The cytotoxic drug cyclo-pentenyl cytosine: from manufacturing to anti-tumor activity and (cardio)toxicity

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CHAPTER 6

CARDIOTOXICITY OF CYTOTOXIC DRUGS

Cancer Treatment Reviews 2004;30:181–191

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ABSTRACT

Cardiotoxicity is a well-known side effect of several cytotoxic drugs, especially of the anthracyclines and can lead to long term morbidity. The mechanism of anthracycline induced cardiotoxicity seems to involve the formation of free radicals leading to oxidative stress. This may cause apoptosis of cardiac cells or immunologic reactions. However, alternative mechanisms may play a role in anthracycline induced cardiotoxicity. Cardiac protection can be achieved by limitation of the cumulative dose. Furthermore, addition of the antioxidant and iron chelator dexrazoxane to anthracycline therapy has shown to be effective in lowering the incidence of anthracycline induced cardiotoxicity. Other cytotoxic drugs such as 5-fluorouracil, cyclophosphamide and the taxoids are associated with cardiotoxicity as well, although little is known about the possible mechanisms. Recently, it appeared that some novel cytotoxic drugs such as trastuzumab and cyclopentenyl cytosine also show cardiotoxic side effects.

Keywords: Cardiotoxicity; cytotoxic drugs; cancer; chemotherapy

INTRODUCTION

Cardiotoxicity occurs during therapy with several cytotoxic drugs and may be the dose limiting factor in cancer treatment and hence tumour response. Furthermore, cardiotoxicity can also be responsible for long term side effects and may cause severe morbidity in surviving cancer patients [1], which may be relevant especially in pediatric oncology. Cardiotoxicity from cytotoxic treatment is known to have a high prevalence [2]. Cardiotoxicity includes a wide range of cardiac effects from small changes in blood pressure and arrhythmias to cardiomyopathy. In literature different mechanisms of chemotherapy induced cardiotoxicity are postulated including cellular damage due to the formation of free oxygen radicals and the induction of immunogenic reactions with the presence of antigen presenting cells in the heart [3]. Moreover, the influence of the cytotoxic agent on certain phospholipids, especially cardiolipin, may also explain the development of cardiotoxicity [4].

The anthracyclines, such as doxorubicin and epirubicin, are potent cytotoxic drugs but their clinical use is often limited by their cardiotoxic side effects. Other cytotoxic drugs that have reported cardiotoxicity include 5-fluorouracil, capecitabine, mitoxantrone, cisplatin, the taxoids paclitaxel and docetaxel and newer drugs such as the monoclonal antibody trastuzumab [5-8].

In this manuscript the different mechanisms of chemotherapy induced cardiotoxicity and attempts to circumvent this side effect are reviewed.

ANTHRACYCLINES

Cardiotoxicity has been extensively reviewed with the use of anthracyclines [2,5,9,10]. Anthracyclines have been reported to cause cardiomyopathy, congestive heart failure and ECG alterations (e.g. nonspecific ST-T changes, decreased QRS voltage and prolongation of QT interval). Both early and late onset cardiac effects are reported. Early onset effects occur within one year after start of the anthracycline therapy and can be acute, subacute or chronically progressive. In children, early onset cardiotoxicity seems to occur less frequently than late onset clinical cardiotoxicity. Late onset effects can occur up to 20 years after completion of anthracycline therapy [11].

Acute toxicity

Acute or subacute cardiotoxicity with anthracyclines is rare and will occur during or immediately following infusion, is usually transient (e.g. electrocardiographic abnormalities such as nonspecific ST-T changes and QT prolongation, pericarditis–myocarditis syndrome and ventricular dysfunction with congestive heartfailure) and will attenuate after discontinuation of the therapy.

Chronic toxicity

The chronic effects start with early cardiac abnormalities which can progress to overt cardiac disease. Chronic effects persist after discontinuation of the anthracyclines and the clinical symptoms may include all signs of cardiomyopathy such as electrophysiologic changes, decrease of left ventricular function, changes in exercise-stress capacity, and overt signs of congestive heart failure [2,5].

Risk factors

Cumulative dose, age, prior irradiation, concomitant administration of other chemotherapeutics and underlying heart disease are considered as being risk factors for anthracycline cardiotoxicity [12]. Of these the cumulative dose seems to be the most important factor. The usual dosage of doxorubicin is 60–75 mg/m^2, every 3 weeks [13]. above a cumulative dose of 450–550 mg/m^2 doxorubicin, cardiomyopathy and congestive heart failure occur most frequently. However, as of individual variation, signs of cardiotoxicity have also been seen with cumulative dosages below 300 mg/m^2 [2,14]. The cumulative probability of doxorubicin induced cardiotoxicity was estimated by Von Hoff at 0.18 at a cumulative dose of 700 mg/m^2, 0.07 at 550 mg/m^2 and 0.03 or less at 400 mg/m^2 [13]. Recently, higher estimations were reported for the elevated cumulative doses, respectively, 0.48 at a cumulative dose of 700 mg/m^2 and 0.26 at 550 mg/m^2. An explanation for this difference can be the difference in determination of congestive heart failure. The risk estimation for the lower dosage (0.05 at 400 mg/m^2) is comparable with Von Hoff's findings [14]. The maximum cumulative dosage needed to obtain minimal cardiotoxicity varies among the different anthracyclines. With epirubicin a lower frequency of cardiotoxicity at therapeutic dosages is reported in comparison with doxorubicin (i.e. an incidence of 0.03 at 900 mg/m^2 epirubicin is reported, the usual dosage is 50–90 mg/m^2, every 3 weeks). A lower frequency of cardiotoxicity has been reported also for mitoxantrone and a new anthracycline (MEN 10755) [15–18].

Previous radiotherapy may enhance anthracycline induced cardiotoxicity. In a study, left sided irradiation in combination with standard adjuvant chemotherapy (doxorubicin at a cumulative dose of 300 mg/m^2) gave 2.6% of cardiac heart failure versus 0.3% for right-sided or no irradiation [19].

Monitoring and markers of cardiotoxicity

Routine cardiac imaging studies (echocardiogram or multiple gated acquisition scans) can be used to identify (sub)clinical myocardial dysfunction. Endomyocardial biopsy directly measures the presence and extent of fibrosis due to anthracycline cardiotoxicity. However, it is limited by its invasiveness, need for histologic expertise and costs. There is a need for simple methods (like serum or plasma markers) to identify patients at risk.

The cardiac biomarker Troponin T is indicative for myocardiocyte damage and is currently used in the diagnosis and prognosis of myocardial ischemia. In children treated with anthracyclines elevation of Troponin T was found. These elevations were, however, well below those observed in patients with myocardial infarction [20].

Studies in adults have given conflicting results regarding Troponin T elevations. In one study no change in Troponin T could be found, whereas in another an elevated level was associated with a greater decrease in left ventricular ejection fraction (10% vs 2%, p=0.017) [21]. Another possible biochemical marker is BNP (b-natriuretic peptide). ANP (atrial natriuretic peptide) and BNP are hormones that are secreted by the myocytes of the heart. The plasma concentrations are increased in patients with asymptomatic and symptomatic left ventricular dysfunction. BNP seems to be a more sensitive marker of cardiac dysfunction than ANP. A few small studies concerning the relationship between anthracyclines, BNP and cardiotoxicity have been published. BNP measurement in 27 patients, treated with anthracyclines for hematological cancers, showed significant BNP elevations after anthracycline treatment. Due to a short follow-up and the small size of the group this, however, could not be related to existing cardiotoxicity [22]. Another study in 30 patients suggested that the natriuretic peptides cannot predict cardiotoxicity, but can be useful in the detection of subclinical left ventricular dysfunction [23]. Further studies are needed to define the role of circulating markers such as Troponin T and BNP as parameters of chemotherapy induced cardiotoxicity.

Mechanisms

OXIDATIVE STRESS HYPOTHESIS

The most common hypothesis for the mechanism by which anthracyclines cause cardiotoxicity includes the formation of free radicals and superoxides [15;24–26]. this hypothesis is based mainly on in vitro experiments and only a few studies have been performed in humans. Several in vitro and in vivo models have been used to study the cardiotoxic effects of anthracyclines assessing a variety of endpoints. With the free radical theory the reaction starts with a one-electron reduction of doxorubicin to form a doxorubicin semiquinone radical by a reduced flavoenzyme such as NADPH-cytochrome P450 reductase. The semiquinon radical forms a complex with iron leading to an anthracycline-iron ($Fe2^{+}$) free radical complex. This complex reduces oxygen to produce superoxide and to regenerate doxorubicin. The superoxide is dismutated into hydrogen peroxide and oxygen (fig. 1). Vasquez *et al* have shown that doxorubicin binds to the reductase domain of endothelial nitric oxide synthase. This causes an increase in superoxide and a decrease in nitric oxide formation. The consequent formation of peroxynitrite could also play a role in the cardiotoxicity [25].

From the combination of superoxide, hydrogen peroxide and free iron, lipid peroxidation may be initiated.

The specific susceptibility of the cardiac cells to the oxidative stress would be due to relatively low levels of antioxidant enzymes in the heart [27]. Indeed studies in rat hearts suggest that doxorubicin is able to cause a further reduction in the a priori low levels of the antioxidant enzymes in rat hearts [28].

Following the oxidative stress theory, cardiotoxicity can be achieved by different mechanisms. Studies indicate that the myocardial damage caused by doxorubicin involves apoptosis. This programmed cell death process would be initiated by the formation of oxidative free radicals. Apoptotic cell death was indeed found in rat cardiomyocytes and bovine aortic endothelial cells upon exposure to doxorubicin [3,29].

Sawyer *et al* [30] also showed apoptosis at low concentrations (1 μM) of daunorubicin, whereas at higher concentrations (>10 μM) necrosis was observed. This is in agreement with the observation of Guchelaar *et al* [31] who reported that in cell lines for a variety of apoptosis-inducing anticancer drugs a relatively increase of induction of necrosis was observed at high drug concentrations whereas at lower concentrations apoptosis dominates.

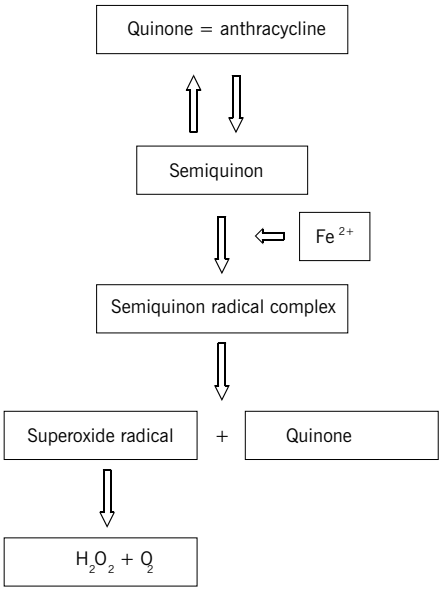

Figure 1

METABOLITE THEORY

Minotti *et al* suggest that cancer patients often have a spontaneous exacerbation of lipid peroxidation and doxorubicin probably inhibits this effect in a paradoxic manner. It is suggested that lipid peroxidation occurs when iron oxidizes incompletely to the ferric form. Doxorubicin and the formed hydrogen peroxide would inhibit cardiac lipid peroxidation by affecting the Fe(II)–Fe(III) equilibrium of iron–oxygen complexes. This would mean that cardiac damage might involve parent doxorubicin or its metabolites other than the semiquinon. This hypothesis is strenghtened by results of a study in which the formation of the metabolite doxorubicinol was demonstrated. This metabolite mediates iron release and negatively affects the function of apoprotein as an iron regulatory protein [32,33].

INFLUENCE ON CALCIUM HOMEOSTASIS

Another possible mechanism involves the influence of anthracyclines on the calcium homeostasis. Before leading to apoptosis, oxidative stress can induce mitochondrial permeability transition with alterations in mitochondrial calcium transport. Changes in calcium transport can lead to tissue injury and cell killing and impaired cardiac contraction. In vitro experiments showed that doxorubicin treatment caused an irreversible decrease in mitochondrial calcium loading capacity [34].

Moreover, anthracyclines could stimulate the release of calcium from isolated cardiac and skeletal muscle sarcoplasmic reticulum vesicles [35]. This theory is strengthened by the observation of Rossi et al. who found a protective effect of the calcium blocking agent verapamil on doxorubicin induced cardiotoxicity in rats. This effect would be due to the calcium blocking capacities of verapamil by inhibiting the intracellular calcium overload and hence antagonizing the effect of doxorubicin on mitochondria [24]. However, others have demonstrated an increase in cardiotoxicity when doxorubicin was given in combination with verapamil and different mechanisms for this effect are postulated. One is based on the capacity of verapamil to inhibit the function of P-glycoprotein and therefore may increase intracellular cytotoxic drug concentrations. This may be useful in overcoming resistance to chemotherapeutic drugs in cancer cells, but the concern is that it could also lead to toxic effects in normal such as cardiac cells. Some in vitro studies indeed showed increased doxorubicin accumulation in rat cardiomyocytes when incubated with a combination of verapamil and doxorubicin [36,37]. Akimoto *et al* [38,39] did not show an increased cellular anthracycline uptake but additive cardiotoxicity by verapamil due to its selective inhibition of cardiac actin gene expression, a similar effect which was demonstrated before with doxorubicin alone. The exact role of the altering capacities of doxorubicin on calcium regulation and its implications for cardiotoxicity remains to be elucidated.

ROLE OF IMMUNE SYSTEM

Involvement of an immunogenic reaction after oxidative stress is an alternative mechanism of anthracycline induced cardiotoxicity. Huber [40] suggested that doxorubicin could lead to a damaged plasma membrane of cardiac myocytes with consequently an enhanced immune response. A study in hypertensive rats showed an increase in antigen presenting dendritic cells after treatment with doxorubicin, indicating a stimulation of expression of antigens. Pretreatment with dexrazoxane attenuated this increase, confirming the suggestion of the involvement of oxidative stress, followed by an immunogenic reaction [41].

Protection

Apart from cumulative dose limitations several attempts have been made to develop chemoprotectants to prevent the cardiotoxicity of anthracyclines without attenuating their anti-tumor effect. Following the free radical hypothesis, antioxidants used as free radical scavengers have been tested in clinical trials but without significant success. Human studies with the scavengers acetylcysteine or tocopherol did not show any cardioprotective effect [42,43]. In one clinical study, administration of melatonin together with different chemotherapeutic regimens was associated with reduced overall toxicity including cardiotoxicity. This effect was thought to be ascribed to its antioxidant capacities [44].

DEXRAZOXANE

Considering the essential role of iron and the doxorubiciniron complex, iron chelators have been developed to circumvent anthracycline induced cardiotoxicity. These agents bind to intracellular iron and remove the iron from the anthracycline–iron complex and are applied aimed at preventing free radical formation [45].

Dexrazoxane (ICRF-187) was found to be the most promising agent. After being tested in animals [46], several clinical trials showed its capacities in reducing doxorubicin induced cardiotoxicity. In two multicenter double blind randomized phase III trials 15% of the patients treated with dexrazoxane experienced a cardiac side effect versus 31% of the patients on placebo (hazard ratio 2.63, $p < 0.001$ with log rank) [47]. Another trial reported 4% in treated versus 24% in nontreated patients ($p = 0.02$) [48]. Reported differences in cardiac side effects may be explained by the different criteria applied for cardiac events and different dosage schedules of doxorubicin. Complete protection, however, could not be achieved in most of the studies [47,48]. Moreover, it is not known if dexrazoxane provides any protection against late cardiovascular effects [49].

In a study in children treated with doxorubicin (38 patients, 18 control and 20 treated with dexrazoxane) a cardioprotective effect of dexrazoxane was found [50]. However, because of the

small number of clinical trials yet performed in pediatric populations there is too little evidence to draw definite conclusions. Indeed the American Society of Clinical Oncology concluded that there is insufficient evidence to recommend the use of dexrazoxane in the treatment of pediatric malignancies [51]. The FDA has approved dexrazoxane for use in adults if cumulative doses of doxorubicin exceed 300 mg/m^2 [5]. Doxorubicin pharmacokinetics seems to be unaffected upon dexrazoxane treatment [52]. A pharmacokinetic study with epirubicin revealed an increased clearance of the anthracycline when dexrazoxane had been administered which theoretically could lead to a decreased epirubicin exposure and hence a possible difference in treatment efficacy of the combined treatment [53]. In a randomized clinical trial however, no statistically significant differences in survival and progression-free survival could be demonstrated between the dexrazoxane and placebo group [54].

Dexrazoxane can be administered intravenously either as a slow injection or fast infusion before doxorubicin is initiated. The dosage to be given is usually a 10-fold of the doxorubicin dose and its dose limiting toxicity appears to be leukopenia [10].

MONOHER

Another radical scavenger that has been studied is the flavonoid monoher. Monoher is able to protect the heart against doxorubicin toxicity without affecting its anti-tumor effect in a mouse model. However, because of its low potency the effective dosage needed in humans would be too high (500 mg/kg in mice) to make it a useful drug. Recently, a derivate of monoher, called frederine was developed which could provide total heart protection in mice with a 5-fold lower dosage as compared to monoher. Clinical trials with this drug will be undertaken [55].

LIPID LOWERING AGENTS

Lipid lowering agents also seem to be able to lower the cardiotoxic effects of anthracyclines [56]. When rats were concomitantly treated with doxorubicin and the lipid lowering and antioxidant agent probucol, an increase in the antioxidant enzymes superoxide dismutase and glutathione peroxidase activities and a decrease in lipid peroxidation were found. According to the oxidative stress theory this improvement of antioxidant state of the heart could possibly lead to a better myocardial structure and function [28,57]. Recently, Feleszko *et al* [58] showed both a potentiation of anti-tumor activity and a cardioprotective effect by the cholesterol lowering HMG coenzyme-A re- ductase inhibitor lovastatin, in mice treated with doxorubicin.

CHANGES IN FORMULATION

Another strategy to achieve reduced cardiotoxicity is the development of liposomal drug formulations of the anthracyclines. Liposomes are preferentially taken up by tissues enriched in phagocytic reticuloendothelial cells and with a sinusoidal capillary system like the liver and spleen.

The continuous capillaries containing tissues like skeletal and cardiac muscles will therefore hardly take up liposomes. Preclinical studies have indeed shown a decreased uptake of doxorubicin in cardiac muscle cells when a liposomal formulation was used. The constituents of the liposomes itself do not seem to have a negative influence on the heart or other tissues. However, there may exist important differences among different liposomal formulations since changes in vesicle size, drug-to- lipid ratio and lipid composition can have great influence on the biodistribution and toxicity of doxorubicin [59,60].

In a retrospective analysis of eight clinical Phase I and phase II trials the safety of more than 500 mg/m^2 pegylated liposomal doxorubicin was studied. The study was performed with a median follow-up of 2.7 years (range 1.2–6.0 years) after the initiation of treatment. None of the evaluable 41 patients experienced clinical congestive heart failure secondary to cardiomyopathy. The left ventricular ejection fraction (LVEF) was reduced with more than 10% in five patients; however, three of these had received conventional doxorubicin before treatment with liposomal doxorubicin. The mean change in LVEF was -2%, which was not considered clinically significant. This study suggests that doxorubicin induced cardiotoxicity can be reduced upon using liposomal formulations of the drug [61].

TAXOIDS

The taxoids paclitaxel and docetaxel are important agents in the treatment of a variety of tumors but have been associated with cardiotoxicity [31]. During administration of paclitaxel, whether or not combined with cisplatin, various cardiac disturbances are reported like brady- and tachyarrhythmias, atrioventricular and bundle branch blocks and cardiac ischemia. Hypotension is also reported, probably as a result of a hypersensitivity reaction [62]. When evaluating three phase I and one phase II studies performed at the John Hopkins institute it appeared that 5% (n = 7) of the patients showed overt cardiac disturbances as ventricular tachycardia and atrioventricular conduction abnormalities. Asymptomatic bradycardia occurred in 29% of patients receiving maximal tolerable doses (110–250 mg/m^2) of paclitaxel in the phase II study. These disturbances, however, did not lead to clinical symptoms. The abnormalities usually started several hours following the initiation of paclitaxel therapy and resolved after discontinuation. This evident time relationship and the fact that most patients had no cardiac risk factors supports the assumption of causality between paclitaxel and the observed cardiac rhythm disturbances [62].

Another concern with the use of taxoids has been the development of congestive heart failure in patients treated with a combination of doxorubicin and taxoids [63–65]. the cardiotoxicity associated with taxoids seems to be mild in most cases. However, in clinical trials patients with prior history of cardiac disturbances were often excluded. Therefore, the rate of cardiotoxicity in

this group of patients is yet difficult to estimate. A study in patients with major cardiac risk factors revealed that paclitaxel could be safely administered as single therapy or in combination with a platinum agent such as cisplatin or carboplatin. Cardiac risk factors included unstable angina, severe coronary artery disease, congestive heart failure and atrial fibrillation [66].

Mechanism

Paclitaxel is formulated in a cremophor EL vehicle to enhance the drug solubility and it is suggested that the vehicle and not the cytotoxic drug itself is responsible for the cardiac disturbances. However, the cardiac rhythm disturbances are not reported with use of other drugs containing cremophor EL such as cyclosporin. The possible mechanism by which cremophor EL would cause cardiotoxicity is massive histamine release. Indeed, stimulation of histamine receptors in cardiac tissue in animal studies has resulted in conduction disturbances and arrhythmias. An alternative explanation for paclitaxel induced cardiotoxicity could be the induction of cardiac muscle damage by affecting subcellular organelles [62,67,68].

Enhanced cardiac toxicity has been found in combined therapy of paclitaxel and doxorubicin. At doses of doxorubicin exceeding 380 mg/m^2, the toxicity increased in combination therapy compared to doxorubicin single therapy. A pharmacokinetic interaction appears to be responsible for this effect as paclitaxel has been found to decrease doxorubicin hepatic elimination and therefore lead to increased plasma concentrations of doxorubicin. This effect depends on the interval and sequence of drug administration as well as the duration of the paclitaxel infusion [69]. A similar effect has been shown for epirubicin. The pharmacokinetics of the active metabolite epirubicinol are changed leading to increased plasma concentrations, whereas epirubicin pharmacokinetics remain unchanged [70]. In a clinical trial, combination therapy with epirubicin doses up to 720 mg/m^2 was associated with a relatively low cumulative risk (7.7%) of congestive heart failure but increased (to 48.7%) at a cumulative dose of 1080 mg/m^2. The study included a group patients with at least one cardiac risk factor and a group without cardiac risk factors (10% and 12% cumulative risk for cardiac heart failure, respectively, at epirubicin doses up to 990 mg/m^2). Cardiac risk factors included were age, hypertension, diabetes and prior radiotherapy to the chest wall [6].

Docetaxel shows no increase in cardiac toxicity when combined with doxorubicin. This is in line with the observation that a pharmacokinetic interaction with doxorubicin as described for paclitaxel has not been observed [71].

Protection

In combination therapy with anthracyclines, the cumulative dose of the anthracycline remains an important risk factor and should be lower as compared to anthracyclines monotherapy. In combination therapy cumulative doxorubicin doses up to 340–380 mg/m^2 are reported to be safe whereas in monotherapy cumulative doses up to 450–550 mg/m^2 can be safely administrated [72,73] As in mono-therapy, epirubicin is associated with less cardiotoxicity compared to doxorubicin in combination therapy with paclitaxel [74]. Sequential administration of doxorubicin and paclitaxel does not seem to increase the risk of cardiotoxicity as compared to doxorubicin alone [72]. However, as shown by Gianni *et al* [69] this seems to depend on interval and sequence.

Taxoid associated cardiotoxicity is limited and therefore no specific agents are developed specifically for taxoid induced cardiotoxicity. The mechanism and clinical relevance of the cardiac rhythm disturbances as observed with paclitaxel therapy is not yet elucidated making it difficult to foresee if and what kind of protection would be rational and successful.

5-FLUOROURACIL

The antimetabolite 5-fluorouracil (5-FU) is associated with myelosuppression, diarrhoea, mucositis and dermatitis. Cardiotoxicity may also occur and estimates of the incidence vary from 1% to 5% to as much as 18% [5,75,76]. Cardiotoxicity with 5-FU is usually described with continuous infusion and less upon bolus injection. Recently, a case report was published reporting acute cardiotoxicity during capecitabine treatment. Capecitabine is an orally administrated 5-FU prodrug and can deliver 5-FU selectively to the tumour although toxicities are reported similar to infused 5-FU [77].

Symptoms of 5-FU cardiotoxicity include cardiac arrhythmias, silent myocardial ischemia, angina, congestive heart failure and even sudden death [7,8,78,79].

Risk factors include preexisting coronary artery disease and concurrent radiotherapy. Measurements to protect against 5-FU induced cardiotoxicity are not available yet, although symptoms (chest pain, nausea, diaphoresis with ECG changes) often disappear upon discontinuation of the infusion [76]. Fatal events, however, have been described. After having experienced cardiac side effects, patients are at increased risk to have a relapse if they are reexposed to 5-FU [75].

Mechanism

Several risk factors seem to be involved in 5-FU related cardiotoxicity like age, high dose chemotherapy, continuous 5-FU infusion and past or concomitant radiation therapy [7].

The pathophysiological mechanism of 5-FU related cardiotoxicity is still unclear and suggested mechanisms cannot be explained by the pharmacological action of 5-FU. Hypotheses postulated are vasospasms leading to ischemia, direct toxicity on the myocardium, activation of coagulation system, coronary artery thrombosis, immunoallergic phenomena and cardiotoxic impurities in the 5-FU formulation [75,76,80,81]. A small study in 11 men treated with 5-FU unexpectedly showed a decrease in blood viscosity instead of an increase. The number of patients, however, was too small to conclude that thrombogenecity is involved in 5-FU cardiotoxicity [8]. Kohne *et al* report two patients with 5-FU cardiotoxicity who were treated successfully with the thymidylate synthase inhibitor raltitrexed without evidence of cardiotoxicity. The authors suggest that as 5-FU also targets thymidilate synthase, its cardiotoxicity is not likely due to its interaction with this enzyme [82].

CYCLOPHOSPHAMIDE AND IFOSFAMIDE

Cyclophosphamide and ifosfamide are alkylating oxazaphosphorine agents that need to be metabolized in vivo in the liver to form the active cytotoxic agent phosphoramide mustard. High dose cyclophosphamide is used in transplant regimens and is associated with acute cardiotoxicity such as cardiac decompensation as well as fatal cardiomyopathy. Acute reversible decrease in systolic function has been described [10,83]. The incidence has been estimated to range from 2% to 10% [5]. Ifosfamide cardiotoxicity is reported in only a single study [84].

Mechanism

The pathogenesis is not fully understood but an increase in free oxygen radicals seems to play a role in oxazaphosphorine induced cardiotoxicity. This increase would be mediated by elevated intracellular levels of the actual cytotoxic metabolite phosphoramide mustard [5].

CISPLATIN

Cisplatin is a platinum substance and used in the treatment of many tumors (i.e. testicular cancer). Several cases of acute myocardial infarction after cisplatin therapy are reported [85,86].

In a retrospective study 87 long term survivors of metastatic testicular cancer treated with cisplatin were evaluated for the occurrence of cardiovascular events. A significantly increase in cardiac events as well as an unfavorable cardiovascular risk profile were observed [87].

Mechanism

Several factors have been suggested to be involved like vascular damage, alterations in platelet aggregation and hypomagnesemia [85,86,88,89]. In experiments on human platelets cisplatin was able to trigger platelet aggregation and/or enhance thromboxane formation by platelets. Activation of an arachidonic pathway in platelets by cisplatin seemed to be involved [89].

TRASTUZUMAB

Trastuzumab is a monoclonal antibody directed against the HER2 receptor protein on breast cancer cells and it has been used alone or in combination with other chemotherapeutic agents. Cardiac toxicity associated with trastuzumab seems to be similar with the congestive heart failure observed with anthracycline therapy. Evaluation of data of 1024 patients who received trastuzumab revealed that combination therapy of trastuzumab with an anthracycline and cyclophosphamide showed 28% of reported cardiac dysfunction against 3–5% with doxorubicin monotherapy (cumulative dosage 400 mg/m^2). Concomitant anthracycline therapy and age appeared to be independent risk factors [90]. When receiving trastuzumab as single therapy in an open label study, 7% of the women developed heart failure [91].

OTHER AGENTS

Cardiotoxicity has been associated incidentically with several other cytotoxic drugs such as cisplatin, melphalan, fludarabin, mitomycin, busulfan, mechlorethamine and dacarbazine. However, the lack of structured data on cardiotoxic side effects of these drugs from clinical studies makes it difficult to assess its importance and evidence.

CONCLUSION

Chemotherapy with certain cytotoxic drugs is associated with severe side effects such as cardiotoxicity. As these side effects can be dose limiting and cause severe morbidity and even mortality. Knowledge about their incidence and mechanism is important.

Cardiotoxicity can occur as acute or as long term side effect. With increasing survival rates interest is also focussed on avoiding the late onset and chronically effects.

Anthracyclines are well known for their cardiotoxic side effects and comprehensive research is done to explore the mechanism of anthracycline induced cardiotoxicity. Until now the most accepted hypothesis is the so-called 'free radical' theory. However, protective measurements following this theory such as administration of free radical scavengers have not appeared to be clinically successful. The antioxidant and iron chelator dexrazoxane has been successfully applied to protect the heart from cardiotoxicity with high dose anthracycline therapy, although complete abolishment of cardiotoxicity cannot not be achieved.

Other cytotoxic drugs like 5-fluorouracil, cisplatin and cyclophosphamide are also associated with cardiotoxicity, but yet little is known about the possible mechanisms and methods of prevention. Paclitaxel enhances the cardiotoxic effects of anthracyclines by inhibiting the latters metabolism and therefore leading to increased anthracycline exposure.

Unfortunately, cardiotoxicity is also associated with newer drugs like trastuzumab and cyclopentenyl cytosine and may hamper the development of potential successful anticancer drugs [92]. Further research is warranted to understand the mechanism of chemotherapy induced cardiotoxicity and to develop strategies to circumvent this side effect.

REFERENCES

1. Meinardi MT, Gietema JA, Veldhuisen DJ van, Graaf WT van der, Vries EGE, Sleijer DT. Long-term chemotherapy-related cardiovascular morbidity. Cancer Treat Rev 2000;26:429-447.
2. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol 1998;25(Suppl 10):72-85.
3. Arola OJ, Saraste A, Pulkki K, Kallajoki M, Parvinen M, Voipio-Pulkki L. Acute doxorubicin cardiotoxicity involves cardiomyocite apoptosis. Cancer Res 2000;60:1789-1792.
4. Hatch GM, McLarty G. Regulation of cardiolipin biosynthesis in H9C2 cardiac myoblasts by Cytidine 5-triphosphate. J Biol Chem 1996;271:25810-25816.
5. Lipp. Cardiotoxicity of cytotoxic drugs. Anticancer drug toxicity. Prevention, management and clinical pharmacokinetics. New York: Marcel Dekker; 1999. p. 471-488.
6. Gennari A, Salvadori B, Donati S, Bengala C, Orlandini C, Danesi R, Del Tacca M, Bruzzi P, Conte PF. Cardiotoxicity of epirubicin/paclitaxel-Containing regimens: role of cardiac risk factors. J Clin Oncol 1999;17:3596-3602.
7. Lieutaud T, Brain E, Golgran-Toledano, Vincent F, Cvitkovic E, LeClercq B, Escudier B. 5-Fluorouracil cardiotoxicity: a unique mechanism for ischaemic Cardiopathy and cardiac failure? Eur J Canc 1996;32a:368-369.
8. Cwikiel M, Persson SU, Larsson H, Albertsson M, Eskilsson J.Changes of blood viscosity in patients treated with 5-fluorouracil. A link to cardiotoxicity? Acta Oncol 1995;34:83-85.
9. Wojtacki J, Lewicka-Nowack E, Lesniewski-Kmak K. Anthracycline-induced cardiotoxicity: clinical course, risk factors, pathogenesis, detection and prevention - review of the Literature. Med Sci Monit 2000;6:411-420.
10. Hochster H, Wasserheit C, Speyer J. Cardiotoxicity and cardioprotection during chemotherapy. Curr Opin Oncol 1995;7:304-309.
11. Steinhertz LJ, Steinherz PG, Tan CTC, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after competing anthracycline therapy. JAMA 1991;266:1672-1677.
12. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents. Incidence, treatment and prevention. Drug Safety 2000;22(4):263-302.
13. Von Hoff DD, Layard MW, Basa P, Davis HJ Jr, Von Hoff AL, Rozensweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710-717.
14. Swain M, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. Cancer 2003;97:2869-2879.
15. Alderton PM, Gross J, Green MD. Comparative study of doxorubicin, mitoxantrone and epirubicin in combination with ICRF-187 (ADR-529) in a chronic cardiotoxicity animal model. Canc Res 1992;52:194-201

.16. Launchbury AP, Habboubi N. Epirubicin and dxorubicin: a comparison of their characteristics, therapeutic activity and toxicity. Cancer Treatment Rev 1993; 19:197-228.

17. Coukell A, Faulds D. Epirubicin - a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the management of breast cancer. Drugs 1997;53:453-482.

18. Cirillo R, Sacco G, Venturella S, Brightwell J, Giachetti A, Manzini S. Comparison of doxorubicin- and MEN 10755- induced long-term progressive cardiotoxicity in the rat. J Cardiovasc Pharmacol 2000;35:100-108.

19. Graaf H, de Dolsma WV, Willemse PHB, van der Graaf WT, Sleijfer DT, de Vries EG, Mulder NH. Cardiotoxicity from intensive chemotherapy combined with radiotherapy in breast cancer. Br J Canc 1997;76:943-945.

20. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, Ottlinger ME. Predictive value of cardiac troponin-T in pediatric patients at risk for myocardial injury. Circulation 1997;96:2641-2648.

21. Sparano JA, Brown DL, Wolff AC. Predicting cancer therapy-induced cardiotoxicity. The role of troponins and other markers. Drug Safety 2002;25:301-311.

22. Suzuki T, Hayashi D, Yamazaki T, Mizuno T, Kanda Y, Komuro I, Kurabayashi M, Yamaoki K, Mitani K, Hirai H, Nagai R, Yazaki Y. Elevated B-type natriuretic peptide levels after anthracycline administration. Am Heart J 1998;136:362-363.

23. Nousiainen T, Jantunen E, Vanninen E, Remes J, Vuolteenaho O, Hartikainen J. Natriuretic peptides as markers of cardiotoxicity during doxorubicin treatment for non-Hodgkin's Lymphoma. Eur J Haematol 1999;62:135-141.

24. Rossi F, Fillippelli W, Russo S, Fillippelli A, Berrino L. Cardiotoxicity of doxorubicin: effects of drugs inhibiting the release of vasoactive substances. Pharm Tox 1994;75:99-107.

25. Vasquez-Vivar J, Martasek P, Hogg N, Masters BS, Pritchard KA Jr, Kalyanaraman B. Endothelial nitric oxide synthase-dependent superoxide generation from adriamycin. Biochem 1997;36:11293-11297.

26. Rajagopalan S, Politi PM, Sinha BK, Myers CE. Adriamycin-induced free radical formation in the perfused rat heart: implications for cardiotoxicity. Cancer Res 1988;48:4766-4769.

27. Doroshow JH, Locker GY, Myers CE. Enzymatic defenses of the mouse heart against reactive oxygen metabolites. J Clin Invest 1980;65:128-135.

28. Li T, Singal PK. Adriamycin induced early changes in myocardial antioxidant enzymes and their modulation by probucol. Circulation 2000;102:2105-2110.

29. Kotamraju S, Konorev EA, Joseph J, Kalylanaraman. Doxorubicin-induced apoptosis in endothelial cells and cardiomyocytes is ameliorated by nitrone spin traps and ebselen. J Biol Chem 2000;43:33585-33592.

30. Sawyer DB, Fukazawa R, Arstall MA, Kelly RA. Daunorubicin-induced apoptosis in rat cardiac myocytes is inhibited by dexrazoxane. Circ Res 1999;84:257-265.

31. Guchelaar HJ, Vermes I, Koopmans RP, Reutelingperger CH. Apoptosis- and necrosis-inducing potential of cladribine, cytarabine, cisplatin, and 5-fluororuacil in vitro: a quantitative pharmacodynamic model. Cancer Chemother Pharmacol 1998;42:77-83.

32. Minotti G, Mancusco C, Frustaci A, Mordente A, Santini SA, Calafiore AM, Liberi G, Gentiloni N. Paradoxical inhibition of cardiac lipid peroxidation in cancer patients treated with doxorubicin. J Clin Invest 1996;98:650-661.

33. Minotti G, Recalcati S, Mordente A, Liberi G, Calafior AM, Mancuso C, Preziosi P, Cairo G. The secondary alcohol metabolite of doxorubicin irreversibly inactivates aconitase/iron regulatory protein-1 in cytosolic fractions from human myocardium. FASEB J 1998;12:541-552.

34. Zhou S, Starkov A, Frober MK, Leino RL, Wallace KB. Cumulative and irreversible cardiac mitochondrial dysfunction induced by doxorubicin. Cancer Res 2001;61:771-777.

35. Shadle SE, Bammel BP, Cusack BJ, Knighton RA, Olson SJ, Mushlin PS, Olson RD. Daunorubicin cardiotoxicity. Biochem Pharm 2000;60:1435-1444.

36. Lampidis TJ, Krishan A, Planas L, Tapiero H. Reversal of intrinsic resistance to Adriamycin in normal cells by verapamil. Cancer Drug Delivery 1986;3:251-259.

37. Santostasi G, Kutty RK, Krishna G. Increased toxicity of anthracycline antibiotics induced by calcium entry blockers in cultured cardiomyocytes. Toxicol Appl Pharmacol 1991;108:140-149.

38. Akimoto H, Bruno NA, Slate DL, Billingham ME, Torti SV, Torti FM. Effect of verapamil on doxorubicin cardiotoxicity: altered muscle gene expression in cultured neonatal rat cardiomyocytes. Canc Res 1993;53:4658-4664.

39. Ito H, Shimojo T, Fujisaki H, Tarnamori M, Ishiyama S, Adachi S, Abe S, Marumo F, Hiroe M. Thermal preconditioning protects rat cardiac muscle cells from doxorubicin induced apoptosis. Life Sci 1999;64:755-761.

40. Huber SA. Doxorubicin-induced alterations incultured myocardial cells stimulate cytolytic T-Lymphocyte responses. Am J Pathol 1990;137:449-456.

41. Zhang J, Herman EH, Ferrans VJ. Dendritic cells in the hearts of spontaneously hypertensive rats treated with doxorubicin with or without ICRF-187. Am J Pathol 1993;142:1916-1926.

42. Dorr R. Chemoprotectants for cancer chemotherapy. Semin Oncol 1991;18:48-58.

43. Myers CE, Bonow R, Palmeri S, Jenkins J, Corden B, Locker G, Doroshow J, Epstein S. A randomised controlled trial assessing the prevention of doxorubicin cardiomyopathy by N-acetylcysteine. Semin Oncol 1983;10(Suppl 1):53-55.

44. Lissoni P, Barni S, Mandala M, Ardizzoia A, Paolorossi F, Vaghi M, Longarini R, Malugani F, Tancini G. Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. Eur J Canc 1999;35:1688-1692.

45. Links M, Lewis C. Chemoprotectants. A review of their clinical pharmacology and therapeutic efficacy. Drugs 1999;57:293-308.

46. Herman EH, Ferrans VJ. Reduction of chronic doxorubicin cardiotoxicity in dogs by pretreatment with (±1,2-bis(3,5- dioxopiperazinyl-1-yl)propane (ICRF-187). Canc Res 1981;41:3436-3440.

47. Swain WM, Whaley FS, Gerber MC, Ewer MS, Bianchine JR, Gams RA. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997;15:1318-1332.

48. Speyer JL, Green MD, Kramer E, Rey M, Sanger J, Ward C, Dubin N, Ferrans V, Stecy P, Zeleniuch-Jacquotte A et al. Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. N Engl J Med 1988;319:745-752.

49. Wiseman LR, Spencer CM. Dexrazoxane. A review of its use as a cardioprotective agent in patients receiving anthracycline-based chemotherapy. Drugs 1998;56:385-403.

50. Wexler LH, Andrich MP, Venzon D, Bery SL, Weaver-McClure L, Chen CC, Dilsizian V, Avila N, Jarosinki P, Balis FM, Poplack DG, Horowith ME. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 1996;14:362-372.

51. Hensley ML, Schuchter LM, Lindley C, Meropol NJ, Cohen GI, Broder G, Gradishar WJ, Green DM, Langdon RJ Jr, Mitchell RB, Negrin R, Szatrowski TP, Thipen JT, Von Hoff DD, Wasserman TH Winer EP, Pfister DG. American Society of clinical oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. J Clin Oncol 1999;17:3333-3355.

52. Hochster H, Liebes L, Wadler S, Oratz R, Werntz JC, Meyers M, Green M, Blum NH, Speyer JL. Pharmacokinetics of the cardioprotector ADR-529 (ICRF-187) in escalating doses combined with fixed dose doxorubicin. J Natl Cancer Inst 1992;84:1725-1730.

53. Basser RL, Sobol MM, Duggan G, Cebon J, Rosenthal MA Mihaly G, Green MD. Comparative study of the pharmacokinetics and toxicity of high-dose epirubicin with or without dexrazoxane in patients with advanced malignancy. J Clin Oncol 1994;12:1659-1666.

54. Venturini M, Michelotti A, Del Mastro L, Gallo L, Carnino F, Garrone O, Tibaldi C, Molea N, Bellina RC, Pronzato P, Cyrus P, Vinke J, Testore F, Guelfi M, Lionettio R, Bruzzi P, Conte PF, Rosso R. Multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer. J Clin Oncol 1996;14:3112-3120.

55. Acker FAA, Boven E, Kramer K, Haenen GRMM, Bast A, Vijgh WJF. Frederine, a new and promising protector against doxorubicin-induced cardiotoxicity. Clin Cancer Res 2001;7:1378-1384.

56. Iliskovic N, SingaL PK. Lipid lowering: an important factor in preventing adriamycin-induced heart faiLure. Am J Pathol 1997;150:727-734.

57. Siveski-Iliskovic, Hill M, Chow DA, Singal PK. Probucol protects against adriamycin cardiomyopathy without interfering with its anti-tumor effect. Circulation 1995;91:10-15.

58. Feleszko W, Mlynarczuk I, Balkowiec-Iskra EZ, Czajka A, Switaj T, Stoklosa T, Giermasz A, Jakobisiak M. Lovastatin potentiates antitumour activity and attenuates cardiotoxicity of doxorubicin in three tumour models in mice. Clin Cancer Res 2000;6:2044-2052.

59. Gabizon A, Dagan A, Goren D, Barenholz, Fuks Z. Liposomes as in vivo carriers of adriamycin: reduced cardiac uptake and preserved antitumor activity. Cancer Res 1992;42:4734-4739.

60. Mayer LD, Tai LCL, Ko DS, Masin D, Ginsberg RS, Cullis PR, Bally MD. Influence of vesicle size, Lipid composition, and drug-to-lipid ratio on the biological activity of liposomal doxorubicin in mice. Cancer Res 1989;49:5922-5930.

61. Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2 . Ann Oncol 2000;11:1029-1033.

62. Rowinsky EK, McGuire WP, Guarieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of paclitaxeL. J Clin Oncol 1991;9:1704-1712.

63. Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, Spreafico C, Laffranchi A, Caraceni A, Martini C et al. Paclitaxel by 3-h infusion in combination with bolus doxorubicin in women with untreated metastic breast cancer: high antitumour efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995;13:2688-2699.

64. Khayat D, Antoine E. Docetaxel in combination chemotherapy for metastatic breast cancer. Semin Oncol 1997;24(Suppl 13):S13-19-26.

65. Eisenhauer EA, Vermorken JB. The taxoids. Comparative clinical pharmacology and therapeutic potential. Drugs 1998;55:5-30.

66. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Paclitaxel administration to gynecologic cancer patients with major cardiac risk factors. J Clin Oncol 1998;16:3483-3485.

67. Bristow MR, Sageman WS, Scott RH, Billingham ME, Bowden RE, Kernoff RS, Snidow GH, Daniels JR. Acute and chronic cardiovascular effects of doxorubicin in the dog: the cardiovascular pharmacology of drug-induced histamine release. J Cardiovasc Pharmacol 1980;2:487-515.

68. Milward LK, Cosson EJ, Stokes KH, et al. Cremophor EL changes the pharmacokinetics of doxorubicin. Proc Am Assoc Cancer Res 1995;36:373 (abstract 2221).

69. Gianni L, Vigano L, Locatelli A, Capri G, Giani A, Tarenzi E, Bonadonna G. Human pharmacokinetic characterization and in vitro study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. J Clin Oncol 1997;15:1906-1915.

70. Danesi R, Conte PF, Del Tacca M. Pharmacokinetic optimization of treatment schedules for anthracyclines and paclitaxel in cancer patients. Clin Pharmacokin 1999;9:135-211.

71. Sparano JA. Doxorubicin/taxane combinations: cardiac toxicity and pharmacokinetics. Semin Oncol 1999;26(3 Suppl 9):14-19.

72. Perez EA. Paclitaxel and cardiotoxicity. J Clin Oncol 1998;16:3481-3482.

73. Gregory RK, Hill ME, Moore J, A'Herne RP, Johnston S, Blake P, Shephard J, Barton D, Gore ME. Combining platinum, paclitaxel and anthracycline in patients with advanced gynaecological malignancy. Eur J Cancer 2000;36:503-507.

74. Luck HJ, Thomssen C, duBois A, Lisboa BW, Untch M, Kuhnle H, Konecny G, Jancke F, Meerphol HG, Lindner C, Hecker D, Diergarten K. Interim analysis of a phase II study of epirubicin and paclitaxel as first-Line therapy in patients with metastatic breast cancer. Semin Oncol 1996;23(Suppl 1):33-36.

75. Becker K, Erckenbrecht JF, Haussinger D, Frieling. Cardiotoxicity of the antiproliferative compound fluorouracil. Drugs 1999;57:475-484.

76. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother 1994;28:374-378.

77. Bertolini A, Flumano M, Fusco O, Muffati A, Scarinci A, Pontiggia G, Scopelli M. Acute cardiotoxicity during capecitabine treatment: a case report. Tumori 2001;87:200-206.

78. Schober C, Papageorgiou E, Harstrick A, Bokemeyer L, Mugge A, Stahl M, Wilke H, Poliwoda H, Hiddemann W, Kohne-Wompner CH et al. Cardiotoxicity of 5-fluorouracil in combination with folinic acid in patients with gastrointestinal cancer. Cancer 1993;72:2242-2247.

79. Kuropkat C, Griem K, Clark J, Rodriguez ER, Hutchinson J, Taylor SG. Severe cardiotoxicity during 5-fluorouracil chemotherapy: a case and literature report. Am J Clin Oncol 1999;22:466-470.

80. Gradishar WJ, Vokes EE. 5-fluorouracil cardiotoxicity: a critical review. Ann Oncol 1990;1:409-414.

81. De Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, Canal P, Chevreau C, Carrie D, Soulie P et al. Cardiotoxicity of high-dose continuous infusion fluorouracil. A prospective clinical study. J Clin Oncol 1992;10:1795-1801.

82. Kohne CH, Thuss-Patience P, Friedrich M, Daniel PT, Kretzschmar A, Benter T, Bauer B, Dietz R, Dorken B. Raltitrexed (Tomudex): an alternative drug for patients with colorectal cancer and 5-fluorouracil associated cardiotoxicity. Br J Cancer 1998;77:973-977.

83. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. J Clin Oncol 1991;9:1215-1223.

84. Kandylis K, Vassilomanolakis M, Tsoussis S, Efremidis AP. Ifosfamide cardiotoxicity in humans. Cancer Chemother Pharmacol 1989;24:395-396.

85. Icli F, Karaoguz H, Dincol D, Dermirkazik A, Gunel N, Karaoguz R, Uner A. Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer 1993;15:587-593.

86. Doll DC, List AF, Greco FA, Hainsworth JD, Hande KR, Johnson DH. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. Ann Intern Med 1986;105:48-51.

87. Meinardi MT, Gietema JA, van der Graaf WT, van Veldhuisen DJ, Runne MA, Sluiter WJ, de Vries EG, Willemse PB, Mulder NH, van den Berg MP, Koops HS, Sleijfer DT. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol 2000;18:1725-1732.

88. Gerl A, Clemm C, Wilmanns W. Acute cerebrovascular event after cisplatin based chemotherapy for testicular cancer. Lancet 1991;338:385-386.

89. Togna GI, Togna AR, Franconi M, Caprino L. Cisplatin triggers platelet activation. Throm Res 2000;99:503-509.

90. Treish I, Schwartz R, Lindley C. Pharmacology and therapeutic use of trastuzumab in breast cancer. Am J Health-Syst Pharm 2000;57:2063-2076.

91. Feldman AM, Lorell BH, Reis SE. Trastuzumab in the treatment of metastatic breast cancer. Anticancer therapy versus cardiotoxicity. Circulation 2000;102:272-274.

92. Politi PM, Xie F, Dahut W, et al. Phase I clinical trial of continuous infusion cyclopentenyl cytosine. Cancer Chemother Pharmacol 1995;36:513-523.