Detection and prevention of cardiac complications of cancer chemotherapy

Détection et prévention des complications cardiaques des chimiothérapies anticancéreuses

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Summary Despite continuous improvements in management of patients with cancer, cardiac side-effects still account for a substantial limitation of chemotherapy. Evaluation of cardiac toxicity in patients includes consideration of biomarkers such as cardiac troponins and B-type natriuretic peptides, together with non-invasive imaging in the form of 2D-, 3D-, or strain-echocardiography, multiple gated radionuclide angiography, quantitative gated blood-pool SPECT, 123I-metaiodobenzylguanidine scintigraphy, or cardiac magnetic resonance imaging. These approaches differ from each other with regards to availability, accuracy, sensitivity to detect early stages of cardiac injury, individual reliability, ease of use in a longitudinal follow-up perspective, and to related cost-effectiveness. Improving prevention of these cardiac side-effects depends on several, currently unresolved issues. Early detection and quantification of cardiac damage is required to adapt chemotherapy in progress for optimal management of patients. Whether increased availability of myocardial strain imaging and repeat blood biomarkers determinations will reliably and consistently achieve these goals remain to be confirmed. Also, protective approaches to reduce cardiac toxicity of anticancer drugs should be reconsidered according to the recently restricted approval for use of dexrazoxane. Anthracycline-based regimens, encapsulated anthracyclines and non-anthracycline regimens should be revisited with

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Abbreviations: 123I-MIBG, iodine-123 metaiodobenzylguanidine; 2D, two-dimensional; 3D, three-dimensional; BNP, brain natriuretic peptide; HER2, human epidermal growth factor receptor 2; LV, left ventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated radionuclide angiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROS, reactive oxygen species; TDI, tissue Doppler imaging; TK, tyrosine kinase; VEGF, vascular endothelial growth factor.
Introduction

Despite continuous improvements in the management of patients with cancer, cardiac side-effects still represent a substantial drawback of chemotherapy. Multiple drug protocols, combination regimens and adjuvant and targeted therapies administered to patients in increased numbers have resulted in significant improvements in prognosis and survival, but these have been blunted by several disadvantages with regard to cardiac safety [1–3]. In turn, detection and prevention of these complications have become quite routine practice, especially in patients with increased risk, such as children, the elderly, patients with coronary artery disease, hypertension, diabetes or a history of smoking and those who have received previous anthracyclines or radiation therapy [4,5].

Conventional approaches for detecting myocardial damage by chemotherapy using two-dimensional (2D) echocardiography or radionuclide ventriculography have recently been challenged by more sophisticated echocardiographic techniques, including myocardial strain imaging and three-dimensional (3D) echocardiography. Biochemical methods using cardiac biomarkers such as troponins and brain natriuretic peptide (BNP) have emerged as sensitive tools for predicting subsequent cardiac dysfunction. Cardiovascular magnetic resonance imaging (MRI) has been proven to be effective and reliable in monitoring left ventricular (LV) function during therapy. In addition, MRI can be used to characterize myocardial tissue and to identify early evidence of myocardial injury.

However, despite increased recognition and detection of the cardiac side-effects of anticancer drugs, prevention has not progressed concomitantly. As a result of recent concerns regarding prevention of anthracycline-related toxicity with dexrazoxane, strategies for cardiac protection should be revisited. In addition, prevention of the cardiac side-effects of the rapidly expanding spectrum of targeted therapies remains at the planning stage and should be implemented.

Cardiac complications of anticancer drugs

Administration of cytotoxic agents and/or targeted therapies may result in several cardiac complications, including LV dysfunction, heart failure, myocardial ischaemia, arrhythmias and conduction abnormalities, depending on the drug or regimen administered and the patient being treated.

Heart failure and LV dysfunction

Anthracyclines

These potent anticancer agents act by intercalation into nuclear DNA, inhibition of topoisomerase II, production of
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5-fluorouracil and its prodrug capecitabine, as well as with taxanes (paclitaxel, docetaxel) and other microtubule inhibitors, all of which increase anthracycline-related cardiac toxicity. The combination of anthracyclines and taxanes—a standard regimen for node-positive breast cancer—increases cardiotoxicity [2–4]. Sequential combination of anthracyclines and cyclophosphamide followed by trastuzumab and paclitaxel in patients treated for human epidermal growth factor receptor 2 (HER2)-positive breast cancer results in a 3-year incidence of heart failure and cardiovascular death of 4.1% compared with 0.8% in patients receiving anthracyclines and cyclophosphamide only [17].

Tyrosine kinase inhibitors

Tyrosine kinase (TK) inhibitors comprise monoclonal antibodies directed against specific malignant cell membrane receptors associated with TK activity and small molecule inhibitors that interact with the intracellular downstream TK signalling pathways.

Trastuzumab is a humanized monoclonal antibody directed against the HER2 protein, which is overexpressed in 20–25% of breast cancers. Heart failure occurs in 1–5% of patients treated with trastuzumab and about 10% present some degree of LV dysfunction [18,19]. In another study, asymptomatic LV dysfunction was found in 7.1% of patients receiving trastuzumab and 2.2% of controls, whereas symptomatic LV dysfunction was encountered in 1.7% vs 0.1%, respectively [20]. This risk is increased with older age, coronary artery disease and combination with anthracyclines or cyclophosphamide. In a review of seven phase II and III trastuzumab clinical trials, the incidence of cardiac toxicity depended on these factors, reaching 27% in combination with anthracyclines or cyclophosphamide, 13% with paclitaxel and only 3–7% without these agents [21]. In a 4-year follow-up of 48 patients with trastuzumab-induced heart failure, Ewer et al. showed that a reduction in LV ejection fraction (LVEF) occurred within a few days after trastuzumab administration in patients who had already received anthracyclines (mean LVEF reduction from 61% to 41%). Discontinuation of trastuzumab was associated with subsequent recovery within 1–3 months. Among 25 patients in whom trastuzumab was readministered, repeat heart failure or LV dysfunction occurred in only three [22].

Clinical characteristics of trastuzumab-induced dysfunction differ from those of anthracycline-induced dysfunction, as they are often transient. Recurrences are seen inconsistently (even rarely) with subsequent administrations. In most instances, withdrawal of trastuzumab allows reversal of LVEF decline. By contrast, with anthracycline-induced myocardial injuries (myocyte loss, myofibrillar disarray, vacuoles), ultrastructural changes are not observed after trastuzumab administration. Consistent with these findings, a revised classification for chemotherapy-induced cardiac dysfunction has been proposed, according to the related mechanism, damage (anthracyclines) or dysfunction (trastuzumab) [23].

LV dysfunction has also been reported in patients receiving bevacizumab, an immunoglobulin G-targeting vascular endothelial growth factor (VEGF)-A. In a meta-analysis by Choueiri et al., which included 3784 patients, the overall incidences of symptomatic heart failure in

Other cytotoxic agents

The alkylating agent cyclophosphamide and related compounds such as ifosfamide may promote LV dysfunction and heart failure, especially at high doses or in combination with anthracyclines or cisplatin. Heart failure has also been reported during therapy with the antimitabolites

reactive oxygen species (ROS), p53 binding to DNA and induction of apoptosis [6,7].

Cardiac side-effects result from induction of oxidative stress and apoptosis. Electrons released by an anthracycline binding to DNA generate redox cycling of the quinone/semiquinone form of the drug, which interacts with iron stores to produce superoxide anions and induce the proapoptotic pathway. Transgenic mice overexpressing the superoxide dismutase and nicotinamide adenine dinucleotide phosphate (NAD[P]H) oxidase knockout mice are protected against anthracycline-induced cardiotoxicity. Similarly, inhibition of the proapoptotic cascade and activation of the antiapoptotic cascade in animal models result in reduced cardiac toxicity [1,3–7]. Pathways involving ROS production and apoptosis interact with each other. Injuries to mitochondrial DNA induced by ROS elicit proapoptotic imbalance [8], which is also enhanced by transmembrane signalling pathways activating Toll-like receptors and, in turn, the apoptotic cascade [9]. In addition, anthracyclines have recently been reported to damage cardiac progenitor cells, resulting in late/delayed LV dysfunction, which may occur 10–20 years after anthracycline treatment in children [10,11].

Acute heart failure is an uncommon but severe cardiac complication of anthracycline-based regimens and predominantly affects children. In a cohort of 1697 patients treated for non-Hodgkin’s lymphoma, acute heart failure was observed in only 0.2% of patients whereas dose-dependent progressive heart failure developed in 3.2% during therapy [12].

Progressive dose-dependent cardiac dysfunction results from repeated administration of anthracyclines. Diastolic dysfunction has been reported to occur with cumulative doses of 200 mg/m² doxorubicin, followed by systolic dysfunction beyond 400–600 mg/m², with individual threshold variability [13,14]. Whereas the former usually remains asymptomatic, patients with systolic dysfunction often present with signs and symptoms of heart failure. Among 3941 patients treated with anthracyclines in the study by Bristow et al., 88 developed symptomatic heart failure during follow-up, depending on the cumulative dose they were given, ranging from 0.14% of those who received less than 400 mg/m² to 7% of those who received 550 mg/m² and 18% of those who received more than 700 mg/m² [15].

Several risk factors for increased cardiac toxicity have been identified, including older age, combination with cyclophosphamide, trastuzumab and taxanes (docetaxel, paclitaxel), and mediastinal irradiation. Children also have an increased risk. In a follow-up study by Lipshultz et al., 32% of children who received more than 410 mg/m² doxorubicin equivalent presented with some degree of LV dysfunction. Also, late/delayed LV dysfunction several years after completion of therapy impairs prognosis in 5–10% of children [16].

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bevacizumab- and placebo-treated patients were 1.6% and 0.4%, respectively. The relative risk of heart failure in patients receiving bevacizumab was 4.74, without difference in incidence of risk between patients treated with low or high doses [24]. Heart failure was more frequent in bevacizumab-treated patients who had already been treated with antracyclines (14%) or had mediastinal irradiation. Of note, cardiac dysfunction occurred only in patients who had presented with previous bevacizumab-induced hypertension [18]. Alemtuzumab, a humanized immunoglobulin G targeted to lymphocytes through the CD52 receptor, may also induce LV dysfunction, but in fewer instances.

Small molecule TK inhibitor-induced LV dysfunction is increasingly recognized, with the rapidly expanding panel of drugs that have received approval for use as therapy for a large variety of tumours. Treatment with imatinib mesylate has been reported to result in cardiac mitochondrial injuries and, in a few case reports, in LV dysfunction [25,26]. Whether imatinib mesylate induces heart failure in a significant subset of treated patients remains, however, under debate [27,28]. Indeed, in a retrospective analysis of 219 patients with gastrointestinal stromal tumours and other sarcomas treated with imatinib mesylate, Trent et al. showed that arrhythmias, acute coronary syndromes and congestive heart failure were uncommon, occurring in less than 1% of patients [28]. Also, assessment of serial plasma NT-proBNP and serum cardiac troponin T measurements before therapy, then 1 and 3 months after the start of therapy, failed to demonstrate increases in NT-proBNP concentrations, indicating that the risk of subclinical cardiotoxicity also remained limited. Only one patient of the 55 included in the study showed increased NT-proBNP concentrations and developed symptomatic heart failure due to pre-existing valvular heart disease [29]. Although LV dysfunction induced by imatinib mesylate has been reversible in most instances after discontinuation of therapy, late persistent irreversible heart failure has also been reported [30,31]. Imatinib mesylate-induced cardiac toxicity is also facilitated by several relevant comorbidities, such as previous cardiovascular disease or renal failure [31].

Sunitinib malate, a multitargeted TK inhibitor acting mainly on the VEGF receptor, has recently been approved for clinical use in patients with metastatic renal cell carcinoma and gastrointestinal stromal tumours; its administration is associated with progressive asymptomatic LV dysfunction in 28% of patients and symptomatic heart failure in 2.7%. Patients with coronary artery disease, previous LV dysfunction and/or LV hypertrophy and patients who have already received antracyclines have been reported to be at increased risk and should be carefully monitored [1—6]. Whether sunitinib-induced LV dysfunction is reversible remains uncertain. Whereas all patients recovered after cardiovascular management and were considered eligible for TK inhibitor continuation in one study [32], other studies reached more controversial conclusions, as LV dysfunction and symptoms persisted in a small subset of patients [33]. Moreover, some asymptomatic patients had recurrent LVEF reductions after restarting sunitinib [34].

Lapatinib, a small molecule targeting HER2 and epidermal growth factor receptor (EGFR), has been developed as an alternative to trastuzumab in the treatment of HER2-positive breast cancer. First trials showed that 1.6% of patients had a reduction in LVEF of more than 20% and that 0.2% had symptomatic heart failure. Previous therapy with antracyclines or trastuzumab was associated with an increased risk (2.2% and 1.7% vs 1.5%, respectively) [35]. Phase III trials also showed that dasatinib, a small TK inhibitor used in the therapy of chronic myeloid leukaemia, may induce LV dysfunction in about 2—4% of patients, including 50% with severe heart failure [2].

**Proteasome inhibitors**

Bortezomib, a novel anticancer agent registered for multiple myeloma, acts by inhibition of proteasome, activation of nuclear factor kappa B (NF-kB) and, in turn, induction of apoptosis. Cardiovascular complications have been reported in a few case reports [36] and in eight of a series of 69 patients receiving the drug, including four with heart failure [37]. Pathological examinations performed in animals showed mitochondrial changes, decreased adenosine triphosphate synthesis and reduced cardiomyocyte contractility [38].

**Myocardial ischaemia**

Myocardial ischaemia is a frequent and potentially harmful side-effect in patients receiving the antimitabolite agent 5-fluorouracil; it includes asymptomatic T-wave changes, chest pain, acute coronary syndromes and myocardial infarction. Acute coronary syndromes have been reported in 1.6—7.6% of patients, with a drug-related cardiovascular mortality rate as high as 2.2%. The incidence of cardiac events in patients receiving 5-fluorouracil was fourfold in those who had prior cardiac disease, especially coronary artery disease [39]. Acute coronary syndromes may also occur in patients with normal coronary angiography. Coronary artery spasm has been documented in a few cases.

Capecitabine, the fluoropyrimidine prodrug of 5-fluorouracil, may also promote myocardial ischaemia and ventricular arrhythmias [40]. Although previous case reports suggested that these complications are usually reversible, caution is required in patients with coronary artery disease, in whom the risk is increased, and in patients who are concomitantly treated with oxaliplatin. Indeed, major cardiac events occurred in 6.5% of patients who were treated with this combination regimen, including sudden death, ventricular tachycardia and acute coronary syndromes (4.6%) [41].

The proteasome inhibitor bortezomib has been reported to cause atherosclerotic plaque progression and tendency to rupture, thereby promoting acute coronary syndromes, which have been reported in few patients [37]. Myocardial ischaemia is observed in 0.29—0.5% of patients treated with paclitaxel and 1.7% of those receiving docetaxel, mainly affecting patients with a past history of coronary artery disease [2,42]. An increased risk of acute coronary syndrome was also seen in patients receiving bevacizumab in controlled clinical trials (1.5% vs 1%) [18]. Patients treated with cisplatin, sorafenib (2.7% vs 1.3%) or erlotinib (2.3% vs 1.2%) are also at increased risk [2—4].
Arrhythmia and conduction disturbances

The microtubule inhibitors paclitaxel and docetaxel (taxanes) induce asymptomatic sinus bradycardia in 29% of patients and more severe cardiac complications in 5%, including bradycardia-related syncope, ventricular arrhythmias and myocardial ischaemia [42].

Arrhythmias have been reported during therapy with anthracyclines, including induced atrial fibrillation, supraventricular and ventricular premature beats and/or tachycardias [12,13]. Interaction with cardiac ion channels and currents are considered to play a pivotal role in the genesis of these arrhythmias, as well as in the occurrence of electrocardiographic changes such as QT interval prolongation and non-specific T-wave changes [2,4,12,13].

Arsenic trioxide, a drug effective in acute promyelocytic leukaemia, increases the QT interval in 50% of patients. Several cases of torsades de pointes have been reported [43].

Detection of cardiac complications

Evaluation of cardiac toxicity in patients treated for cancer includes consideration of blood biomarkers such as troponins and B-type natriuretic peptides, together with non-invasive imaging in the form of 2D-, 3D- or strain-echocardiography, multigated radionuclide angiography (MUGA), quantitative gated blood-pool single-photon emission computed tomography (SPECT), iodine-123 metaiodobenzylguanidine (123I-MIBG) scintigraphy or cardiac MRI. These approaches differ from each other with regard to availability, accuracy, sensitivity to detecting early stages of cardiac injury, individual reliability, ease of use from a longitudinal follow-up perspective and cost-effectiveness.

Imaging techniques

Nuclear cardiac imaging

Serial LVEF determination by technitium-99m MUGA has for a long time been regarded as the gold standard for measuring cardiotoxicity in adult patients. Using this highly reproducible approach, an absolute LVEF less than 50% or a decrease of more than 10% from baseline have been recommended for discontinuation of anthracyclines [44,45]. However, as alteration of LVEF has been considered as a too-late detector of myocardial damage, more sensitive methods have been developed.

123I-MIBG scintigraphy images the efferent sympathetic nervous innervations of the heart and detects changes in myocardial adrenergic innervations before LV function is impaired. Several studies showed a dose-dependent decline in 123I-MIBG myocardial uptake in patients treated with anthracyclines [44,46].

By inhibiting the microtubular transport system, the taxanes paclitaxel and docetaxel impair storage of free fatty acid in the cytosolic lipid pool of cardiomyocytes, resulting in reduced mitochondrial uptake of free fatty acids. Myocardial perfusion scintigraphy with 123I-methylpentadecanoic acid (123I-BMIPP), a tracer of free fatty acids, has proven effective in the detection of early myocardial dysfunction associated with taxane administration, especially when taxanes are combined with carboplatin [47].

More sophisticated radionuclide imaging techniques provide potentially useful information. Indium-111-radiolabelled trastuzumab has been investigated to detect myocardial uptake of the drug, hypothesizing that trastuzumab-induced cardiotoxicity is based on the myocardial expression of HER2, either constitutively or after induction by pretreatment with anthracyclines [44,48].

Echocardiography

Conventional 2D echocardiography

Monitoring with 2D echocardiography is the technique used most frequently in clinical practice. Assessment of LV systolic dysfunction is intended to detect impairment of contraction (reduced interventricular septum motion, shortening fraction reduced by more than 20%), which usually reflects ongoing cardiotoxicity that will presumably progress with subsequent administrations. An absolute fractional shortening less than 26% has been proposed as the threshold below which anthracyclines should be discontinued [49]. Similarly, using Simpson’s biplane method, an absolute LVEF less than 50% or a decrease greater than 10% from baseline have been recommended as discontinuation thresholds. Unfortunately, impairment of these variables is often detected only after considerable cell loss has taken place [50]. Considering that changes in systolic function occur too late to allow effective prevention, diastolic function has been investigated to see whether relaxation measurements can predict cardiotoxicity at an earlier stage. Stoddart et al. showed that most patients who develop systolic dysfunction present with prior impairment of LV diastolic filling Doppler variables at cumulative doses as low as 120 mg/m², including gradual increases in isovolumetric relaxation time and E-wave deceleration time [14].

Detection of early LV dysfunction has also been proposed using stress echocardiography, an approach that demonstrated that exercise- and dobutamine infusion-induced reductions in LV posterior wall thickening and impairment of end-systolic wall strain preceded LV systolic dysfunction in patients treated with anthracyclines. Also, a fall in LV contractile reserve of greater than five units during a low-dose dobutamine stress test after the third cycle of an anthracycline-based regimen was predictive of an LVEF less than 50% after completion of therapy [51].

However, several shortcomings should be taken into account when using these approaches. Resting 2D echocardiography is usually late in detecting cardiac toxicity. Diastolic measures have proven difficult to interpret for individual monitoring. Stress-coupled examinations are time-consuming and rarely available for use in daily practice.

Tissue Doppler imaging and myocardial strain and 3D echocardiography

Assessment of LVEF in patients treated for cancer has been compared using 2D and 3D echocardiography, MUGA and cardiac MRI. Although 2D echocardiography demonstrates a weak correlation with MRI for LVEF evaluation at baseline and during follow-up, both 3D echocardiography and MUGA...
show a stronger correlation compared with cardiac MRI [52].

Tissue Doppler imaging (TDI) has also been proposed as a means of tracking early changes in cardiac function. In a small follow-up study of patients who received a mean doxorubicin cumulative dose of 227 mg/m², Tassan-Mangina et al. reported reduced radial and longitudinal relation variables (Em) and reduced maximal velocity of systolic myocardial wave (Sm), whereas systolic function variables remained unchanged [53]. However, despite interesting results in mice models in which TDI proved useful in predicting cardiotoxicity, the use of TDI in humans has been rather disappointing. Indeed, TDI performed before and during treatment in 80 women receiving epirubicin-based chemotherapy for breast cancer failed to demonstrate relevant short-term effects of low-dose epirubicin (mean dose 274 mg/m²) that could reliably predict subsequent toxicity [54].

Mercuro et al. showed that early impairment of systolic function may also be detected using strain echocardiography. They reported a significantly reduced strain rate appearing for cumulative doses as low as 200 mg/m² epirubicin, whereas other early variables, such as Em or Em/Am, remained unchanged with 300 mg/m² [55,56]. Similar results were obtained in children by Ganame et al., who found reduced peak longitudinal and radial systolic strain rate and strain after completion of three cycles of anthracycline-based chemotherapy [57].

Myocardial deformation imaging using 2D-based (speckle-tracking) strain and strain rate has also been proven to be useful in monitoring patients receiving trastuzumab, in whom a drop of at least one standard deviation in 2D longitudinal strain rate was predictive of a subsequent reduction in LVEF [58–60]. These changes were supported by histological findings in an animal model, in which strain rate more sensitively detected damage in myocardial tissue than standard echocardiographic variables [61].

Cardiac MRI

Cardiac MRI can be used to evaluate LV performance and characterize myocardial tissue. However, although MRI has been validated as being more accurate and reproducible in assessing LV volumes and function compared with 2D echocardiography, the related expenditure, low availability and requirement for trained physicians often preclude its use for serial monitoring of LVEF in a daily practice setting [50,52].

MRI also provides additional data on tissue characterization. In a study performed in patients receiving doxorubicin, myocardial oedema was seen in about 50% of patients, associated with progressive increases in LV end-diastolic diameter and volume [62]. Another study showed late gadolinium enhancement of the subepicardial lateral wall in 10/160 patients treated with trastuzumab for HER2-positive breast cancer who developed drug-induced cardiomyopathy. Of note, these changes persisted after discontinuation of trastuzumab in six patients in whom LV function recovered [63]. Similar approaches were developed in animal models of anthracycline cardiotoxicity to determine whether changes in gadolinium signal intensity on T1-weighted MRI images—a marker of myocardial injury, necrosis or fibrosis—would forecast a subsequent drop in or preservation of LV performance [64].

Biomarkers

Biochemical methods of detecting and monitoring cardiac dysfunction or injury after administration of anticancer agents have been developed using natriuretic peptides and troponins.

Natriuretic peptides

BNP was initially considered as a promising marker for the detection of chemotherapy-induced cardiac dysfunction. However, although Daugard et al. observed increased BNP values in patients with a more than 10% reduction in LVEF, follow-up of patients with serial BNP measurements failed to prove reliable usefulness, as neither baseline concentrations nor subsequent changes during therapy were predictive of a change in LVEF [65]. Using serial plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) sampling in children receiving anthracyclines, Germanakis et al. showed higher NT-proBNP concentrations in children with LVEF mass reduction compared with in those in whom LV mass remained unchanged [66]. Similarly, Kouloubinis et al. demonstrated a significant correlation between increased concentrations of plasma pro-atrial natriuretic peptide and NT-proBNP and a subsequent decrease in LVEF among children treated with epirubicin [67].

NT-proBNP has also been evaluated as an early predictive marker of cardiac dysfunction in patients receiving anthracyclines. Cardinale et al. determined serial plasma NT-proBNP concentrations during a 72-hour period following chemotherapy and observed three different patterns: no change in NT-proBNP concentration in the six serial samples (31% of patients); transient increases in NT-proBNP, with concentrations normalizing within 72 hours (35% of patients); persistent elevation of NT-proBNP, with an elevated concentration at 72 hours (33% of patients). A progressive decline in LV function was observed in the third group, in whom LVEF decreased from 66% to 45% during the subsequent 12 months [68].

Monitoring follow-up using NT-proBNP may also be useful for prognosis classification. Gimeno et al. stratified patients with non-Hodgkin lymphoma with regard to prognosis according to their baseline NT-proBNP concentration; they showed that baseline concentration was predictive of subsequent adverse outcome (death from any cause, including tumour progression) [69]. Although these findings still remain unexplained [70], they provide additional support for natriuretic peptide monitoring for prognosis stratification and treatment optimization in some instances, such as treatment of lymphoma.

Troponins

Cardiac troponins are sensitive and reliable biochemical markers of myocardial injury in patients with acute coronary syndromes and myocarditis. Troponin I has also been recognized as a sensitive marker of myocardial damage during cancer chemotherapy. Increases in troponin I occurring during treatment with anthracyclines were reported to be predictive of future cardiac dysfunction [71], thereby allowing prognosis stratification. In a study by Cardinale et al., multiple blood sampling for troponin concentrations during therapy with high-dose anthracycline regimens showed
a correlation between troponin concentration and the subsequent 1-year cardiovascular event rate [72]. Patients in whom the troponin I concentration remained below normal values after each cure and after completion of therapy (n = 495) were at very low risk (< 1% cardiovascular events). Patients with increased troponin concentrations during successive cures and after completion of therapy (n = 63) were at very high risk of cardiac events (84%). Patients with increased initial values but troponin concentrations within the normal range after therapy completion (n = 165) had an intermediate risk (37%).

Assessment of ongoing cardiac toxicity using serial troponin determinations has also proven useful in the management of patients treated with trastuzumab. A follow-up study performed in 251 women receiving trastuzumab for HER2-positive breast cancer showed that cardiac toxicity (reduction in LVEF of > 10% or LVEF < 50%), observed in 42 women (17%), was more frequent in those with elevated troponin I concentrations (62% vs 5%). Increases in troponin concentrations after any trastuzumab treatment cycle were also associated with a reduced LVEF recovery rate (35% vs 100%), indicating that trastuzumab-induced increases in troponin concentrations predict both cardiac toxicity and potential recovery of LV function [73].

Prevention

Strategies for reducing cardiac toxicity associated with anthracyclines have been developed using two different approaches: replacement of conventional anthracyclines by liposomal anthracyclines; and combination of anthracyclines with antioxidants or cardiovascular drugs (Table 1).

Liposomal anthracyclines

Liposome-encapsulated anthracyclines have been developed to more specifically target tumour cells rather than cardiac cells. In a study by Heintel et al., non-pegylated liposomal doxorubicin was evaluated in 37 patients with non-Hodgkin lymphoma and pre-existing cardiac disease or elderly patients not eligible for conventional anthracyclines. High remission rates without major cardiac toxicity were observed in this high-risk population [74]. Pegylated (polyethyleneglycol-encapsulated) liposomal doxorubicin was tested as an adjuvant therapy in older women with breast cancer. In a study by Wildiers et al., cardiac follow-up was documented using Doppler-based strain imaging and 2D echocardiography coupled with serial determinations of troponin and BNP concentrations. After six cycles of treatment, LVEF remained unchanged, while significant decreases in radial strain and strain rate were seen. Although the study was not intended to compare cardiac side-effects between pegylated and conventional anthracyclines, cardiac toxicity appeared less pronounced with the pegylated liposomal regimen [75]. Jurcut et al. compared strain rate imaging and conventional echocardiography in elderly women with breast cancer who received pegylated liposomal doxorubicin. Although significant reductions in longitudinal and radial strain and strain rate were found after six cycles of treatment, LVEF and LV dimensions remained unchanged using this preventive approach [76].

The ongoing Liposomal doxorubicin-Investigational chemotherapy-Tissue Doppler imaging Evaluation (LITE) study intends to compare LV function in 80 patients with breast cancer treated with either liposomal doxorubicin or standard epirubicin. The study will also provide clinical and mechanistic insights into the potential role of liposomal anthracyclines in the future [77].

Antioxidants

Prevention of anthracycline-related cardiac toxicity using antioxidant drugs has been supported by the involvement of oxidative stress in inducing this myocardial injury [4,6-12].

Dexrazoxane, a chelating agent that limits formation of anthracycline-iron complexes that are believed to generate myocyte-damaging free radicals, has been the most widely used compound. Studies performed in adults—mainly women treated with anthracyclines for breast cancer—demonstrated reduced cardiac toxicity when dexrazoxane was also used. Combining data from 968 patients, LVEF reductions were less common in women receiving dexrazoxane (1% to 7.3%) compared with in controls (8% to 23%) [78,79].

Cardiac cumulative and late-delayed toxicity is also a major limiting factor in children treated with anthracyclines. Lipshultz et al. measured serial troponin I concentrations in children treated with doxorubicin for acute leukaemia. Increases in troponin concentrations were observed in 21% of children receiving dexrazoxane and in 51% of controls [80]. Another study in 75 children treated for leukaemia or lymphoma showed fewer late (8 years) impairments of LVEF, occurring in 17% of those who received dexrazoxane and in 41% of controls [81].

Unfortunately, dexrazoxane was recently shown to increase the risk of subsequent malignancies, myeloid leukaemias and myelodysplastic syndromes in patients who received the drug in combination with anthracyclines. Dexrazoxane, a bisdioxopiperazine, blocks topoisomerase II turnover, thereby potentiating doxorubicin- and etoposide-induced impairment of DNA repair. Tebii et al. compared occurrences of such second malignant diseases among children treated for Hodgkin’s disease, with (n = 239) or without (n = 239) combination dexrazoxane. The children showed an increased 4-year incidence of acute myeloid leukaemia/myelodysplastic syndrome (2.55% vs 0.85%) and second malignant neoplasms (3.43% vs 0.85%) [82]. Similarly, Salzer et al. showed an increased second malignancy rate in children treated for lymphoblastic leukaemias who received dexrazoxane [83]. In light of these recent concerns, approval for the use of dexrazoxane has been restricted to adults only—mainly women treated for metastatic breast cancer who have already received moderate-to-high cumulative doses of anthracyclines.

Among other available antioxidants, probucol (a lipid-lowering drug with antioxidant properties) has been reported to protect against anthracycline cardiotoxicity by activating superoxide dismutase and glutathione peroxidase.
Table 1 Potential strategies for prevention of anthracycline-associated cardiac toxicity.

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<td>Pts with previous anthracycline-based regimen; pts with heart disease, elderly [74]; clinical experience currently available</td>
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<td></td>
<td>Activates superoxide dismutase &amp; glutathione peroxidase</td>
<td>Enzymatic activity (myocyte level)</td>
<td>Approved lipid-lowering drug</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost, side-effects</td>
</tr>
<tr>
<td>Iloprost</td>
<td>[87]</td>
<td>+</td>
<td>−</td>
<td></td>
<td>EF, histology</td>
<td>Approved</td>
<td>BP</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>[88]</td>
<td>+</td>
<td>−</td>
<td></td>
<td>Limits apoptosis</td>
<td>Approved</td>
<td>Side-effects</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>[85]</td>
<td>+</td>
<td>− (+ expected [86])</td>
<td></td>
<td>Limits apoptosis</td>
<td>Approved</td>
<td>BP</td>
</tr>
<tr>
<td>Carvediol</td>
<td>[89]</td>
<td>+</td>
<td>EF</td>
<td></td>
<td>EF</td>
<td>Approved</td>
<td>HR, BP</td>
</tr>
<tr>
<td>Enalapril</td>
<td>[90]</td>
<td>+</td>
<td>EF, HF</td>
<td></td>
<td>Approved</td>
<td></td>
<td>BP, renal filtration</td>
</tr>
<tr>
<td>Valsartan</td>
<td>[91]</td>
<td>+</td>
<td>EF</td>
<td></td>
<td>Approved</td>
<td></td>
<td>BP, renal filtration</td>
</tr>
</tbody>
</table>

AML: acute myeloid leukaemia; BNP: brain natriuretic peptide; BP: blood pressure; EF: ejection fraction; HR: heart rate; pts: patients; Tn: troponins.
Cardiovascular drugs

Several cardiovascular drugs have been evaluated for their potential prevention of cardiac toxicity in patients receiving anthracyclines.

Given that amiodipine reduced doxorubicin-induced activation of caspase-3 and cardiomyocyte apoptosis in an animal model [85], Outumuro et al. suggested that calcium channel antagonists should be routinely added to anthracyclines [86]. Similarly, on the basis of doxorubicin-induced cyclo-oxygenase 2 expression and its protective effects on related cardiotoxicity in mice, Neelan et al. demonstrated a protective action of the prostacycline analogue iloprost [87]. In animals, protective antiapoptotic effects have been shown by combining anthracyclines with sildenafl, an inhibitor of phosphodiesterase-5 that decreases caspase-3 activation, mitochondrial electrochemical gradient loss and the resulting induction of the apoptotic cascade [88]. However, this approach has not been translated into clinical practice.

Conversely, several studies have been performed in patients by inhibiting receptors of either the beta-adrenergic or the renin-angiotensin system. In a study of 50 patients receiving doxorubicin or epirubicin alone or in combination with carvedilol 12.5 mg daily, Kalay et al. showed that LVEF after completion of therapy was higher (69.9% vs 52.3%) in patients who received carvedilol. Three preventative mechanisms are advocated, including the antioxidant effects of the drug, activation of the sarcoplasmic reticulum calcium adenosine triphosphatase or inhibition of the apoptotic cascade by carvedilol [89]. Inhibition of the renin-angiotensin system has been investigated by Cardinale et al. in 114 patients. After a 1-year follow-up, anthracycline-induced LV dysfunction was prevented by enalapril 20 mg daily in 56 patients compared with in 58 controls (62.4% vs 48.3%). Also, fewer patients presented with symptomatic heart failure (0% vs 12%) and arrhythmias (2% vs 10%). Reduced ROS production has been reported to support this action [90]. Inhibition of angiotensin II receptors may also be effective, as demonstrated in a study by Nakamae et al. involving 40 patients treated with anthracyclines for non-Hodgkin’s lymphoma, in which increases in LV end-diastolic diameter were prevented in those who received valsartan [91].

Targeted therapies

In contrast with anthracyclines, prevention of trastuzumab-induced LV dysfunction rather depends on treatment sequencing than on drug combinations to reduce toxicity. Indeed, both the incidence and severity of trastuzumab-induced LV impairment are increased by factors such as age, previous cardiac disease, radiation therapy and chemotherapy with anthracyclines, cyclophosphamide and paclitaxel. Data obtained from phase II and III trials showed that concomitant administration of trastuzumab and anthracyclines dramatically increases toxicity, thereby suggesting a timely separated sequential administration [22,92]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 study enrolled 1804 women with HER2-positive breast cancer and an LVEF greater than 50% in an adjuvant setting. The patients received four cycles of an anthracycline-based regimen followed by four cycles of paclitaxel and were subsequently randomized to a 1-year therapy with trastuzumab or placebo starting concurrently with paclitaxel. LV dysfunction occurred in 3.9% of women treated with trastuzumab and 1.3% of controls. Age, therapy for hypertension and a mildly reduced baseline LVEF (50—54%) were associated with an increased risk [17]. In the European Herceptin Adjuvant (HERA) trial, trastuzumab was initiated for 1 or 2 years in 1693 women, several months after the anthracycline-based regimen was completed. Using this delayed-onset approach, the incidence of trastuzumab discontinuation due to LV dysfunction was only 4.3% [19]. Whereas asymptomatic LVEF decline and severe heart failure were more frequent in women with trastuzumab than in controls (3.04% vs 0.5% and 2.15% vs 0.12%, respectively), the incidence of LV dysfunction, as in the NSABP B31 trial, was substantially lower than in former studies in which no delay separated completion of anthracycline chemotherapy and trastuzumab [17]. Guidelines for trastuzumab administration have recently been proposed, in which therapy is delivered on the basis of a persistent LVEF greater than 50% or until recovery above 50% after 3-week intervals of drug discontinuation, when a transient decline is observed [93].

As combination therapy with anthracycline-based regimens and trastuzumab is associated with increased cardiac toxicity, non-anthracycline regimens with trastuzumab have recently been evaluated. The BCIRG study compared doxorubicin and cyclophosphamide followed by docetaxel with or without trastuzumab and a combination of carboplatin and docetaxel with trastuzumab in 3222 women with HER2-positive breast cancer. While adjuvant trastuzumab for 1 year improved disease-free and overall survival, the risk-benefit ratio favoured the non-anthracycline regimen over the anthracycline-based regimen, given similar efficacy and reduced cardiac toxicity [94]. Accordingly, adjuvant trastuzumab therapy should not be regarded as an additional risk for cardiac toxicity only, but also as one of the alternatives to design regimens intended to reduce anthracycline-induced cardiac side-effects by reducing the associated anthracycline-dose administered. Such an approach has recently been investigated in an animal model, in which the antioxidant probucol reduced the combined toxicity of doxorubicin and trastuzumab [95].

LV dysfunction associated with bevacizumab is less commonly encountered, occurring in 4% of unselected patients. Cardiac dysfunction occurs mostly in patients with bevacizumab-induced hypertension, of whom 9.2% have severe hypertension. Patients who have already received anthracyclines have an increased risk (14%). Severe LV dysfunction and heart failure affect 0.3% of patients only [96]. Accordingly, control of blood pressure level should be considered as a first-line approach to prevent LV impairment. Blood pressure control has also been emphasized in the management of patients receiving sunitinib and sorafenib, which may elicit severe hypertension in 6.9% and 7.2%, respectively [96]. In a recent study, amiodipine 5 mg daily provided effective blood pressure control in 88.5% of patients treated with bevacizumab [97].
Conclusion

Improving prevention of the cardiac side-effects of cancer chemotherapy depends on several currently unresolved issues. Early detection and quantification of cardiac damage is required to adapt chemotherapy in progress and for optimal management of patients. Whether increased availability of myocardial strain imaging and repeat blood biomarker determinations will reliably and consistently achieve these goals remain to be confirmed. Also, protective approaches to reduce the cardiac toxicity of anticancer drugs should be reconsidered given the recent withdrawal of dexrazoxane. Anthracycline-based regimens, encapsulated anthracyclines and non-anthracycline regimens should be revisited for antitumour efficacy and cardiac toxicity. Cardiovascular drugs that have proved effective in the prevention of anthracycline-induced cardiac toxicity in experimental models should be investigated in clinical trials. Finally, the efficacy of cardiovascular drugs that have already been tested in clinical settings should be confirmed and compared in larger numbers of patients.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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Detection and prevention of cardiac complications of chemotherapy


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