Anticancer therapy induced cardiotoxicity: review of the literature

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Innovative anticancer strategies have contributed to an improved survival of patients suffering from malignancies, and in some cases, have turned cancer into a chronic disease. Therefore, the early and particularly late onsets of adverse cardiovascular effects of systemic anticancer treatments are of increasing interest. Among a rapidly increasing variety of anticancer drugs, the anthracyclines and the monoclonal antibody, trastuzumab, are the agents with a well-known cardiotoxicity. The diagnostic work-up, the cardiotoxic risk of anthracyclines and trastuzumab, and additionally, cardiotoxicity as a risk factor of a multimodal therapeutic approach in breast cancer patients is discussed in this study. *Anti-Cancer Drugs* **21:578–590**

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Introduction

Cardiotoxicity is a well-known negative side effect of numerous anticancer drugs. Cytostatic antibiotics of the anthracycline class (daunorubicin, doxorubicin and epirubicin) are perhaps the most notorious chemotherapeutics with cardiac side effects; however, other agents such as cyclophosphamide, ifosfamide, cisplatin, carmustine, busulfan, chlormethine, mitomycin, paclitaxel, etoposide, teniposide, the vinca alkaloids, fluorouracil, cytarabine, amsacrine, cladribine, asparaginase, tretinoin, and pentostatin have also been associated with cardiotoxicity [1–3].

Anthracyclines, 5-fluorouracil, its prodrug capecitabine and trastuzumab are anticancer drugs with the highest risk of developing heart failure. Cardiotoxicity is rare within most agents, but may occur in $>20\%$ of patients treated with anthracyclines or 5-fluorouracil [1–5].

Besides the typical chemotherapeutics, targeted therapies that are mainly targeted toward human epidermal growth receptor 2 (HER2) are also associated with a clinically relevant cardiotoxic profile [5].

Newer cancer therapies have improved the long-term survival of patients with malignancies, and in some cases, turned cancer into a chronic disease. Therefore, the early and particularly late onsets of adverse cardiovascular effects are growing more important.

Cardiac events may include symptomatic or asymptomatic blood pressure changes, thrombosis, electrocardiographic changes, arrhythmias, myopericarditis, myocardial infarction, cardiomyopathy, cardiac failure (especially left ventricular failure), and congestive heart failure [3]. These may occur within days or weeks after treatment, or sometimes within months or years after termination of chemotherapy.

On account of currently inadequate predictive models, prevention modalities, and therapeutic options of chemotherapy induced cardiac damage; early detection of heart failure is relevant for both the opportune modulation of therapy and the application of heart protectants and supporting drugs.

Methods

The MEDLINE database was searched from 1980 to 2009 using variations on the search terms: cardiotoxicity, cardiovascular toxicity, cardiomyopathy metastatic (breast) cancer, HER2 overexpression, trastuzumab, tyrosine kinase inhibitors, vascular endothelial growth factor (VEGF) inhibitors, anthracyclines, and radiotherapy. Moreover, The American Society of Clinical Oncology Annual Meeting proceedings were searched from 2000 to 2009 for reports of new or ongoing trials. A search was also conducted for published practice guidelines, meta-analyses, and systematic reviews.

Relevant articles and abstracts were selected, and the reference lists from these sources were searched for additional trials.

Articles were selected for inclusion in this review if they were fully published reports or published abstracts of clinical trials or meta-analyses of clinical trials. Trials published in a language other than English or German were excluded because of limited translation resources.

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Pathophysiology

The pathophysiological mechanisms of chemotherapy-induced cardiotoxicity are particularly analyzed for anthracyclines and the monoclonal antibody trastuzumab, which are the main anticancer drugs with well-known cardiac side effects.

The anticancer efficacy of anthracyclines is caused by deranged DNA repair mechanisms, including inhibition of DNA fragmentation polymerases and anticipation of DNA, RNA, and protein synthesis. However, cardiac damage cannot be attributed to the same mechanisms because the heart is a postmitotic organ with nonreplicating cells. Therefore, the only mechanism of any adaptation including the mechanism of repair is hypertrophy of the remaining myocardium.

Cardiotoxicity of anthracyclines appears to be distinct from their therapeutic mechanism, and has been attributed to a large number of effects, including apoptosis, alterations in iron homeostasis, deregulation of calcium homeostasis both in the sarcoplasmic reticulum and in the mitochondria and mitochondrial dysfunction. However, the common trigger of these events seems to be linked to oxidative stress caused by the production of reactive oxygen species resulting in myocardial fibrosis and necrosis [6]. Furthermore, a direct toxic effect to the adrenergic neurotransmitter system is the affect of a myocardial contraction [7].

A number of observations are consistent with the importance of oxidative stress in doxorubicin cardiotoxicity:

(1) Overexpression of metallothionein, a free radical scavenger, in the hearts of transgenic mice minimizes the degree of doxorubicin-induced injury [8].
(2) Inhibition of the formation of peroxynitrite, a reactive oxidant produced from nitric oxide and superoxide, improves cardiac function in doxorubicin-induced injury in mice [9].
(3) Probucol, a strong antioxidant, prevents the reduction in glutathione peroxidase and reduces myocardial lipid peroxidation associated with doxorubicin therapy in a rat model [10]. The applicability of this finding to humans is uncertain as the intravenous administration of doxorubicin produces potent acute inhibition of lipid peroxidation, suggesting that other mechanisms must also be involved [11].
(4) Dexrazoxane is an EDTA-like chelator that may prevent anthracycline damage in humans by binding the iron, which is a cofactor for free radicals [12].

In contrast, trastuzumab attributed cardiotoxicity is not fully understood, but it is known to be a direct result of the *HER2*-receptor blockade [13]. The *HER2*-receptors are physiologically expressed on myocytes both for the protection of cardiotoxins and for embryonic cardiac development [14,15].

Data from in-vivo and in-vitro studies indicate the importance of HER2-signaling in the normal heart and support the view that trastuzumab-induced cardiotoxicity is directly related to HER2 blockade:

(1) In animal models, HER2-signaling is important for embryonic cardiac development and for protection from potential cardiotoxins [14,15].
(2) Crone *et al.* [16] showed that suppression of the *HER2* gene in mice results in dilated cardiomyopathy. Mice with ventricular-restricted knockout of the *HER2* gene spontaneously develop signs of a dilated cardiomyopathy and their cardiomyocytes show enhanced susceptibility to anthracycline-induced cell death.
(3) Although the role of HER2 in the pathophysiology of heart failure is not well understood, serum HER2 levels are increased in patients with chronic heart failure and the levels correlate inversely with left ventricular function [17,18].

Taken together, these data suggest that trastuzumab-induced cardiotoxicity is at least partly a direct result of HER2 blockade.

The terms 'type I' and 'type II' chemotherapy-related cardiac dysfunction are based on these differences:

Type I is associated with the treatment of anthracyclines and results in myocytal damage and clinical heart failure. Type II more often leads to a loss of contractility and less myocytal death, showing more reversibility and is not exclusively attributed to trastuzumab treatment.

Individual risk

The individual potential for cardiotoxicity subject to risk factors should be recognized before therapy is initiated, and in case an attempt to modify therapy should be made. Risk factors predisposing patients to cardiotoxicity are summarized in Table 1 [19].

Diagnostic work-up

With the rapidly increasing arsenal of antitumor agents, the myocardial surveillance of patients who receive a potentially cardiotoxic-targeted immuno or chemotherapy is currently gaining importance. The intention of routine monitoring is the early detection of restricted cardiac function, and as a consequence, the opportune dose reduction or interruption and/or application of cardioprotectants.

Even years after the anticancer treatment, cardiac function has to be continuously monitored because of the possibility of a late onset cardiotoxicity [20,21]. Restrictively, the methods of myocardial monitoring have been validated solely for the anthracycline and trastuzumab-induced cardiac damage.

Table 1 Risk factors predisposing patients to (predominantly anthracycline-associated) cardiotoxicity

Risk factors	Increased risk in case of	
Age	Younger age	
Sex	Female	
Rate and schedule of administration	Rapid injection (high peak)	
Cumulative dose [19]	Exceeding the cumulative dose of	
	Daunorubicin	550–800 mg/m^2
	Doxorubicin	400–550 mg/m^2
	Epirubicin	900–1.000 mg/m^2
	Idarubicin	150–225 mg/m^2
	Amsacrin	580 mg/m^2
	Mitoxantron	>100–140 mg/m^2
Total daily dose	Higher daily doses; contrariwise, cumulative dose of doxorubicin increased up to 800 mg/m^2	
	Fractionated dose q1w (weekly)	
	Protracted infusion > 6 h	
Concurrent/earlier mediastinal radiation	Concurrent/earlier mediastinal radiation exceeding the cumulative dose of	
	Doxorubicin	450 mg/m^2
Preexisting cardiovascular disorders	Hypertension Coronary heart disease	
Electrolyte mismatch	Hypocalcemia	
	Hypomagnesemia	

The most specific method to diagnose myocardial changes when undergoing treatment with anthracyclines is endomyocardial biopsy [7,22]. Ultrastructurally, regions with loss of myofibrils, vacuoles, deterioration of Z-lines, degeneration of mitochondria, and fibrosis have been described [23]. The inhomogeneous allocation of the changes within the heart muscle is caused in the limited sensitivity of the biopsy itself [24]. The extent of histological signs of cardiotoxicity correlate with the cumulative dose of anthracyclines and is a prognostically relevant factor [7,23,25]. However, the availability of endomyocardial biopsy in the daily routine is limited by the invasiveness and the adverse effects of the investigation and by the high technical effort and personal complexity.

Two noninvasive methods of cardiac monitoring were established in the clinical routine: echocardiography and radionuclideventriculography.

Echocardiography for cardiac monitoring in patients treated with anthracyclines is recommended by the American College of Cardiology, the American Heart Association, and the American Society of Echocardiography [26,27]. Echocardiography is an ultrasound technique, which can reproduce a majority of possible manifestations of cardiotoxic damage under real time conditions such as local or global wall motion abnormalities, valves dysfunction, pericardial effusions, and reduced left ventricular ejection fraction (LVEF) [28–30]. The ejection fraction (EF) is calculated by planimetric measurement of the diastolic and systolic dilatation of the left ventricle. With the rotation ellipsoid and its reduction, the EF is evaluated semiquantitatively and is specified in percentage [31]. Limiting factors are air overlap, adiposity, and muscle-skeletal deformations besides the expert knowledge of the examiner. The minor reliability and the high variability between different examiners restrict the significance of this method [32].

Radionuclideventriculography (RVG) is a nuclear medicine test with intravenous application of a radioactive marker labeling red blood cells. The patient is placed under a γ-camera so that the heart function is visualized. The first-pass-RVG measures the first flow through the heart and the equilibrium-RVG measures the continuous flow over 5–10 min triggered by electrocardiography. The combination of the two methods offers the evaluation of both systolic and diastolic function, but no information about the anatomic heart structures like valves dysfunction or vegetations [33]. This technique is like echocardiography validated for monitoring of cardiac function during treatment with cardiotoxic chemotherapeutics [7,34]. RVG is well reproducible and there is no significant intra- and interexaminer variability [35]. The technical and personal effort accounts for the limitation of this method. In addition, a radiation dosage of 6.2 mSv for the patient must be considered.

Serum markers

Natriuretic peptides

Atrial natriuretic petide (ANP) and its prohormone, pro-ANP, are hormones secreted from the cardiac atrium and in some cases from the ventricles in relation to volume and pressure overload. Brain natriuretic peptide (BNP) is also a natriuretic hormone similar to ANP. It is identified in the brain and heart in contrast to ANP, which is particularly in the ventricles. ANP and BNP were cleaved from the C-terminal end of their prohormones pro-BNP and pro-ANP and were released into circulation together with the N-terminal fragment (N-terminal pro-BNP/NT-pro-BNP/N-terminal pro-ANP/NT-pro-ANP).

The physiological functions of ANP and BNP are natriuretic, diuretic, and hypotensive effects. Furthermore, the inhibition of the renin-angiotensin system, endothelin secretion and renal sympathetic activity is attributed to the release of both the hormones into circulation [36].

In heart failure, ANP and BNP were released related to the ventricular filling pressure. The plasma concentrations of both the neurohormones increase in clinical symptomatic or asymptomatic systolic or diastolic dysfunction. ANP and BNP are important serological parameters for diagnosis, prognosis, and response to treatment in patients with acute or chronic heart failure [37–42].

On account of a wide range of concentration, BNP is the more valuable neurohormone in diagnosis, estimation of prognosis and treatment efficacy in heart failure. In contrast to ANP, BNP can be detected in the circulation in less than 20% of healthy individuals but is equal to ANP in patients with heart failure [43,44].

Normal values for both BNP and NT-pro-BNP are nearly 10 pmol/l. NT-pro-BNP has a higher value in patients with left ventricular dysfunction than BNP. Physiological higher values of NT-pro-BNP were detected in women and older individuals and in patients with renal failure [45,46]. Lower concentrations are found in obese individuals [47–49].

Cardiac troponins

Cardiac troponins are proteins with three subunits known as troponin T (cTnT), troponin I (cTnI), and troponin C. Their physiological function is the regulation of the calcium-mediated interaction of actin and myosin during the contraction of the heart muscle cells. The cTnT and cTnI are secreted by the heart and skeletal muscle. The generally used monoclonal antibody-based assay only detects cardiac isoforms of troponin. This specificity for cardiac isoforms is the basis for clinical practice. Both cTnI and cTnT are undetectable in the blood of healthy individuals.

In some patients treated with chemotherapy, increased cTnT concentration in blood can be measured. Cardinale *et al.* [50–52] showed that elevated levels of troponin during treatments with chemotherapy are associated with a decrease of LVEF. In contrast, patients without elevated concentrations of troponin during chemotherapy have a transient reduction of the LVEF returning to baseline in the long-term follow-up. cTnI is a specific and sensitive marker for myocardial damage and can be suggestive for the extent of left ventricular dysfunction at an early stage of therapy [50–55]. The elevated levels of cTnI can be detected in the serum a few days after administration of chemotherapy [53,56].

Anthracyclines

Anthracyclines were discovered in the 1960s and were applied in various solid tumors and hematological diseases. Anthracyclines are the best analyzed anticancer drugs regarding cardiac side effects [57]. Their anticancer mechanisms include the intervention of DNA replication by modification of base pairs and cellular proteins and in the release of free oxygen radicals [6,57].

Anthracycline-induced cardiac side effects

Anthracycline-induced cardiac dysfunction can be divided into early side effects, which occur within hours to days after the onset of infusion and chronic or late side effects, which develop within months or years and often lead to cardiomyopathy with poor prognosis.

Early cardiac side effects include symptomatic and asymptomatic dysfunction like arrhythmias, ECG changes and increased serum levels of BNP and cardiac troponin and in rare cases, myocarditis and pericarditis. In most cases, these manifestations are reversible within 1 week when discontinuing the anthracycline infusion [58]. Usually, the anthracycline-based regimen can be continued later in these patients [24,28,57,59,60]. Nevertheless, some cases of progressive heart failure have been described [1,3,30,61]. Patients suffering from early cardiac side effects are not at higher risks of developing chronic heart failure in the future [58].

Late onset cardiotoxicity can occur within months till years after the end of cardiotoxic treatment [20,21]. A typical manifestation is the progressive reduction of the EF leading to dilatated or restrictive cardiomyopathy [6]. This manifestation is associated with worse prognosis because of decompensation, severe arrhythmias or valve damage [57,62,63].

The anthracycline-induced myocytal damage results from the production of toxic free oxygen radicals and an increase in oxidative stress. These mechanisms lead to lipid peroxidation of membranes, vacuolation and fibrosis [10,64,65].

The risk factors of developing anthracycline-induced heart failure are cumulative dosage, age over 70 years, earlier or simultaneous irradiation therapy, concurrent treatment with other chemotherapeutic cardiotoxic agents, example, taxanes or trastuzumab and a preexisting heart disease [66–68].

Incidence of anthracycline-induced cardiac side effects and cumulative dose

The cumulative dose of anthracyclines and the application time are the most important and suggestible risk factors. In the cases of doxorubicin and epirubicin, the cumulative doses with the most toxic effect are well known; the cumulative dose of doxorubicin of 400, 550, and 700 mg/m^2 results in heart failure in 3, 7 and 18% of the patients, respectively. The higher doses of 550 and 700 mg/m^2 elevate the risk of anthracycline-induced heart failure especially in children, women, and patients above 65 years [67,69–73].

Therefore, therapy with doxorubicin is recommended not to exceed a cumulative dose of 450 mg/m^2, and 900 mg/m^2 in case of epirubicin, which is the most used structural analog of doxorubicin [2].

There are autopsy studies evaluating the ultrastructural and histological changes in myocytes after chemotherapy with anthracyclines. Isner *et al.* [24,74] analyzed the histological particularities in 64 patients treated with an anthracycline-based regimen retrospectively. Vacuolization of cardiac muscle cells and myofibrillar dropout were the two characteristic signs of scoring the dimension of cardiac toxicity.

Twenty (31%) of the 64 analyzed patients had clinical overt signs of cardiotoxicity whereas the other 44 patients had no signs of cardiac dysfunction. In 13 of these 20 patients with clinical manifestations, histological changes were seen whereas such structural changes were absent in

seven patients. In 23 of the 44 patients without any clinical signs of cardiac damage, the heart biopsy showed unexpectedly mild signs of structural changes in most cases but severe signs in four cases.

For higher cumulative doses of doxorubicin ($> 450\,mg/m^2$), mediastinal irradiation and age more than 70 years, obvious histological signs of cardiotoxicity could be detected.

Doxorubicin and structural analogs

To reduce the risk of early or late cardiac dysfunction, protracted infusion and the development of structural analogs (e.g. liposome encapsulated anthracyclines) and the use of cardioprotectants were considered.

The continuous infusion of anthracyclines was compared with the bolus therapy regarding the incidence of cardiac changes. In some studies, the possible benefit of prolonged anthracycline administration with lower risk of cardiac dysfunction could be observed [75–81]. The longer time of hospitalization and the need of a central venous line make this approach impractical for clinical routine.

The structural analogs are mitoxantrone and epirubicin. Epirubicin has a lesser potency compared with doxorubicin and therefore, a lower risk for heart failure [2,82–84]. The maximum cumulative dose of mitoxantrone associated with a low risk of cardiotoxicity is $140\,mg/m^2$, and the induced heart dysfunction can be effectively treated with the standard medical therapy of heart failure [85–87].

For the anthracyclines, doxorubicin and daunorubicin, cardiac safety can be enhanced with the encapsulation in liposomes with a favorable pharmacokinetic profile. These galenics permit higher cumulative doses with equivalent efficacy and a significant lower risk of developing cardiac dysfunction. In biopsies, less myocytal changes were detected during liposomal formulations, example of doxorubicin [88–90].

Cardioprotectants

Dexrazoxane is an adjunctive agent, which is given with anthracyclines to prevent cardiotoxicity. Dexrazoxane is an EDTA-like chelator binding on iron, which is developed by lipid peroxidation [12]. Numerous studies have shown that concurrent administration of dexrazoxane reduces the risk of cardiac damage. Dexrazoxane could either be applied at the beginning of an anthracycline-based therapy or after a cumulative dose of $300\,mg/m^2$. In a meta-analysis of six randomized trials that included 1013 adult and pediatric patients, dexrazoxane significantly reduced the incidence of heart failure (relative risk = 0.28, 95% confidence interval 0.18–0.42) [91]. Restrictively, the investigators suggested a lower tumor reduction in patients who had received concurrently anthracyclines and dexrazoxane. Despite the cardiac benefit, a number of issues have created uncertainty about the role of dexrazoxane, including the possibility of a lower response rate to chemotherapy The investigators concluded that treatment with dexrazoxane as a cardioprotectant is justified individually when the risk of cardiac dysfunction is expectedly high [12]. With a view of inconsistent results in the literature, the interference between dexrazoxane and anticancer therapy has not been clarified up to now [91–94].

In addition, dexrazoxane may enhance anthracycline myelosuppression [95]. Moreover, there is no reported experience with using dexrazoxane in conjunction with liposomal anthracyclines [92–94]. Dexrazoxane as a cardioprotectant is approved in the United States and the European Union.

The American Society of Clinical Oncology has published detailed guidelines for the adjunctive use of dexrazoxane. Key points from these guidelines include the following:

(1) The agent can be considered for patients being treated for metastatic disease who have received a cumulative dose of doxorubicin $\geq 300\,mg/m^2$ and may benefit from continued treatment.
(2) For patients who had received adjuvant doxorubicin, the data are unclear.
(3) The uncertainty regarding tumor response rates needs to be balanced against the risk of cardiotoxicity.
(4) Adult patients in an adjuvant setting should not receive dexrazoxane outside a clinical trial setting.
(5) Patients receiving dexrazoxane require continued close LVEF monitoring.

The benefit of prophylactic standard cardiac like β receptor blockers or angiotensin converting enzymes inhibitors is not clear [96–100].

Cardiac surveillance during anthracycline-based treatments

Invasive and noninvasive techniques have been analyzed in the past. Standard noninvasive diagnostic techniques include echocardiography and RVG, cardiac MRI and determination of myocardial serum markers. The invasive diagnostic techniques include endomyocardial biopsy.

Echocardiography is a simple method for the early detection of the signs of cardiotoxicity without exposure to nuclear radiation. The limitations of echocardiography include a low reproducibility and a high variability by different investigators. The global ventricular function should be documented in detail and in course controlled by the same examiner [26,27,101,102].

Kremer and Caron showed in a study with 51 patients also containing children that the characteristic early sign of doxorubicin-induced cardiotoxicity is the decline of the LVEF monitored by the multigated acquisition scan. A decline in LVEF of 15–22% from baseline was noted before developing clinical symptoms of heart failure. Clinical manifestations of cardiac dysfunction could be

documented when the LVEF decreased below 30% [34]. Therefore, LVEF is recommended to be measured continuously to identify early signs of cardiotoxicity before clinically overt manifestations [103–105].

Lee *et al.* [106] retrospectively evaluated the heart function in 12 patients by serial radionuclide angiographies. They showed that a change in the left ventricular diastolic function can occur before the LVEF decrease. In summary, diastolic function and systolic function should be examined for the early detection of doxorubicin-induced cardiotoxicity.

Another method for detecting structural and morphologic signs of cardiotoxicity is the cardiac MRI. It is used in many indications like coronary heart disease, post infarction diagnosis, and chemotherapy-induced heart failure [107–110].

Guideline criteria for monitoring patients receiving doxorubicin and the four-fold reduction in the incidence of clinical congestive heart failure with management concordant to the guidelines are given in Fig. 1 and Table 2.

Table 2 Guidelines for monitoring patients receiving doxorubicin

Determine baseline left ventricular ejection fraction before administration of doxorubicin
Patients with normal baseline LVEF: $\geq 50\%$
Second examination after application of 250–300 mg/m^2
Repeat study after 400 mg/m^2 in patients with known risk factors of cardiac failure or after 450 mg/m^2 in absence of risk factors
Perform sequential investigation before each dose
Discontinue doxorubicin therapy: functional signs of cardiotoxicity or/and absolute decrease in LVEF $\geq 10\%$ (EF units) associated with a decline to a level of $\leq 50\%$ (EF units)
Patients with abnormal baseline LVEF: $\leq 50\%$
Doxorubicin therapy should not be initiated with baseline LVEF $\leq 30\%$
In patients with LVEF >30 and $<50\%$ LEVF should be analyzed before each dose
Discontinue doxorubicin: absolute decrease in LVEF $\geq 10\%$ (EF units) and/or final LVEF $\leq 30\%$

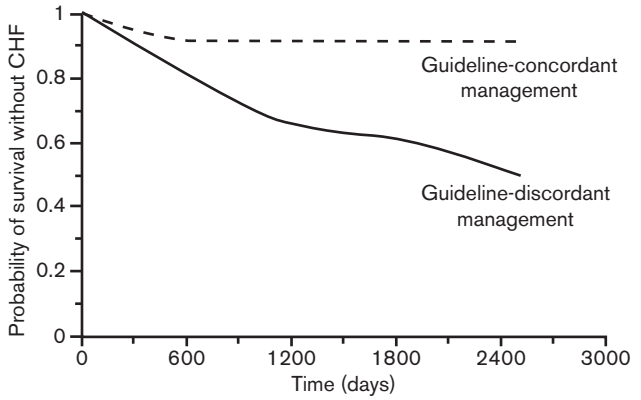
Adopted from Schwartz *et al.*, *Am J Med 1987; 82:1109.*
EF, ejection fraction; LVEF, left ventricular ejection fraction.

Chemotherapy associated cardiotoxicity in patients with breast cancer

Adjuvant setting

Adjuvant chemotherapy in the early stages of breast cancer promotes disease-free and overall survival, respectively, so that it is recommended for the majority of pre- and postmenopausal women with nodal positive and nodal negative breast cancer. Short or long-term toxicity has to be evaluated for the different single and combined therapeutic schemes. The risk of developing cardiotoxicity depends on the applied chemotherapeutics. For anthracycline and trastuzumab-based regimes, the cardiotoxicity rate, the reversibility of heart failure and the time of appearance after application have been well evaluated.

Fig. 1



Management of either concordant or discordant with the guideline criteria for monitoring patients receiving doxorubicin; probability of survival without clinical congestive heart failure (CHF). Data from Schwartz *et al.*, *Am J Med* 1987;82:1109.

The most used adjuvant chemotherapeutic regimes include a combination of anthracyclines and/or taxanes.

Taxanes like paclitaxel and docetaxel are among the most active agents in breast cancer. They have been shown to benefit the outcome in the adjuvant setting in women with nodal positive and negative early breast cancer.

Adverse effects include particularly hypersensitivity reactions, peripheral neuropathy, myalgias, arthralgias, alopecia, and fluid accumulation (most frequently attributed to docetaxel). To reduce these negative effects the prophylactic administration of glucocorticoides, histamine 1, and histamine 2 receptor blockers is recommended.

The cardiac side effects during treatment with paclitaxel or docetaxel are mostly asymptomatic bradycardias and heart block diagnosed in routine ECG and echocardiography; however, conduction abnormalities, cardiovascular collapse, and pectanginal symptoms were also seen. On account of the low incidence of cardiac side effects of paclitaxel or docetaxel, routine cardiac monitoring is not recommended for patients without cardiac risk factors. Moreover, there is no evidence that cardiac complications are caused by the application of the taxane itself [111–115]. Malhotra *et al.* [116] showed that the combined application of taxanes and anthracyclines or the sequential application can increase the risk of cardiac side effects.

The most common cardiac symptoms during treatment with the antimetabolite 5-flurouracil are chest pain either nonspecific or pectanginal [117,118]. In a review including 262 cases, Saif *et al.* [119] showed that 76% of the cardiac events occurred within 72 h after the administration of the first cycle. The most often reported symptoms are pectanginal symptoms (48%), myocardial infarction (23%), arrhythmias (16%), acute pulmonal edema (7%), and cardiac arrest and pericarditis (2%). The pathophysiological mechanisms leading to cardiac

side effects are thought to be vasospasms and endothelial cytotoxicity [120–123]. Some studies could show that the incidence of cardiac side effects ranges from 1 to 19% and depends on the method of administration (bolus injection vs. infusional), preexistent coronary heart disease and concomitant application of chest radiation or anthracyclines [4,117,118,124,125]. The signs of cardiac toxicity during treatment with capecitabine are similar to that of infusional 5-fluorouracil [126–129].

Metastatic setting

In patients with metastatic breast cancer (MBC), the improvement of the overall survival and progression free survival are because of improved systemic therapies, however, with a higher risk of negative side effects.

In hormone receptor positive tumors, the endocrine therapeutic approach is preferred to much more aggressive mono or combined chemotherapeutic regimes. Cardiotoxicity is not a typical side effect of endocrine treatment. There exists no data of the risk of developing cardiac damage in short or long-term survival after antihormonal treatment.

For primary hormone nonresponsive breast cancer chemotherapy and molecularly targeted biological agents, lapatinib, trastuzumab, and the VEGF receptor antagonist bevacizumab are effective therapeutic options, respectively. The most effective chemotherapeutics are anthracyclines, taxanes, alkylating agents, and antimetabolites.

Trastuzumab

HER2 is a transmembrane growth factor with physiological importance for cell growth and differentiation. Twenty-five to thirty percent of patients with the diagnosis of breast cancer show an amplification of the *HER2* gene that leads to an overexpression of the HER2 receptor. The overexpression of HER2 in patients with breast cancer is associated with poor outcome [73,130–132]. Trastuzumab is a recombinant humanized IgG_1 monoclonal antibody targeted against the HER2-receptor on the cell surface. It binds specifically to the extracellular domain of HER2, which results in an inhibition of the signal transduction for cell growth. In clinical and preclinical studies in breast cancer patients, overexpressing HER2 trastuzumab has proven efficacy as both a single-agent or as a combined immunochemotherapy regime [133–137]. As an adjuvant drug, trastuzumab leads to lower risk of recurrence and survival benefit, whereas in metastatic disease a significant reduction in the tumor was shown [138].

Pathophysiology of trastuzumab-induced heart failure

The pathophysiology of trastuzumab-induced heart failure is not fully understood. Moreover, numerous patients who received trastuzumab had been treated before or simultaneously with anthracyclines so that late or modified heart damage dependent on anthracyclines seemed to be reversible. However, in the absence of ultrastructural changes, myocardial biopsies could not support this argument [139]. In addition, patients who never received anthracyclines developed signs of heart failure during treatment with trastuzumab. Some investigators postulated that trastuzumab-induced cardiotoxicity is a direct result of HER2 receptor blockade; the HER2 signal transduction is fundamental for cardiac development in the embryo and for protection against cardiac toxins [14,15]. In this context, studies in *HER2* gene knock-out mice showed development of progressive heart failure and a higher sensibility for anthracycline-associated myocyte damage [16]. In addition, patients with chronic heart disease showed increased HER2 levels in the serum, which correlated inversely to the left ventricular function [17,18].

Incidence of trastuzumab-induced cardiotoxicity

Cardiotoxicity is the generally described side effect for trastuzumab. The incidence of cardiac dysfunction ranged from 3 to 7% during single-agent trastuzumab therapy and increased to 27% during combination therapy [136,140]. The clinical symptoms are mostly asymptomatic and unspecific like tachycardia, palpitations, arrhythmias and distress. The development of clinically manifested heart failure is rare [136,140].

A review of six phase II and one phase III trials including 1219 women with MBC analyzed the risk of developing any cardiac dysfunction during single-agent trastuzumab therapy or in combination with other chemotherapeutics. Expectedly, the most often applied chemotherapeutics were anthracyclines/cyclophosphamide (AC) and paclitaxel [140]. The incidence of cardiac dysfunction ranged from 3 to 7% for trastuzumab alone, and was 27 versus 8% for trastuzumab + AC versus AC and 13 versus 1% for trastuzumab + paclitaxel versus paclitaxel.

The highest rates of New York Heart Association class III–IV heart failure were shown for the combination of anthracyclines and trastuzumab (16%, 2–4% for trastuzumab alone, 2% for trastuzumab + paclitaxel, 1% for paclitaxel alone).

The combination of an anthracycline-based chemotherapy with trastuzumab should be indicated critically after an individual risk-benefit analysis. The cumulative dose of such a therapeutic approach should be significantly less than the cumulative dose in single-agent anthracycline therapy because of a significant higher risk of progressive heart failure [141]. The cumulative dose of anthracyclines (doxorubicin) without trastuzumab is up to 450 mg/m^2 with a risk of heart failure of 5% [71,72]. The mechanism of the more severe cardiotoxicity in combination treatment is not completely understood, but upregulation of HER2 receptors by anthracyclines seems to be one of the effects [142].

Guarneri *et al.* [143] analyzed the rate of any cardiac toxicity in 173 women with MBC receiving trastuzumab for at least 1 year. Cardiac events varied from an asymptomatic decrease of LVEF below 50% to clinical signs of congestive heart failure. Among the 49 patients, 28% developed cardiac dysfunction: three patients (1.7%) had an asymptomatic LVEF decrease of 20% from baseline, 27 patients (15.6%) experienced grade 2 cardiotoxicity, and 19 patients (10.9%) experienced grade 3 cardiotoxicity. After discontinuation of trastuzumab all but three patients showed an LVEF improvement. There was one cardiac-related death (0.5%). Fifteen patients developed clinical symptoms and were set on specific cardiac therapy example β receptor blockers in combination or without angiotensin-converting enzyme inhibitors, respectively. Only three women did not recover despite the discontinuation of trastuzumab and initiation of symptomatic treatment.

Ewer *et al.* [139] also showed that in 38 patients with overexpressing HER2 breast cancer, LVEF decreased after the initiation of trastuzumab. Once treatment with trastuzumab was interrupted, the mean time to normalization of the cardiac output was 1.5 months. A majority of those patients (88%) were retreated with trastuzumab without any documented progressive heart failure. In both the studies, the cardiac dysfunction during trastuzumab was reversible and reinitiation was mostly tolerated.

Cardiac surveillance during trastuzumab-based treatment

Among several methods, echocardiography is considered the method generally accepted for the cardiac surveillance of patients receiving trastuzumab. As mentioned earlier, this method is feasible and widely available.

Tables 3 and 4 summarize the proposed guidelines for the management of patients with breast cancer during adjuvant (Table 3) and metastatic (Table 4) treatment with trastuzumab based on physical status and LVEF [144,145].

In summary, trastuzumab-induced cardiotoxicity differs in many aspects from that induced by anthracyclines [135,146,147]. In contrast to the anthracycline-related cardiac dysfunction, there is no clear relation to a cumulative dose of trastuzumab. After treatment interruption, clinical or subclinical signs of heart failure are mostly reversible and reinitiation of trastuzumab after recovery is often well tolerated.

Table 3 Guidelines for cardiac monitoring during adjuvant trastuzumab therapy

Physical status	LVEF	Trastuzumab	LVEF monitoring	Management
Asymptomatic	Normal	Continue	As scheduled	None
	↓ <16 points below baseline but normal	Continue	As scheduled	If LVEF <40%, treat with an ACE inhibitor
	↓ ≥16 points below baseline or subnormal (regardless of the amount of reduction)	Hold temporarily	Repeat after 4 weeks; if improved, restart treatment; if not improved, stop trastuzumab	If LVEF <40%, treat with an ACE inhibitor
Symptomatic	<normal	Hold permanently	Per cardiologist's discretion	Treat for heart failure

Adopted from Saad *et al.*, *Community Oncology* 2007; 4:739.
ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction.

Table 4 Proposed guidelines for the management of patients with metastatic disease who are treated with trastuzumab, based on physical status and LVEF

Physical status[a]	LVEF	Trastuzumab	LVEF monitoring	Management
Asymptomatic[b]	↓ but normal	Continue	Repeat in 4 weeks	
	↓ >10 points but normal	Continue	Repeat in 4 weeks	Consider β-blockers
	↓ 10–20 points and LVEF >40%	Continue	Repeat in 2–4 weeks Improved: monitor Not improved: stop trastuzumab	Treat for left ventricular dysfunction
	↓ >20 points to <40% or LVEF <30%	Hold	Repeat in 2 weeks Improved to >45 percent: restart trastuzumab Not improved: stop trastuzumab	Treat for left ventricular dysfunction
Symptomatic[c]	↓ <10 points	Continue		Search for noncardiac pathology (e.g. anemia)
	↓ >10 points and LVEF >50%	Continue	Repeat in 2–4 weeks Stable or improved: continue trastuzumab Worsened: stop trastuzumab	Treat for heart failure
	↓ >30 points	Stop		Treat for heart failure

Adopted from Keef *et al.*, *Cancer* 2002; 95:1597.
LVEF, left ventricular ejection fraction.
[a]Weekly monitoring of heart rate and body weight.
[b]Asymptomatic changes in heart rate and/or weight, but without symptoms of dyspnea on exertion.
[c]Symptomatic new, spontaneous report of symptoms of dyspnea on exertion, pulmonary vascular congestion, or edema.

Lapatinib

Lapatinib, an oral, reversible dual tyrosine kinase inhibitor of epidermal growth factor receptor and HER2 is indicated for MBC overexpressing HER2 (ErbB2). Lapatinib is approved in combination with capecitabine after failure of earlier anthracycline, taxane, and/or trastuzumab-based therapies [148].

Cardiac safety of lapatinib was analyzed in clinical trials. Perez *et al.* [149] reported on a pooled analysis, which included 3689 patients who were treated with lapatinib between 2001 and 2006. They observed a low incidence of cardiotoxicity of 1.6%. In these cases, cardiac events were mostly asymptomatic with a reversible decrease in LVEF and no cardiac death was attributed to the therapy with lapatinib. In view of the a reversibility of the cardiac dysfunction, pathophysiological type II of cardiotoxicity is suggested. Rates of occurrence in the control group receiving nonlapatinib regimes showed similar frequencies of cardiac events.

Bevacizumab

Bevacizumab is a humanized monoclonal IgG_1 antibody binding to the VEGF receptor on tumor cells. The most frequently reported side effect is severe hypertension (grade 3) in 3–16% of the patients. Development of a left ventricular dysfunction in 2% of the cases is a rare side effect during single-agent bevacizumab. In patients pretreated with anthracyclines or an earlier chest wall irradiation, the risk of developing a chronic heart failure is 4% with an increase to 14% during simultaneous application of anthracyclines and bevacizumab [57,73,150,151].

Cardiotoxicity and concurrent/sequential (mediastinal) irradiation

Radiation therapy is an important treatment modality to improve disease-specific survival mainly in patients with early stage breast cancer, Hodgkin's lymphoma and other tumors localized in the chest region.

Radiotherapy-induced cardiac toxicity

Any structure of the heart can be reversibly or irreversibly damaged including the myocardium, pericardium, heart valves, coronary arteries, capillaries, myocytes, and the conducting system. Among these side effects, pericarditis is the most frequently seen acute cardiac toxicity of irradiation. Data on the late onset cardiac effects of radiation therapy were collected from patients with breast cancer and Hodgkin's lymphoma. Such late onset clinical manifestations include coronary heart disease, restrictive cardiomyopathy by myocyte fibrosis, chronic heart failure with an increased decline of the diastolic function than systolic function and valvular disease [152–154]. These cardiac manifestations occur within years or decades after treatment and can influence mortality and morbidity.

Pathophysiology of radiotherapy-induced cardiac toxicity

The pathophysiological mechanisms of cardiotoxicity by radiation therapy are damage of blood vessels by oxygen stress, DNA disruption, and inflammation. Histological examinations show diffuse interstitial and myocardial fibrosis in combination with unmodified myocytes and signs of constriction of arterial lumens and capillary [155]. Furthermore, abnormalities of the endothelial cell membranes, swollen cytoplasm, thrombosis, and rupture of the vascular walls were seen and lead to reduction of myocytes supplying capillaries followed by myocardial cell death, ischemia, and fibrosis [154,156–159].

Risk factors of radiotherapy-induced cardiac toxicity

The risk factors of developing radiotherapy-induced cardiac failure depend on preexisting risk factors for coronary heart disease, the radiation dose, the dose per fraction, the volume of the irradiated heart tissue, and the combination of cardiotoxic chemotherapeutics and irradiation.

The long-term effects of radiotherapy have been well evaluated through the multiple databases in the tumor register in women with diagnosed breast cancer and chest or chest-wall irradiation, respectively.

In the last 10–20 years, the risk of cardiac toxicity after radiotherapy has been significantly decreased by newer irradiation techniques (lower total dose and reduced heart volume in the radiation field) [160]. In patients with left and right sided tumors treated with radiotherapy, no differences in developing cardiac side effects have been registered since 1980. Before 1980, the risk of cardiac failure was significantly higher in patients with left side irradiated tumors than right side tumors [161,162]. Probably because of a short follow-up in most of the studies, coronary heart disease and symptomatic or clinical asymptomatic heart failure have not been detected [163,164].

Conclusion

Cardiotoxicity is a well-known negative side effect of anticancer treatments. Guidelines to prevent these adverse effects were developed and include routine measurement of LEVF, consideration of cardiac risk factors in the medical history, maintaining the cumulative dose of anthracyclines and avoiding the concomitant application of cardiotoxic drugs. These modifications have significantly reduced the rates of cardiac failure [147].

Yet, there are no evidence-based data that dose reduction or interruption can reduce cardiac failure. Careful monitoring and early detection of (asymptomatic) LVEF reduction from baseline is a reliable screening parameter for the individual decision to continue or stop treatment. Heart failure because of trastuzumab treatment is less associated with myoctal death and is more likely reversible as compared with anthracyclines.

Cardiac biomarkers in the serum can detect cardiotoxicity in the earliest stages. It could be considered in the future to combine standard and newer diagnostic tools to prevent the fatal complication of heart failure.

The combination of cardiotoxic drugs or treatment despite cardiac risk factors should be an individual decision with respect to the physical status, the quality of life, and the prognosis. The benefit of typical heart failure medications, for example, angiotensin converting enzyme inhibitors, β-blockers or dexrazoxane, which are specific for anthracycline-induced heart failure is still in discussion and should be decided in the individual case.

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