

Multi-targeted Kinase Inhibitors

Several approved multi-targeted kinase inhibitors have the potential to induce QTc interval prolongation [59], all of which have been shown preclinically to interact with HERG K^+ channels. In the phase III randomized trial of vandetanib in medullary thyroid cancer [116], vandetanib induced a QTc interval prolongation of any grade in approximately 14 % of patients, but only 8 % had grade 3 QTc interval prolongations (i.e., which could potentially be serious) [117]. FDA approval of this drug incorporates specific guidelines for QTc interval and electrolyte monitoring and dose adjustment in the event of QTc interval prolongation [117].

FDA approval of sunitinib described a <0.1 % incidence of Torsade de Pointes risk in patients exposed to this drug [92]. For this reason, caution is recommended when administering it to any patients with electrolyte disturbances, previous history of QT interval prolongation, or other preexisting cardiac conditions.

Nilotinib and dasatinib, both ABL inhibitors, have been associated with heart failure and QTc prolongation

(see Table 15.5), with specific guidelines for the management of this toxicity in the FDA approval [78, 94].

Other Agents

Other agents such as vascular disruptors (lonafarnib [96] and combretastatin A4 phosphate [97]), protein kinase C inhibitors (enzastaurin) [98–102], or Hdm-2 inhibitors (serdemetan) [118] were shown to induce QTc interval prolongation in phase I clinical trials. Even hormonotherapy has been described as inducing QTc interval prolongation (see Table 15.5) [104, 119].

Other Chemotherapy-Induced Arrhythmias

Arrhythmias other than those associated with QTc interval prolongation have also been described. Post-chemotherapy arrhythmias are one of the most common reasons for cardiology consultations in cancer centers [120]. A variety of types have been reported, mainly sinus bradycardia, atrioventricular block, atrial fibrillation, or ventricular tachycardia; however, others have been described [60, 120].

The chemotherapeutic agent most commonly associated with rhythm disturbances is paclitaxel. The most frequent events are asymptomatic sinus bradycardia (29 %) and first-degree atrioventricular block (25 %) [121]. Fortunately, more severe conduction abnormalities are rare [122]; among 3,400 patients in an NCI database, only four experienced second- or third-degree heart block [121]. The physiopathology of these rhythm disturbances is as yet unclear; it is unknown whether it is a direct toxicity of paclitaxel on the Purkinje system, secondary to histamine release induced by the Cremophor EL vehicle, or both [121]. Paclitaxel itself might have some proarrhythmogenic potential. In the phase III randomized trial of nab-paclitaxel versus paclitaxel in metastatic breast cancer patients, bradycardia is described as an important, although infrequent (<1 %), side effect of nab-paclitaxel, which does not require the Cremophor EL vehicle [123]. Other anticancer agents have been associated with rhythm disturbance, including 5-fluorouracil, cisplatin, gemcitabine, IL-2, anthracyclines, and melphalan (Table 15.6) [11].

Table 15.6 Patients with chemotherapy-induced arrhythmia

Drug	Bradycardia	Atrial fibrillation	Ventricular tachycardia	Reference
Paclitaxel	29 % bradycardia	0.18 %	0.26 %	Rowinsky and Donehower [121]
	25 % first-degree atrioventricular block			Guglin et al. [120]
	<0.1 % second- to third-degree atrioventricular block			
Fluorouracil	2.8 %	4.2–6.5 %	1.1 %	Talapatra et al. [124]
				De Forni et al. [48]
				Guglin et al. [120]
Cisplatin	Case reports	Case reports	x-x	Hashimi et al. [125]
				Canobbio et al. [126]
				Altundag et al. [127]
				Guglin et al. [120]

Gemcitabine	2.3 %	8.1 %	1.6 %	Lin et al. [128] Gridelli et al. [129] Santini et al. [130] Sauer-Heilborn et al. [131] Zwitter et al. [132]
Anthracyclines	3.4 %	2.2–10 %	6 %	Kilickap et al. [133] Guglin et al. [120] Kilickap et al. [134] Steinberg et al. [11]
IL-2	1.08 % Associated to polychemotherapy	4.3–13.3 %	0.2–1.1 %	Lee et al. [135] Margolin et al. [136] Guglin et al. [120]
Melphalan	5 % In combination with bortezomib	6.6–11.8 %	0.7–1.5 %	Lonial et al. [137] Moreau et al. [138] Phillips et al. [139] Mileshkin et al. [140] Palumbo et al. [141]

Hypertension

Hypertension is one of the most common toxicities associated with VEGF pathway inhibitors for both monoclonal antibodies (such as bevacizumab) or multi-targeted tyrosine kinase inhibitors such as sunitinib, sorafenib, axitinib, cediranib, and telatinib, among others. Several mechanisms of action have been identified. First, inhibition of the VEGF pathway decreases nitric oxide levels, which leads to vasoconstriction. This might be responsible for the rapid increase in blood pressure after initiation of anti-VEGF therapy [142]. Additionally, sustained VEGF pathway inhibition induces endothelial cell apoptosis, which ultimately causes a reduction in the number of capillaries and increases overall vascular resistance. This second mechanism has been observed in patients treated with bevacizumab [143], sunitinib [144], and telatinib [145] and appears to be reversible within 2 weeks of treatment discontinuation [146, 147].

Incidence of drug-induced hypertension ranges from 15 to 25 % with sunitinib [148, 149], 20 % with sorafenib [150], and up to 35 % with bevacizumab, all of which are dose-dependent [151, 152]. Serious complications have been reported, such as intracranial hemorrhage and hypertensive urgency. Prior uncontrolled hypertension is a relevant risk factor for developing these complications; therefore, blood pressure normalization prior to antiangiogenic treatment initiation is essential.

Venous Thromboembolic Disease

Chemotherapy and Other Drugs

A number of agents are associated with an increased incidence of venous thromboembolic events, including cisplatin [153], vorinostat [114, 154], thalidomide [155, 156], and erlotinib [157]. Proposed mechanisms include alterations in platelet aggregation as well as direct effects on the endothelium [8].

The role of prophylactic administration of aspirin or low-molecular-weight heparin in this setting is uncertain and may benefit some high-risk patients [158].

Hormonotherapy

Tamoxifen, an estrogen receptor antagonist, has shown an increased incidence of thromboembolic events [159] and should be used cautiously in women with previous thromboembolic events. This higher risk has not been observed in the same patient population when treated with aromatase inhibitors, although a higher incidence of adverse cardiac events has been described [160]. Some data suggest a cardioprotective role for tamoxifen, supporting these differences.

Radiation-Induced Heart Disease

Although it is not a systemic therapy, radiation therapy is included in the current review because it has been shown to increase toxicities secondary to systemic therapy. External radiation therapy to the mediastinum can induce toxicity in the pericardium, coronary arteries, heart valves, and myocardium [161, 162]. A number of factors have been associated with cardiotoxicity risk – namely, radiation dose [4], the heart volume exposed, radiation delivery technique, and patient's age at the time of exposure, with patients under the age of 20 years apparently more susceptible to DNA damage [162, 163]. Two large studies of survivors of childhood cancer show an increased risk of cardiotoxicity after radiation therapy, with hazard ratios between 2 and 25, depending on the radiation doses [4, 164]. The underlying mechanism is microvascular destruction and apoptosis due to direct cellular injury, which produces fibrosis in the years subsequent to therapy. Incidence of cardiac damage from radiation has been reducing with improvements in radiation techniques.

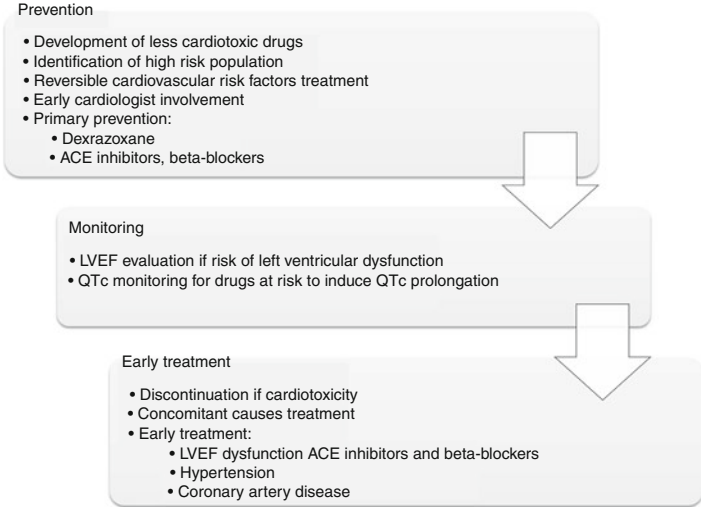

FIGURE 15.2 Proposed algorithm for cardiotoxicity prevention, monitoring, and management

Cardiotoxicity Prevention and Management

As described in Fig. 15.2, several approaches are available to limit the occurrence of cardiotoxicity and to treat it optimally in the event that it does occur [5, 7, 165, 166].

Prevention

Drug Development

Prevention of cardiotoxicity has been integrated into the early phases of drug development. Extensive efforts have been invested in the design of less cardiotoxic drugs. One of the first examples was the alternative formulations of anthracyclines; epirubicin is a semisynthetic epimer of doxorubicin with an improved cardiotoxic profile, while liposomal anthracycline formulations diminish the distribution of the drug into the heart [27]. More recent examples are nab-paclitaxel, in which paclitaxel is associated with albumin in an attempt to improve

its activity and reduce its toxicity [123], and plitidepsin, a romidepsin analog that has reduced QTc interval prolongation in the early phases of clinical development [89].

Regarding tyrosine kinase inhibitors, some of the cardiotoxic effects are thought to be a result of off-target effects of the drug, resulting from the inhibition of another kinase not involved in the drug's anticancer activity [167]. In some cases, drug reformulation to decrease its affinity for this off-target kinase could improve its cardiotoxic profile. The successfully redesigned formulation of imatinib for GIST is a good example of this approach [168].

In addition to the guidelines described in this chapter for the evaluation of QTc interval during clinical development [66], specific guidelines have been issued for preclinical evaluation of the arrhythmogenic risk of non-antiarrhythmic drugs [169], which also applies to anticancer agents.

Identification of High-Risk Populations

Cardiovascular risk factors are often underestimated in cancer patients. Some studies show that a high proportion of patients have at least one cardiovascular risk factor. Based on observational data published by Schmidinger et al., 48.8 % of patients had hypertension, 26 % had hypercholesterolemia, 22 % had type II diabetes, and 12.8 % were hypertriglyceridemic [57].

As has been described throughout this chapter, adequate control of these reversible risk factors and electrolyte disturbances are essential to diminish and control cardiotoxicity [59]. Early involvement of cardiologists in the clinical management should be encouraged in patients with a preexisting heart condition or those taking drugs that can significantly prolong the QTc interval [59].

Primary Prevention

Two randomized studies have evaluated preventive strategies for chemotherapy-related cardiomyopathy. Cardinale et al. studied enalapril, an angiotensin-converting enzyme inhibitor, versus placebo in a patient population with increased troponin I levels soon after

the start of chemotherapy [170]. Results showed a significantly reduced incidence of left ventricular dysfunction at 12 months with enalapril compared to placebo ($p<0.001$). In a smaller study by Kalay et al., 25 patients treated with anthracyclines were randomly assigned to beta-blocker treatment (carvedilol) or placebo. A lower incidence of anthracycline-induced myocardiopathy at 6 months was observed in the carvedilol group compared with placebo. These studies suggest that optimizing hemodynamic and neurohumoral status before left ventricular dysfunction onset could be beneficial and these two agents might be the preferred treatment for hypertension in this setting [171].

Dexrazoxane is an iron chelator similar to ethylenediaminetetraacetic acid. Although dexrazoxane has been shown to reduce heart failure incidence in children and adults treated with anthracyclines [172], concerns have been raised regarding a possible increased risk of secondary malignancies and a potential decrease in antitumor efficacy. In light of this, the FDA has limited its use to cumulative doxorubicin doses exceeding 300 mg/m^2 [173].

Monitoring

Left Ventricular Ejection Fraction Evaluation

Cardiac assessment prior, during, and after anthracycline treatment is a subject of controversy because many guidelines and algorithms have been published but none have been validated. Cardiac monitoring should include the patient's medical history, with a physical examination focusing on signs and symptoms of heart failure and assessing LVEF by echocardiography or radionuclide angiography. For patients without increased risk of cardiotoxicity, an estimation of LVEF after the patient has completed four to five chemotherapy cycles (200–300 mg/m^2 of doxorubicin or equivalent) is recommended to identify patients with an asymptomatic decrease in systolic function and then to reconsider further therapies. Patients at higher risk should be monitored more frequently [8].

In general, a 15 % decrease within the normal range or a 10 % decrease to a value below the lower limit of normal

LVEF is considered a significant decline of left ventricular function. These events should trigger additional evaluations, and a less cardiotoxic regimen should be considered.

Studies of optimal monitoring intervals to maximize sensitivity and specificity for detection of anthracycline-related cardiomyopathy are unclear, and further investigation will be extremely valuable.

In addition to imaging techniques, a number of serum cardiac markers are under evaluation. Serum troponin I levels are thought to reflect myocyte death and correlate with cumulative doxorubicin dose and congestive heart failure. For example, elevation of troponin I levels 72 h and 1 month after chemotherapy administration predict a late decline in LVEF and cardiac events. Similar results with troponin T have been documented [174, 175]. Elevated B-type natriuretic peptide (BNP) levels after anthracycline administration may also correlate with left ventricular dysfunction and clinical heart failure, but no standard cutoff has been established owing to interindividual variability [176–178]. Additional research is needed before the incorporation of these markers into routine practice.

QTc Interval Assessment

As previously noted, specific guidelines for drugs undergoing clinical development have been issued, ensuring evaluation of QTc interval changes related to drug administration. In addition, a number of approved drugs known to induce QTc interval prolongation, such as romidepsin, vandetanib, or nilotinib, have specific recommendations for cardiac monitoring during administration in the FDA label [78, 113, 117].

Early Treatment

Any anticancer drug should be immediately discontinued in the event of a cardiovascular event such as a significant decrease in LVEF or the occurrence of a QTc prolongation

>500 ms. Reversible associated factors should be ruled out prior to further treatment and corrected, if present.

Little information regarding cardiac dysfunction once treatment is established is available. An observational study showed an improvement in LVEF in patients with LVEF ≤ 45 % if treatment with enalapril and carvedilol was established during the 6 months after completion of anthracycline treatment [179]. A number of studies have evaluated the effect of enalapril in childhood cancer survivors with asymptomatic cardiac dysfunction. Although temporary improvement of LVEF has been observed, it is unclear whether this would impact the global outcome in the future [180, 181].

No specific guidelines have been issued for chemotherapy-induced heart failure treatment, but it is widely believed that evidence-based guidelines for the general population would also be useful for cancer patients, despite not having been specifically validated in this setting. In individual cases with reasonable prognosis and good quality of life, an implanted cardioverter-defibrillator [182] and cardiac resynchronization therapy may be used to improve left ventricular dysfunction. Data regarding the potential use of stem cell therapy for anthracycline-induced cardiomyopathy treatment are yet to be published.

Summary

Cancer patients have an increased risk of developing heart disease as a result of chemotherapy, targeted therapies, and radiation therapy. Individuals at a high risk of developing such toxicity need to be identified prior to treatment initiation to minimize this risk through cardioprotective measures or modifications to the proposed treatment regimen. Cardiovascular monitoring is essential, both during and after antineoplastic treatment, for early detection and effective management of cardiotoxicity.

An interdisciplinary approach between oncologists and cardiologists is needed to ensure optimal patient outcomes. A new discipline termed cardio-oncology or onco-cardiology is currently being developed.

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