

REVIEW ARTICLE

Cardiotoxicity and Oncological Treatments

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SUMMARY

Background: Cardiotoxic and other side effects limit the usefulness of treatments for cancer.

Methods: This article is based on pertinent articles that were retrieved by a selective search in PubMed and other databases, and on the guidelines of the European Society of Cardiology, the Association of Scientific Medical Societies in Germany, and the European Society of Medical Oncology.

Results: Prospective studies have shown that some treatments for cancer are cardiotoxic. The heart damage that they cause can manifest itself as arrhythmia, arterial hypertension, thromboembolism, angina pectoris, myocardial infarction, or heart failure. It has been observed that potentially lethal complications can arise as late as 40 years after treatment of the original cancer. The anthracycline drug doxorubicin, given in a dose of 500 mg/m² of body surface area, has been found to cause cardiac complications in 4–36% of the patients treated with it. Trastuzumab and epirubicin cause dose-limiting cardiac events in 1.7–5% of patients, depending on the dosage. Paclitaxel causes bradycardia, intracardiac conduction block, or arrhythmia in 0.5% of patients. 18% of patients treated with sunitinib or sorafenib have clinical manifestations relating to the heart (angina pectoris, dyspnea). 5-fluorouracil can cause angina pectoris at the beginning of treatment and rarely causes myocardial infarction. Cardiac radiation therapy, a form of treatment practiced in earlier decades, can cause cardiac complications 20 years after the event. The opportunity to prevent cardiac complications of anthracycline drugs with dexrazoxane is decidedly limited, but initial studies have shown that treatment with beta-blockers and ACE inhibitors lessens the likelihood of cardiotoxic side effects. When cardiac complications arise, the generally applicable rules for the treatment of each type of cardiac problem should be followed. The oncological treatment protocol should be adjusted or switched to one that is less damaging to the heart.

Conclusion: Treating physicians need to be thoroughly acquainted with the cardiotoxic effects of anti-cancer drugs so that they can diagnose them early on and avoid jeopardizing the overall success of treatment.

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The number and variety of treatment options for cancer patients have increased significantly in recent years. More specific treatment approaches are possible thanks to newly introduced, targeted agents. However, side effects such as cardiotoxicity can restrict the use of some therapies (*Table 1*) (1, 2).

A distinction is made between acute cardiotoxicities, such as cardiac arrhythmia during anthracycline infusions, and chronic cardiotoxicities, such as restricted left ventricular pump function with clinical symptoms of cardiac insufficiency even decades after the end of treatment. Chronic cardiotoxicity has serious consequences (2). Late cardiotoxic complications have been observed in 8.3% of patients 30 years after anthracycline use (3, 4). The 2.2% to 13% mortality rate following high-dose 5-fluorouracil treatment also demonstrates how dangerous such side effects can be (5).

The precise mechanism of cardiotoxicity has been most thoroughly researched in the case of anthracyclines. The molecular basis of this is binding to topoisomerase-2 β (6). Combination therapies (e.g. anthracycline + trastuzumab) can increase cardiotoxicity (2, 6–8). Genetic factors seem to increase the probability of cardiotoxic side effects (9).

This article reports on cardiotoxicity, a significant side effect that frequently limits oncological treatments. It focuses on anthracyclines, the monoclonal antibody trastuzumab, and radiotherapy. One section also addresses the subject of cardiotoxicity in the treatment of children with malignant diseases.

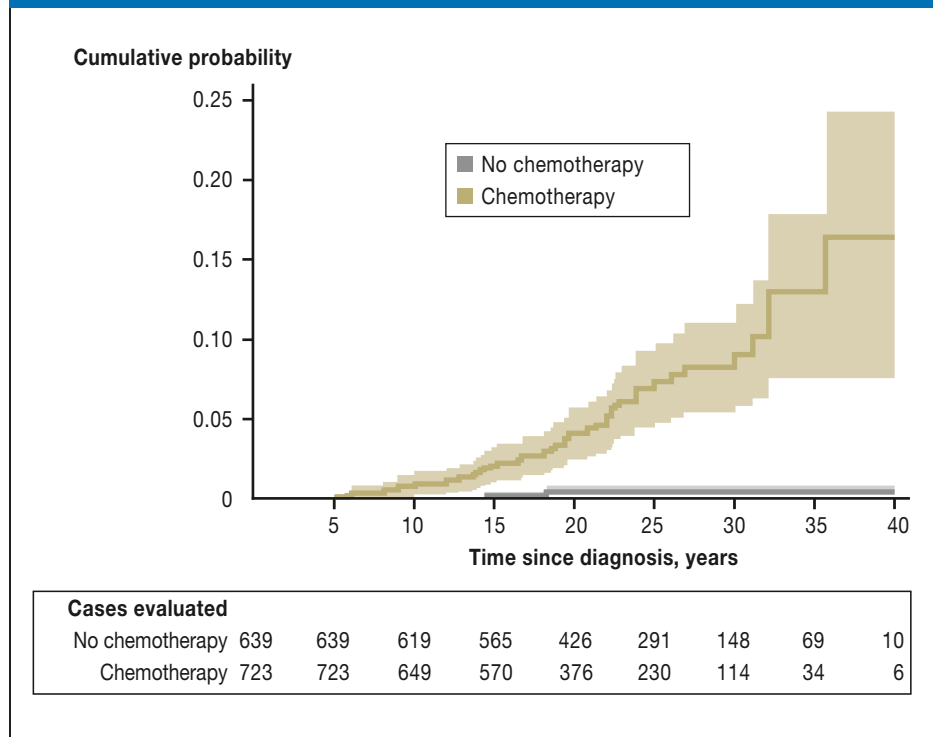
Diagnosis

Cardiac dysfunction during oncological treatment can manifest in various different ways. Cardiac arrhythmias, ECG alterations, pericarditis–myocarditis syndrome, and other manifestations have been described as early forms (8). The late form of cardiomyopathy can be detected on the basis of a reduction in left ventricular ejection fraction (LVEF) with resulting systolic heart failure. Like other forms of heart failure, it becomes clinically manifest as reduced performance, shortness of breath, weight gain, and edema (8). Diagnosis is established on the basis of clinical history and physical examination and confirmed using the gold standard of transthoracic echocardiogram (TTE). Potentially, TTE should be performed before every cardiotoxic chemotherapy (8, 10). Risk-adjusted monitoring should be performed during treatment.

Cumulative incidence of cardiac events

(acute cardiac insufficiency, cardiac ischemia, heart valve diseases, arrhythmia, and/or pericarditis) in long-term survivors of childhood cancer (according to [e19]: van der Pal H. et al.: High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol* 2012; 30: 1429–37. Reproduced with the kind permission of the American Society of Clinical Oncology [ASCO]; the authors, editors, and ASCO are not responsible for errors or omissions in translations).

FIGURE 1



Sensitive, reproducible ways to diagnose cardiotoxicity associated with tumor treatment are scintigraphy and, as a last resort, endomyocardial biopsy. Neither of these procedures is part of routine practice, as scintigraphy is associated with a significant radiation burden and endomyocardial biopsy with the danger of local complications and a potentially fatal pericardial effusion. Endomyocardial biopsy is indicated only in exceptional cases of progressive disease forms, to verify diagnosis. The role of magnetic resonance imaging of the heart (cardiac MRI) as a noninvasive method has yet to be established (8, 10).

In recent years, various authors have investigated the value of serum markers in diagnosing cardiotoxicity. The main serum markers are the natriuretic peptides BNP and NT-proBNP and the cardiac structural protein troponin (8, 10). These are established as markers for the diagnosis and prognosis of patients with heart disease. As a predictive marker for the assessment of cardiomyopathy induced by tumor treatments, they are controversial and should not be used to rule out or diagnose cardiotoxicity (11–17).

In everyday clinical practice, all patients should be monitored for potentially cardiotoxic complications in routine medical examinations even years and decades after oncological treatment; by far the most significant such complication is the manifestation of cardiac insufficiency following anthracycline treatment, with symptoms such as reduced performance, dyspnea, or edema (13, 14).

The cardiotoxicity of specific tumor treatments

Anthracyclines

Anthracyclines such as doxorubicin and epirubicin are frequently used, highly effective agents in the treatment of malignant diseases. Cardiotoxic side effects are their main side effects. The most dangerous of these is congestive cardiomyopathy with reduced LVEF, which can develop as much as 40 years after anthracycline treatment in childhood (e.g. for acute lymphoblastic leukemia) (Figure 1) (14, 18, 19). Its precise probability in individual cases is difficult to estimate; for doxorubicin at a cumulative dose of 500 mg/m², for example, the proportion of patients who suffer cardiac complications has been described as between 4% and 36% (17).

Risk factors are age, pre-existing cardiac damage, radiation in the region of the heart, but in particular cumulative anthracycline dose (17).

Anthracyclines should be used only after thorough clinical examination, including ECG and echocardiography with measurement of LVEF (17). For liposomal doxorubicin insufficient data is available on many diseases, but its use is justified for certain indications (18).

Trastuzumab

Trastuzumab, an antibody, was developed as an inhibitor of the tyrosine kinase-associated HER2 receptor (20). The first trial to demonstrate the clinical efficacy of trastuzumab was the 1996 Phase II trial conducted by Baselga et al. (21). Since then, trastuzumab

TABLE 1

Associations between oncological treatments and manifestations of cardiotoxicity (according to 5, 39, 40, e1–e8, e20, e21)

Drug	Restricted left ventricular function %	Cardiac ischemia %	Association with arterial hypertension %	Association with thromboembolism %
Anthracyclines				
Doxorubicin	3 to 26	–	–	–
Epirubicin	0.9 to 3.3	–	–	–
Idarubicin	5 to 18	–	–	–
Liposomal anthracyclines	2	–	–	–
Alkylating agents				
Cyclophosphamide	7 to 28	–	–	–
Ifosfamide	17	–	–	–
Cisplatin	–	–	–	8.5
Antimetabolites				
Clofarabine	27	–	–	–
Capecitabine	–	3 to 9	–	–
5-Fluoruracil	–	1 to 68	–	–
Antimicrotubule agents				
Docetaxel	2.3 to 8	1.7	–	–
Paclitaxel	–	1 to 5	–	–
Monoclonal antibodies				
Bevacizumab	1.7 to 3	0.6 to 1.5	4 to 35	12
Trastuzumab	2 to 28	–	–	–
Proteasome inhibitors				
Bortezomib	2 to 5	–	–	–
Small-molecule tyrosine kinase inhibitors				
Dasatinib	2 to 4	–	–	–
Imatinib	0.5 to 1.7	–	–	–
Lapatinib	1.5 to 2.2	–	–	–
Sunitinib	2.7 to 11	–	5 to 47	–
Erlotinib	–	2.3	–	3.9 to 11
Sorafenib	–	2.7 to 3	17 to 43	–
Immunomodulators/piperidinediones				
Lenalidomide	–	–	–	3 to 75
Thalidomide	–	–	–	1 to 58
Radiotherapy	>4	1 to 13	–	–

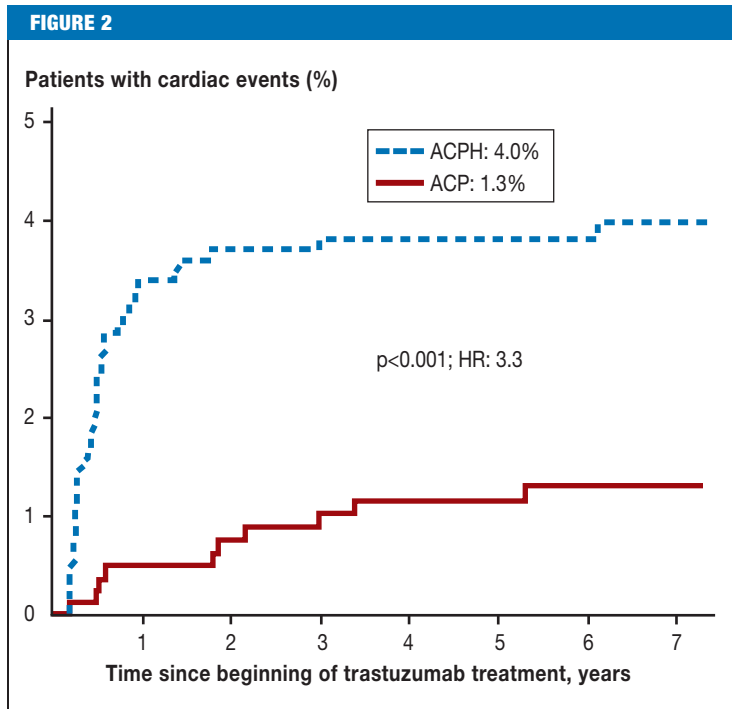
treatment has become an established therapy for HER2-positive breast cancer. However, the licensing trial of trastuzumab in patients with metastatic breast cancer found an unacceptably high rate of cardiac events (NYHA [New York Heart Association] Class III and IV heart failure) for the very combination of trastuzumab and an anthracycline that was most effective: these occurred in 27% of cases, versus 8% for the combination including paclitaxel (19). In order to quantify the cardiotoxicity of trastuzumab and anthracycline combination therapy, the German HERCULES Trial investigated treatment with epirubicin (a less cardiotoxic epimer of doxorubicin), cyclophosphamide, and trastuzumab. Cardiac function was examined prospectively using a series of echocardiograms. The results of the trial showed a significantly lower rate of dose-limiting cardiac events after five years: 1.7% (at 60 mg/m²) versus 5% (at 90 mg/m² epirubicin) (22).

In cases of HER2 overexpression, trastuzumab can reduce the mortality rate by one-third when compared

to adjuvant chemotherapy alone (relative risk [RR]: 0.66; 95% confidence interval; 0.57 to 0.77; p<0.00001); for node-positive disease, this is an absolute rate of 8.8% fewer deaths within 10 years. The risk of serious cardiac events, however, increases between three- and five-fold (to 4%) (Figure 2) (23–27). These particularly affect patients with pre-existing cardiac risk.

In contrast with anthracycline-induced cardiomyopathy, trastuzumab-induced cardiomyopathy appears to be reversible; there is no further increase in risk after the end of treatment (Figure 2) (24).

In view of breast cancer's high survival rates, in the future it will be important to test the indications for anthracyclines with and without trastuzumab against other combination therapies that may be less cardiotoxic, to determine factors that predict response to anthracyclines and potential cardiotoxicities, and to use this information to put together more tailor-made treatments.



Cumulative incidence of cardiac events (acute cardiac insufficiency, cardiac death) in the National Surgical Adjuvant Breast and Bowel Project Trial B-31 (NSABP B-31). ACP: Doxorubicin, cyclophosphamide, paclitaxel; ACPH: Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab; HR, hazard ratio; (according to [24]: Romond EH et al.: Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel [ACP] with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012; 30: 3792–9. Reproduced with the kind permission of the American Society of Clinical Oncology [ASCO]. The authors, editors, and ASCO are not responsible for errors or omissions in translations)

Taxanes, 5-fluorouracil, and signal transduction inhibitors

Cardiac toxicity caused by paclitaxel takes the form of sub-acute or acute bradycardia, heart block, and atrial or ventricular arrhythmias (28). Its incidence is 0.5% (28). Paclitaxel itself does not induce congestive heart failure (26). However, paclitaxel combined with anthracyclines does foster anthracycline-associated cardiotoxicity. Interaction leads to reduced anthracycline elimination, resulting in higher plasma levels (29).

In 5-fluorouracil treatment, cardiac symptoms generally occur during the initial hours following the start of therapy. The most frequent symptom is reversible, typical angina pectoris, but myocardial infarctions have also been described (30). Complex arrhythmias are rarer. The clinical symptoms of ECG alterations can last more than 10 days. Transient regional or diffuse disruptions to left ventricular contractility are seen on echocardiograms (31). Coronary vasospasms are discussed as the basic pathological mechanism of 5-fluorouracil-induced cardiotoxicity (32). In cases of pre-existing coronary heart disease, the risk of clinically manifest cardiac side effects is increased by a factor of 6.83 (33). The cardiac side effects of the orally avail-

able prodrug capecitabine are similar to those of parenteral 5-fluorouracil (34).

Vascular endothelial growth factor (VEGF) and its signal cascades probably play an important role in myocardial response to acute and chronic ischemias (32). For bevacizumab, a monoclonal anti-VEGF antibody, myocardial dysfunction is described, in addition to arterial hypertension and arterial thromboembolic events, in approximately 1.6% of cases (35, 36).

As multikinase inhibitors, sunitinib and sorafenib also inhibit the VEGF receptor (37). In a prospective study involving 74 patients who received either sorafenib or sunitinib, a cardiac event was observed in 34% of patients, and clinical symptoms (angina pectoris, dyspnea) in 18%. In 12% of patients, echocardiography revealed a significant reduction in left ventricular ejection fraction (LVEF) or regional contractile dysfunction. ECG alterations were recorded in 16% of patients (38).

Radiotherapy

The risk of cardiotoxicity following radiotherapy to the thorax using a modern procedure is considered to be low, but it is relevant in the case of the treatment of long-term survivors who received radiotherapy in the past, administered via methods that are now obsolete (39). The high cure rate of Hodgkin’s lymphoma and breast cancer in particular means that comprehensive data on long-term risks of cardiac morbidity and mortality is available (39).

Following mantle field irradiation for Hodgkin’s lymphoma at typical doses of between 30 and 42 Gy, a two-fold increase in the relative risk of ischemic heart diseases (RR: 1.9) was reported after an average follow-up time of 11.2 years. The main reason for this figure is the number of patients with additional cardiovascular risk factors (40).

Cardiac MRI in 20-year survivors of mantle field irradiation at a median dose of 40 Gy and superhigh doses around cardiac structures detected hemodynamically relevant valve damage in 42% of cases, perfusion deficits in 68%, and evidence of prior infarctions in 29% (e1). Although no evidence was found of a direct relationship between reconstructed radiation dose and specific abnormal findings (e2), doses of around 40 Gy (heart valves), 35 Gy (pericardium, myocardium), and 30 Gy (coronary arteries) are seen as critical. In combinations including anthracyclines, the critical dose thresholds are lower (e3).

In pediatric oncology in particular, radiation doses have already been massively reduced. In long-term follow-up care of 1132 children from consecutive German–Austrian treatment studies on Hodgkin’s lymphoma with a median follow-up time of 15.1 years, heart disease could be detected in 4.4% of cases, and in two-thirds of these the abnormality was damage to heart valves. No comparison with an untreated control group was made (e4). At a dose of around 20 Gy, the current standard in pediatric oncology, only one case was observed. The future risk for patients receiving

treatment today can therefore be estimated as considerably lower (e4).

In a recently published large case-control study, the risk of ischemic heart disease increased in proportion to the mean radiation dose received by the heart up to 20 years after radiotherapy; however, the observation period in the study lasted from 1958 to 2001 (e5). Overall, following radiotherapy planned using CT and administered via a linear accelerator for breast cancer, which has been standard practice since the 1990s, significant cardiotoxicities can no longer be detected (e6, e7). However, the risk inherent in combined radiotherapy and potentially cardiotoxic cytostatic agents or antibodies cannot yet be conclusively assessed, due to the long follow-up periods required. Every effort should therefore always be made, when planning radiotherapy, to reduce the dose received by cardiac structures.

Pediatric oncology

Cardiotoxic side effects are particularly important in pediatric oncology, as nowadays 80% of children who receive oncological treatment are still alive 15 years later (German Childhood Cancer Registry: Annual Report 2012). Anthracycline-induced cardiotoxicity is particularly relevant to the treatment of children with malignant diseases, partly because in the past 40% to 50% of these children were treated with anthracyclines, and this figure has now risen to 60% (e8). The cumulative incidences reported in patients who are children or were treated with anthracyclines in childhood vary widely; this reflects the many different risk factors for cardiotoxicity and varying study design: the probability of cardiac insufficiency has been reported as being between 0 and 16%, and the risk of subclinical cardiotoxicity between 0 and 57% (e9).

The known risk factors for anthracycline-induced cardiotoxicity in childhood and adolescence are shown in Table 2.

Unfortunately, insufficient data is available on the effects of different anthracyclines on the risk of cardiotoxicity in children and adolescents (e10, e11). There is also a lack of data on the effect of protective substances (e9)—with the exception of dexrazoxane, which is now contraindicated for children and adolescents because of an increased risk of secondary malignancy, among other reasons (dexrazoxane product characteristics).

This makes genuine prevention impossible for pediatric patients. It is therefore all the more important to provide these patients with adequate follow-up care and, where necessary, to begin treatment early. Further pediatric studies investigating the issue of cardiotoxicity would also be worthwhile.

Monitoring, prophylaxis, and treatment

Monitoring

The following measures can be used to identify cardiotoxic side effects:

- Medical history (risk factors and cardiac symptoms such as dyspnea or reduced performance)

TABLE 2

Significant known risk factors for anthracycline-induced clinical heart failure in children and adolescents (4, e19, e20, e22)

Risk factors	Absolute risk	Relative risk	95% CI
Cardiac irradiation	Cardiac irradiation: 27.3% No cardiac irradiation: 2.5%	11.1	3.7 to 33.5
Age	<15 years: 1.6% = 15 years: 0.69%	2.3	1.4 to 4
Cumulative anthracycline dose	≥500 mg/m ² : 2.4% <500 mg/m ² : 0.9%	2.6	1.1 to 6
Sex	Female: 1.5% Male: 0.7%	2.1	1.3 to 3.5

95% CI: 95% confidence interval

- Clinical examination (for edema)
- ECG
- Echocardiogram as gold standard.

On an echocardiogram, restriction of left ventricular ejection fraction below the normal value of 55% or more than 10% below a previous finding and evidence of regional wall motility dysfunction should be regarded as abnormal (15, 16). Frequent monitoring via echocardiogram is recommended before, during, and after potentially cardiotoxic treatment, at intervals appropriate to the severity and progression of the disease (e12). A suggestion for diagnosis and treatment is provided in Figure 3 (according to e13).

Prophylaxis/cardioprotective agents

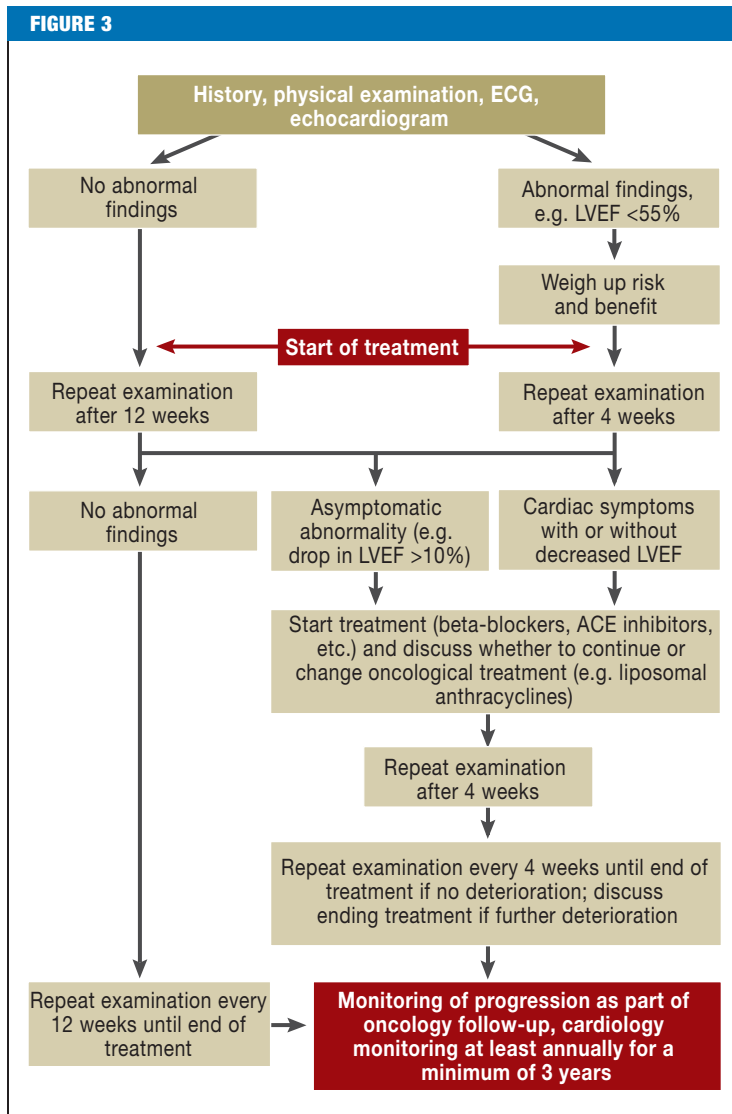
In the literature, oxidative stress was seen as the most likely cause of anthracycline-induced cardiomyopathy. However, antioxidants and free-radical interceptors demonstrated no effect (2).

Dexrazoxane is discussed as a possible option. Dexrazoxane is an intracellular iron chelator which is authorized for the prevention of anthracycline-induced cardiomyopathy in breast cancer patients. One of its potential side effects is cardiac arrhythmia such as tachycardia (dexrazoxane product characteristics). A 2011 Cochrane analysis showed that in randomized trials, dexrazoxane is suitable for the prevention of cardiotoxicity in adults with breast cancer or soft-tissue sarcoma (relative risk reduction: 0.29; 95% confidence interval: 0.20 to 0.41), with no evidence of lower treatment efficacy or higher risk of secondary tumors (e9).

A further review article showed a three-fold increase in the incidence of neoplasia, severe myelosuppression, and infections in children following dexrazoxane treatment (e14). According to its German product characteristics, dexrazoxane is contraindicated for patients under the age of 18 (dexrazoxane product characteristics).

Treatment

If a patient suffers the most serious type of cardiotoxicity, symptomatic left ventricular systolic heart failure,



Suggested diagnosis and treatment procedure for cardiotoxic treatment (adapted according to [e13]). LVEF: left ventricular ejection fraction

oncological treatment must be adjusted and the use of less cardiotoxic treatment regimens (e.g. liposomal anthracyclines or anthracycline-free regimens) should be discussed. In addition, patients should be treated in line with the general rules for the treatment of systolic heart failure. ACE inhibitors (angiotensin receptor blockers if these are not tolerated) and beta-blockers are the most important pharmacological treatments. The aims are to achieve blood pressure less than 140/90 mm Hg and heart rate less than 70 b.p.m. with an increase to the maximum tolerated dose (e15). One potentially interesting option is the angiotensin receptor blocker telmisartan, which led to reversibility of myocardial dysfunction in a fairly small randomized trial (e16).

The following agents may also be used: aldosterone antagonists, digitalis glycosides, diuretics, and ivabradine (e15–e20).

General treatment measures stated in guidelines include fluid restriction (approx. 1.5 L/day), physical activity, a healthy diet (e.g. restricted salt intake), and others (e14–e18).

Other causes that lead to restricted left ventricular ejection fraction, such as coronary heart disease or myocarditis, must also be considered during differential diagnosis. If necessary, they must be included in the diagnosis procedure (left heart catheterization, cardiac MRI) (e18).

In a pilot study involving 90 patients with leukemia or other blood cell malignancies who received prophylactic treatment consisting of enalapril/carvedilol or placebo, a combined endpoint consisting of deterioration of left ventricular function, cardiac insufficiency, and total mortality at six months was significantly reduced by administering enalapril/carvedilol (6.7% for active treatment versus 22% for placebo) (e17).

Conflict of interest statement

Prof. Schlitt has received consultancy fees (Advisory Board) from Boehringer Ingelheim. He has received lecture fees and reimbursement of conference fees and travel expenses from Sanofi-Aventis, Servier, Boehringer Ingelheim, and Bayer AG. He has also received trial funding (third-party funds) from GSK, Sanofi-Aventis, Mitsubishi, Endotis, Bayer AG, Boehringer Ingelheim, Novartis, Actelion, and BMS.

Prof. Thomssen has received consultancy fees (Advisory Board) from Roche, Pfizer, AstraZeneca, Novartis, Celgene, and Genomic Health. He has received reimbursement of conference fees, travel expenses, and lecture fees from Roche, Pfizer, Novartis, Celgene, and Genomic Health.

Prof. Vordermark has received lecture fees as a speaker from Roche, Bristol-Myers Squibb, Lilly, and Astra Zeneca.

Dr. Jordan has received lecture fees as a speaker from MSD, Amgen, Helsinn, Riemser, and TRM.

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KEY MESSAGES

- In recent years the mortality rates of malignant tumors have been successfully reduced using multimodality therapies.
- Cardiotoxicity as a side effect of chemotherapy agents and targeted drugs (e.g. trastuzumab) can be treatment-limiting.
- With current, modern methods of radiotherapy, the only cases in which radiogenic cardiotoxicity remains an issue are pulmonary and mediastinal tumors.
- The gold standard for the diagnosis of cardiotoxicity is echocardiography. The value of biomarkers is disputed.
- Tailor-made treatment protocols using less cardiotoxic substances (liposomal anthracyclines) reduce the risk. Dexrazoxane (in anthracycline treatment or anthracycline-free regimens only) may be used in patients with advanced or metastatic breast cancer if its risks and benefits are considered thoroughly.
- Cancer drugs may need to be adjusted during treatment. General rules on the treatment of systolic heart failure must be followed.

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REVIEW ARTICLE

Cardiotoxicity and Oncological Treatments

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