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# Dexrazoxane

## A Review of its Use as a Cardioprotective Agent in Patients Receiving Anthracycline-Based Chemotherapy

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**Data Selection**

**Sources:** Medical literature published in any language since 1966 on dexrazoxane, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

**Search strategy:** AdisBase search terms were 'dexrazoxane', 'ADR 529', 'ICRF 187', NSC 169780', 'antineoplastics' and 'heart-disorders'. Medline and EMBASE search terms were 'dexrazoxane', 'razoxane', 'ADR 529', 'ICRF 187' and 'NSC 169780'. Searches were last updated 30 January 98.

**Selection:** Studies in patients undergoing anthracycline-based chemotherapy for malignancy who also received dexrazoxane. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

**Index terms:** Dexrazoxane, cardiotoxicity, pharmacokinetics, pharmacodynamics, therapeutic use.

## Contents

## Summary

**Abstract**

Dexrazoxane has been used successfully to reduce cardiac toxicity in patients receiving anthracycline-based chemotherapy for cancer (predominantly women with advanced breast cancer). The drug is thought to reduce the cardiotoxic effects of anthracyclines by binding to free and bound iron, thereby reducing the formation of anthracycline-iron complexes and the subsequent generation of reactive oxygen species which are toxic to surrounding cardiac tissue.

Clinical trials in women with advanced breast cancer have found that patients given dexrazoxane (about 30 minutes prior to anthracycline therapy; dexrazoxane to doxorubicin dosage ratio 20 : 1 or 10 : 1) have a significantly lower overall incidence of cardiac events than placebo recipients (14 or 15% *vs* 31%) when the drug is initiated at the same time as doxorubicin. Cardiac events included congestive heart failure (CHF), a significant reduction in left ventricular ejection fraction and/or a ≥2-point increase in the Billingham biopsy score. These results are supported by the findings of studies which used control groups (patients who received only chemotherapy) for comparison. The drug appears to offer cardiac protection irrespective of pre-existing cardiac risk factors. In addition, cardiac protection has been shown in patients given the drug after receiving a cumulative doxorubicin dose ≥300 mg/m$^2$.

It remains to be confirmed that dexrazoxane does not affect the antitumour activity of doxorubicin: although most studies found that clinical end-points (including tumour response rates, time to disease progression and survival duration) did not differ significantly between treatment groups, the largest study did show a significant reduction in response rates in dexrazoxane versus placebo recipients.

Dexrazoxane permits the administration of doxorubicin beyond standard cumulative doses; however, it is unclear whether this will translate into prolonged survival.

Preliminary results (from small nonblind studies) indicate that dexrazoxane reduces cardiac toxicity in children and adolescents receiving anthracycline-based therapy for a range of malignancies. The long term benefits with regard to prevention of late-onset cardiac toxicity remain unclear.

With the exception of severe leucopenia [Eastern Cooperative Oncology Group (ECOG) grade 3/4 toxicity], the incidence of haematological and nonhaematological adverse events appears similar in patients given dexrazoxane to that in placebo recipients undergoing anthracycline-based chemotherapy. Although preliminary pharmacoeconomic analyses have shown dexrazoxane to be a cost-effective agent in women with advanced breast cancer, they require confirmation.

**Conclusions:** Dexrazoxane is a valuable drug for protecting against cardiac toxicity in patients receiving anthracycline-based chemotherapy. Whether it offers protection against late-onset cardiac toxicity in patients who received anthracycline-based chemotherapy in childhood or adolescence remains to be determined. Further clinical experience is required to confirm that it does not adversely affect clinical outcome, that it is a cost-effective option, and to determine the optimal treatment regimen.

## Anthracycline-Induced Cardiac Toxicity

The use of anthracyclines is significantly limited by cardiac toxicity, which occurs in 1 to 2% of patients given a cumulative doxorubicin dose < 450 mg/m$^2$. This increases to 20 to 40% at cumulative doses >600 mg/m$^2$. Children appear to be more susceptible to the cardiotoxic effects of this class of drugs than adults, although toxicity may not become apparent until years after cessation of therapy.

Cardiac toxicity is thought to occur principally as a result of oxidative stress placed on cardiac myocytes by reactive oxygen species (generated by the stable complex formed between anthracyclines and iron). Consequently, the ability of free-radical scavengers and metal-chelating agents to reduce cardiac toxicity has been investigated.

## Pharmacological Properties

Dexrazoxane, a cyclic derivative of edetic acid (EDTA), provides cardiac protection from anthracyclines primarily through its metal-chelating activity. The hydrolysis products of dexrazoxane have been shown to chelate both free and bound intracellular iron, including iron that is bound in anthracycline complexes, thereby preventing the generation of cardiotoxic reactive oxygen species. The hydrolysis products are thought to be responsible for most of the activity of the drug.

The cardioprotective activity of dexrazoxane has been demonstrated in animal models of anthracycline-induced cardiac toxicity. Dexrazoxane administration was associated with a significant reduction in the number of cardiac lesions and increased survival after toxic doses of anthracyclines. In studies in beagle dogs and rats, the drug appeared more effective when administered prior to or simultaneously with the anthracycline. In addition, delayed administration until after the sixth dose of doxorubicin was less effective than administration at the time of the initial doxorubicin dose (in contrast, delayed administration did not appear to reduce dexrazoxane's cardioprotective effect in patients).

Studies in patients receiving anthracycline therapy for cancer indicate that the pharmacokinetic properties of dexrazoxane fit a 2-compartment model with first-order elimination kinetics. Absorption is linear within the dose range 60 to 900 mg/m$^2$: the mean peak plasma concentration is 36.5 mg/L after a 15-minute intravenous infusion of dexrazoxane 500 mg/m$^2$. The distribution half-life is about 15 minutes and the steady-state volume of distribution has been estimated to be about 1.1 L/kg. Protein binding is usually <2%.

Dexrazoxane is hydrolysed to its active ring-opened forms by the enzyme dihydropyrimidine amidohydrolase (DHPase). Unchanged dexrazoxane, a diacid-diamide cleavage product and 2 monoacid-monoamide ring products have been detected in the urine.

Total body clearance is about 0.29 L/h/kg. Most of the drug is eliminated in the urine (about 50% over 24 hours), the elimination half-life ranging from 2 to 4 hours.

A study comparing the pharmacokinetic properties of dexrazoxane in adults and children found that the steady-state volume of distribution was higher in children, as was the total body clearance rate. There are no data at present on the properties of the drug in patients with renal or hepatic impairment.

The pharmacokinetic properties of doxorubicin (60 mg/m$^2$) are generally unchanged when the drug is administered 15 to 30 minutes after dexrazoxane (600 to 900 mg/m$^2$) intravenous infusion. However, the properties of epirubicin may be altered by dexrazoxane when the drug is administered at doses ≥100 mg/m$^2$.

## Clinical Efficacy

Clinical trials have shown dexrazoxane to significantly reduce the incidence of

cardiac toxicity in patients receiving anthracycline-based chemotherapy for advanced breast cancer. Cardiac events indicative of cardiac toxicity included congestive heart failure (CHF), a reduction in the resting left ventricular ejection fraction (LVEF) to <45% or a ≥20% reduction in LVEF from baseline and/or a ≥2 point increase in the Billingham biopsy score. In these studies, the dexrazoxane to doxorubicin dosage ratio was 10 : 1 or 20 : 1.

In 2 multicentre double-blind comparative studies, the incidence of doxorubicin (50 mg/m$^2$)-induced cardiac toxicity was 15 and 14% in patients given dexrazoxane (500 mg/m$^2$ about 30 minutes prior to each dose of the anthracycline) versus 31% in both groups of placebo recipients. CHF occurred in 15% of placebo recipients but in no patients treated with dexrazoxane in one of these studies. Where reported in comparative studies, clinically relevant reductions in LVEF were less common in patients treated with dexrazoxane than in dexrazoxane-untreated control patients or placebo recipients.

In most studies, dexrazoxane therapy was started at the same time as anthracycline therapy; however, it may also be cardioprotective when administration is delayed until a cumulative dose of doxorubicin ≥300 mg/m$^2$ has been given (incidence of cardiac events 60% in patients given placebo throughout (for up to 13 cycles of chemotherapy) versus 25% in patients initially given placebo (for 6 cycles of chemotherapy) then switched to dexrazoxane according to protocol amendment).

The extent of cardiac protection offered by dexrazoxane appeared similar in patients with or without pre-existing cardiac risk factors.

Dexrazoxane did not affect the clinical outcome of anthracycline therapy in most studies. However, the largest study did show a significantly lower rate of tumour response to doxorubicin therapy in patients given dexrazoxane versus that in placebo recipients (46.8 *vs* 60.5%). Other studies (including one by the same investigators) have failed to show any detrimental effect of dexrazoxane on the antitumour activity of anthracyclines.

The cardiac protection offered by dexrazoxane permits the administration of doxorubicin beyond standard cumulative doses. However, it remains unclear whether this will prolong the time to disease progression or the overall survival duration. While there was a trend towards prolonged survival in dexrazoxane recipients in most studies, the difference did not reach statistical significance (except in a retrospective analysis of patients given placebo or placebo followed by dexrazoxane as a result of protocol amendment).

Preliminary results (from small nonblind studies) indicate that dexrazoxane is also an effective cardioprotective agent in children and adolescents receiving anthracycline-based chemotherapy for a range of malignancies: the incidence of cardiac toxicity was 22 *vs* 67% in dexrazoxane-treated and -untreated patients in one study. Further investigation in this high-risk patient group, with regard to long term benefit, is warranted.

## Tolerability

Available data from clinical trials in women with advanced breast cancer indicate that coadministration of dexrazoxane with anthracycline-based chemotherapy does not compromise tolerability in most patients.

As expected, haematological toxicity was common in all treatment groups, but was generally more frequent in patients given dexrazoxane than in control groups (either placebo or no additional treatment). In comparisons with placebo, the incidence of severe leucopenia [Eastern Cooperative Oncology Group (ECOG)

grade 3/4] at nadir was significantly higher in dexrazoxane recipients (78 *vs* 68%; $p < 0.01$). However, the incidences of severe granulocytopenia and thrombocytopenia did not differ significantly between treatment groups.

The incidence and nature of other adverse events including vomiting, mucositis, infection, fever with neutropenia, alopecia, diarrhoea, fatigue, anaemia, haemorrhage, sepsis and stomatitis were similar between treatment groups. Pain on injection was more common with dexrazoxane than with placebo, whereas severe nausea (ECOG grade 3/4) appeared more common with placebo in comparative trials.

Limited data indicate that the drug has similar tolerability in children and adolescents to that observed in women with advanced breast cancer.

**Pharmacoeconomic Analysis**

Pharmacoeconomic analyses [based on data from a retrospective study of patients with breast cancer given placebo for up to 13 cycles of chemotherapy or placebo for 6 cycles then dexrazoxane (as a result of protocol amendment in 2 phase III studies)] indicate that the administration of dexrazoxane to prevent anthracycline-induced cardiac toxicity was cost-effective. Dexrazoxane cost $US5662 per cardiac event prevented and $US12 992 per CHF event prevented (based on 1995 costs). It was also found to cost $US2809 per life-year gained; however, survival data used in this analysis require confirmation. The investigators concluded that dexrazoxane compared well in terms of cost-effectiveness with other medical interventions in routine use in the US and Canada, including invasive cardiac monitoring to prevent heart failure.

**Dosage and Administration**

For protection against anthracycline-induced cardiac toxicity, the recommended dexrazoxane to anthracycline dosage ratio is 10 : 1 in the US (i.e. 500 mg/m$^2$ for a 50 mg/m$^2$ doxorubicin dose) or 20 : 1 in Europe. Dexrazoxane should be administered by intravenous infusion (slow push or rapid drip infusion), starting approximately 30 minutes before anthracycline infusion. In Europe, dexrazoxane should be initiated at the same time as anthracycline therapy whereas in the US delayed administration until a cumulative dose of 300 mg/m$^2$ doxorubicin is given is recommended. The maximum dose given in any cycle should not exceed 1000 mg/m$^2$.

Dexrazoxane may potentiate haematological toxicity induced by chemotherapy or radiation; thus monitoring of haematological parameters is recommended. The drug should not be given to pregnant or breast-feeding women, and caution is required in patients with renal or liver impairment.

## 1. Anthracycline-Induced Cardiac Toxicity

Anthracyclines are widely and successfully used to treat a range of malignancies including sarcomas, lymphomas, leukaemias, breast cancer, myeloma, small-cell lung cancer, bladder cancer and paediatric solid tumours. However, their use is significantly limited by their cardiotoxic effects.[1-5] Both doxorubicin and epirubicin have been associated with cardiac toxicity in adults and children: in children, the toxicity may not become apparent until 10 to 15 years after cessation of therapy.

At cumulative doses of doxorubicin <450 mg/m$^2$, the overall incidence of clinically apparent doxorubicin-induced cardiomyopathy is 1 to 2%. This increases to 20 to 40% at cumulative doses >600 mg/m$^2$.[5-7] In clinical practice (in the absence of cardiomyopathy or prior exposure to alkylating agents) anthracycline therapy is usually stopped once the cumulative dose reaches 450 to 500 mg/m$^2$. This limit is lower (400 mg/m$^2$) in patients who

have already received mediastinal irradiation. In addition, children appear to be more susceptible to the cardiotoxic effects of anthracyclines than adults: cardiac events are observed with cumulative doses of doxorubicin as low as 90 mg/m$^2$ in young patients.[8-10] There is marked individual variation in susceptibility, and reducing the anthracycline dose can compromise clinical success, while not necessarily reducing cardiac toxicity.

Cardiac toxicity typically becomes apparent 1 to 2 months after the last dose of doxorubicin (defined as a chronic subacute type); however, it may also occur during treatment (acute transient type), or develop years after cessation of therapy (mainly in patients exposed to the drugs as children; late-onset type). The characteristics of each type are summarised in table I.

Although several mechanisms may contribute to cardiac toxicity, it is thought to occur principally as a result of the oxidative stress placed on cardiac myocytes by reactive oxygen species. These radicals, which are highly toxic to surrounding tissues, are generated by the stable complex formed between anthracyclines and iron that is capable of catalysing electron transfer.[12-17] The toxic potential of these anthracycline-iron complexes is exacerbated in cardiac cells as they contain relatively low levels of enzymes which detoxify free radicals (including superoxide dismutase and catalase). In addition, doxorubicin has been shown to reduce cardiac levels of the antioxidant glutathione peroxidase in mouse heart.[18,19] Furthermore, the anthracycline-iron complex is, itself, toxic to cardiac tissue.[20]

Early attempts to reduce anthracycline-induced cardiac toxicity used the antioxidants tocopherol (vitamin E) and acetylcysteine to act as free-radical scavengers. However, neither of these agents was effective in humans.[21,22] Subsequent studies using the intracellular metal-chelating agents belonging to the dioxopiperazine class of compounds have shown more promising results.[16] Dexrazoxane, a cyclic derivative of the powerful metal-chelating agent edetic acid (EDTA), has been shown to provide cardiac protection when administered in conjunction with anthracyclines to patients with cancer (see section 3).

**Table I.** Types of cardiac toxicity induced by anthracyclines[11]

| |
|---|
| **Acute** |
| Uncommon, transient |
| Occurs immediately after a single dose or single course of therapy |
| May involve abnormal ECG findings including ST-T wave changes, prolongation of the QT interval and arrhythmias |
| Conduction disturbances are rarely observed, as are myopericarditis and cardiac failure |
| **Chronic** |
| Life-threatening, related to cumulative dose (about 550 mg/m$^2$ for doxorubicin), rapid onset and progression, may be resistant to treatment |
| Usually manifests within 1 year of therapy (symptoms may include tachycardia, tachypnoea, dilation of the heart, exercise intolerance, pulmonary and venous congestion, poor perfusion and pleural effusion) |
| Reflects progressive injury and loss of cardiac myocytes. Initial functional compensation by remaining myocytes may mask toxicity; however, with increasing cumulative doses of anthracycline decreased systolic performance becomes apparent (i.e. decrease in fractional shortening and left ventricular ejection fraction with eventual progression to congestive heart failure) |
| **Late-onset** |
| May occur several years or decades after cessation of anthracycline therapy |
| May include late-onset ventricular dysfunction, heart failure, conduction disturbances and arrhythmias |
| Myocyte damage and ventricular dysfunction after the initial insult may lead to late-onset cardiac decompensation |

This article provides an overview of the pharmacological properties of dexrazoxane, followed by a review of studies investigating the clinical efficacy and tolerability of the drug in patients receiving anthracycline-based cancer therapy.

## 2. Pharmacological Properties of Dexrazoxane

### 2.1 Mechanism of Action

The cardioprotective activity of dexrazoxane [the *S*(+)-enantiomer of razoxane] is thought to result primarily from the ability of the drug's hydrolysis products to chelate free or bound intracellular iron in the myocardium. This reduces the number

of metal ions complexed with anthracyclines and consequently reduces the formation of superoxide radicals after redox recycling. The ability of dexrazoxane and its 1-ring-opened hydrolysis intermediates and 2-ring-opened hydrolysis product (fig. 1) to remove iron from transferrin and ferritin (iron transport and storage proteins) and from anthracycline-iron complexes has been demonstrated *in vitro*.[23-25] Both the 1-ring-opened intermediates and the 2-ring-opened product removed iron faster from anthracycline complexes than did the parent drug (half-times of 1.7 to 16.7 minutes, 1 to 3 minutes and 230 to 450 minutes, respectively, in one *in vitro* study[25]).

Consistent with *in vitro* studies of the relative iron-chelating activities of dexrazoxane and its hydrolysis products, a comparative study *in vivo* found that while dexrazoxane inhibited doxorubicin-induced lipid peroxidation in mouse cardiac microsomal membranes by 65%, its final hydrolysis product caused complete inhibition of lipid peroxidation.[26]

### 2.2 Animal Studies of Cardiac Protection

Preclinical studies conducted in animals (including mice, rats, hamsters, rabbits and dogs) given cardiotoxic doses of anthracyclines (doxorubicin, epirubicin, idarubicin or daunorubicin) showed dexrazoxane to be an effective cardioprotective agent, significantly reducing the incidence of cardiac lesions and increasing the survival rate compared with controls (i.e. no treatment with dexrazoxane).[27-35] Cardioprotection was also observed in spontaneously hypertensive rats, which are particularly sensitive to anthracycline-induced cardiac toxicity.[29]

Villani et al.[33] observed that coadministration of dexrazoxane 125 mg/kg/week with doxorubicin 3 mg/kg/week for 5 weeks significantly reduced doxorubicin-induced bodyweight loss and QT and ST prolongation in rats and the decrease in contractile force caused by doxorubicin. The incidence and severity of myocardial lesions was also significantly lower in animals given both dexrazox-

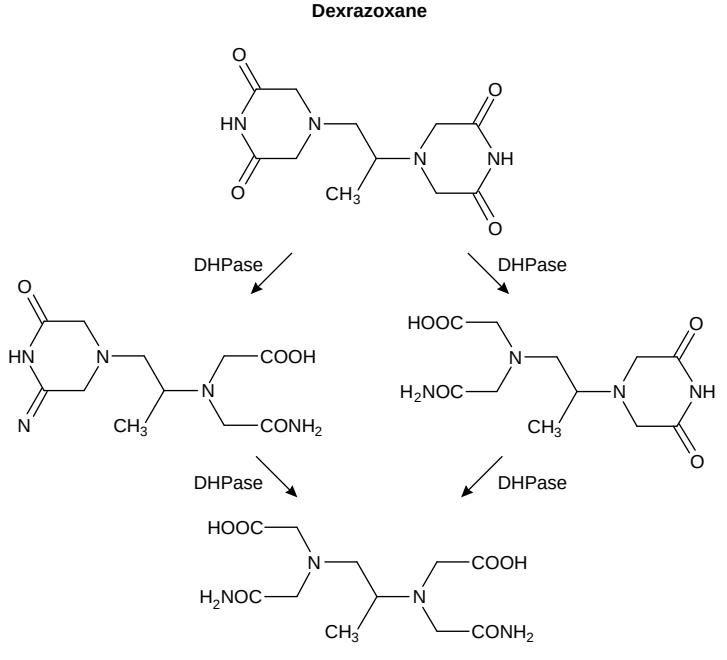


**Fig. 1.** Structural formulae of dexrazoxane and its hydrolysis products after catalysis by dihydropyrimidine amidohydrolase (DHPase).

ane and doxorubicin than in animals treated with doxorubicin alone (fig. 2).

In another study in rats, cardiac output after 12 weeks was reduced by about 35% in animals given a single dose of doxorubicin (4 mg/kg), whereas a reduction of about 15% was evident in rats pretreated with dexrazoxane (40 or 60 mg/kg) prior to doxorubicin.[27] Deaths due to cardiac toxicity were observed in animals given only doxorubicin.

Studies investigating the timing of dexrazoxane administration in beagle dogs and rats have generally observed that the drug is more effective when administered shortly before or simultaneously with, rather than after, the anthracycline.[36,37] In addition, another study found that dexrazoxane (20 mg/kg/week) given before the first doxorubicin (1 mg/kg/week) dose was significantly more effective than delaying dexrazoxane administration until the sixth doxorubicin dose (mean cardiomyopathy score after 15 weeks' treatment 4.0 *vs* 4.8; $p < 0.05$).[34] This contrasts with findings in patients with cancer (see section 3), in whom the drug can be administered with the first dose of anthracycline or once a cumulative dose of 300 mg/m$^2$ has been given.

## 2.3 Pharmacokinetic Properties

Limited data from phase I studies in patients receiving anthracycline-based chemotherapy for cancer indicate that the pharmacokinetics of dexrazoxane fit a 2-compartment open model with first-order elimination kinetics.[38-40] Pharmacokinetic parameters were the same after a 30-minute or 8- or 48-hour infusion in adults and were independent of dose (up to 7400 mg/m$^2$ over 1 hour).[38,39,41] They are summarised in table II.

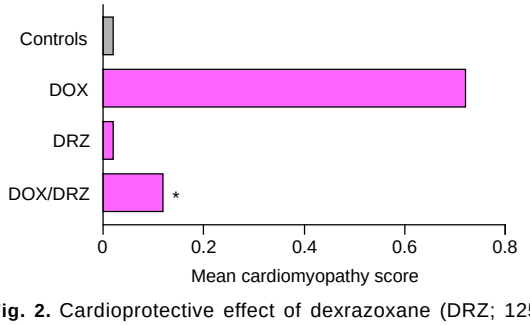


**Fig. 2.** Cardioprotective effect of dexrazoxane (DRZ; 125 mg/kg/wk) in rats treated with doxorubicin (DOX; 3 mg/kg/wk) for 5 weeks.[33] Control animals were not treated with either DOX or DRZ. * $p < 0.05$ *vs* DOX alone.

### 2.3.1 Absorption and Distribution

A linear relationship has been shown between the area under the plasma concentration-time curve (AUC) and dexrazoxane doses ranging from 60 to 900 mg/m$^2$. The mean peak plasma concentration of dexrazoxane ($C_{max}$) after a 15-minute infusion of a 500 mg/m$^2$ dose was 36.5 mg/L.[42]

After intravenous administration, the drug is rapidly distributed into tissues and fluids, the highest concentrations of the parent drug and its hydrolysis product being found in hepatic and renal tissues. The drug does not cross the blood-brain barrier to a clinically significant extent.

The distribution half-life ($t_{½\alpha}$) has ranged from about 12 to 60 minutes (generally thought to be about 15 minutes),[38,39] and the steady-state volume of distribution has varied in clinical trials but is generally considered to be about 1.1 L/kg.[11] Protein binding is very low, usually <2%.

### 2.3.2 Metabolism and Elimination

Dexrazoxane is hydrolysed by the enzyme dihydropyrimidine amidohydrolase (DHPase) to its 1-ring- and then 2-ring-opened EDTA-like hydrolysis products (fig. 1), which are both capable of binding to metal ions. The ring-opened products of dexrazoxane are, thus, capable of chelating free iron or displacing iron bound in the iron-anthracycline complex, thereby preventing iron-bound oxygen radical formation (thought to be important in cardiac toxicity) [see section 1]. *In vitro* studies have shown dexrazoxane to be hydrolysed by DHPase in liver and kidney, but not heart, extracts.[43-45]

Unchanged dexrazoxane, a diacid-diamide cleavage product and 2 monoacid-monoamide ring products have been detected in the urine. The levels of each have not been determined.[42]

Total body clearance of dexrazoxane is about 0.29 L/h/kg.[38]

**Table II.** Summary of the pharmacokinetic properties of dexrazoxane in adult patients with cancer[38,39,42]

| | |
|---|---|
| Mean $C_{max}$ (500 mg/m$^2$ dose) | 36.5 mg/L |
| $t_{½\alpha}$ | ≈15 min |
| $Vd_{ss}$ | ≈1.1 L/kg |
| Binding to plasma proteins | <2% |
| Metabolism | Hydrolysis by DHPase to active ring-opened products |
| Elimination | Predominantly renal |
| Mean total body clearance | ≈0.29 L/h/kg |
| $t_{½\beta}$ | 2 to 4h |

**$C_{max}$** = peak plasma concentration; **DHPase** = dihydropyrimidine amidohydrolase; **$t_{½\alpha}$** = distribution half-life; **$t_{½\beta}$** = elimination half-life; **$Vd_{ss}$** = volume of distribution at steady state.

Dexrazoxane is predominantly eliminated in the urine: 24-hour urinary output was 60% in children 9 to 16 years and 46% in adults in one study.[38]

The elimination half-life ($t_{½\beta}$) of 2 to 4 hours suggests the existence of a deep tissue compartment in equilibrium with the peripheral compartment.

#### 2.3.3 Effect of Age or Renal or Hepatic Impairment

Results of a small study comparing the pharmacokinetic properties of dexrazoxane in adults and children showed that the mean steady-state volume of distribution was significantly higher in children than in adults (0.96 *vs* 0.66 L/kg; $p < 0.05$), as was the total body clearance rate (0.36 *vs* 0.20 L/h/kg; $p < 0.05$).[38] No other parameters differed significantly between age groups.

The pharmacokinetics of dexrazoxane have not been determined in patients with hepatic or renal impairment. However, as most of an administered dose is eliminated via the kidneys, caution is advised in patients with renal impairment. It is also recommended that routine liver function tests be performed in patients with liver impairment.

#### 2.3.4 Anthracycline Interactions

Administration of dexrazoxane 600 to 900 mg/m$^2$ 15 to 30 minutes prior to doxorubicin 60 mg/m$^2$ did not significantly modify the pharmacokinetic properties of either dexrazoxane or the anthracycline in studies in patients with cancer.[41,46] In addition, the pharmacokinetic properties of both epirubicin and dexrazoxane were not significantly changed when dexrazoxane (600 to 1000 mg/m$^2$) was administered 15 to 30 minutes prior to epirubicin (60 to 120 mg/m$^2$) in patients with advanced malignancies in 2 studies.[47,48] Basser et al.[47] did observe a significant increase in systemic clearance and AUC for epirubicin when the drugs were administered at the higher doses of 135 mg/m$^2$ epirubicin with 900 or 1200 mg/m$^2$ dexrazoxane. In addition, Jakobson et al.[48] observed that increasing the dose of epirubicin from 60 to 100 mg/m$^2$ caused a 30% increase in $t_{½\beta}$ and decrease in total body clearance of dexrazoxane.

## 3. Clinical Efficacy

The ability of dexrazoxane to protect against anthracycline (doxorubicin or epirubicin)-induced cardiac toxicity has been investigated in adults and children receiving chemotherapy for a range of malignancies, predominantly breast cancer or sarcomas.

The cardioprotective efficacy of dexrazoxane has been determined by use of clinical and functional end-points [measured by ECG, chest x-rays or multigated acquisition (MUGA) scans], and occasionally by histological end-point (Billingham score of biopsy samples). In most studies, cardiac toxicity was defined as the presence of one or more of the following cardiac events: clinical signs of congestive heart failure (CHF); a reduction in the resting left ventricular ejection fraction (LVEF) to <45% or a ≥20% reduction in LVEF from baseline; an increase of ≥2 in the Billingham biopsy score.

Studies generally excluded patients with active cardiac disease or those who had received previous anthracycline therapy within 6 months of trial commencement. Patients with one or more cardiac risk factors (usually defined as age >65 years, smoking, previous irradiation to the heart, mediastinum or chest wall, previous anthracycline therapy for malignancy in childhood or adolescence, a history of hypertension, cardiac failure, diabetes mellitus, angina, rheumatic heart disease or an abnormality on ECG) were divided evenly between treatment groups in randomised studies.

Tumour response was assessed using standard Eastern Cooperative Oncology Group (ECOG)[49] or WHO criteria.[50]

### 3.1 Advanced Breast Cancer

The cardioprotective activity of dexrazoxane in patients treated with anthracyclines for advanced breast cancer has been investigated in numerous clinical trials (mainly phase I or II).[7,51-60] The results of the largest studies are summarised in table III. Studies have compared dexrazoxane-treated patients with control groups of patients (i.e. those who received only chemotherapy)[57,58,60] and patients given placebo.[7,59]

The 2 multicentre double-blind comparisons with placebo showed a clear cardioprotective effect of dexrazoxane prior to study completion; thus, the study protocol was amended such that placebo recipients were switched to dexrazoxane once the cumulative dose of doxorubicin reached ≥300 mg/m$^2$ (i.e. after 6 treatment cycles). Consequently, a retrospective analysis[59] compared the incidence of cardiac events in patients randomised to receive placebo prior to protocol amendment (they received placebo with up to 13 cycles of chemotherapy) with that in patients who were initially given placebo and then switched to dexrazoxane (in accordance with protocol amendment) to determine whether delayed administration of dexrazoxane still offered cardiac protection.

Dexrazoxane was administered about 30 minutes before each dose of anthracycline (doxorubicin or epirubicin alone or combined with fluorouracil and cyclophosphamide once every 3 weeks), and it was usually started when anthracycline therapy was initiated. The dosage ratio of dexrazoxane to doxorubicin was 10 : 1 (used in the placebo comparisons) or 20 : 1.

#### 3.1.1 Cardiac Toxicity

Clinical trials have found the incidence of anthracycline-induced cardiac events to be significantly lower in patients given dexrazoxane than in controls (dexrazoxane-untreated patients or placebo recipients) [table III]. As mentioned earlier, this was based on the incidence of CHF, reductions in the LVEF and biopsy results. In the 2 placebo-controlled studies (in which dexrazoxane was given 30 minutes before the first dose of doxorubicin 50 mg/m$^2$; dosage ratio 10 : 1), 14 and 15% of dexrazoxane recipients had cardiac events compared with 31% of patients in each placebo group.[7] In addition, the incidence of CHF was significantly lower in dexrazoxane recipients in one of these studies (0 *vs* 15%; $p < 0.001$), but not in the other (2 *vs* 7%). Significant reductions in CHF were also observed in dexrazoxane recipients in the 2 studies conducted by Speyer et al.[58,61] The benefits of dexrazoxane were most pronounced when cumulative doxorubicin doses were >500 mg/m$^2$.[7] Where reported, clinically relevant reductions in LVEF were observed in fewer patients treated with dexrazoxane than in controls (table III, fig. 3). In addition, biopsy results indicated less cardiac toxicity in patients who received dexrazoxane (increase in Billingham biopsy score of ≥2 in 5 of 13 patients in the control group *vs* 0 of 13 patients receiving dexrazoxane in one study[58]).

Delayed administration of dexrazoxane until after a cumulative dose of doxorubicin ≥300 mg/m$^2$ has been given also appears to be cardioprotective. The retrospective analysis of patients randomised in the 2 phase III studies[7] to receive placebo before and after protocol amendment (described previously)[59] found that the incidence of cardiac events in patients given placebo then dexrazoxane (after a cumulative doxorubicin dose of ≥300 mg/m$^2$ was reached) was 25%, versus 60% in patients given placebo throughout the study period (≤13 cycles; $p < 0.001$). The incidence of CHF was also significantly lower in patients given dexrazoxane; 3 versus 22% ($p < 0.001$).[59]

Dexrazoxane appears to reduce the incidence of anthracycline-induced cardiac toxicity in patients with or without pre-existing cardiac risk factors.[56,58,60-62] In a noncomparative study conducted specifically in patients with pre-existing cardiac risk factors, no cardiac toxicity was detected up to a cumulative doxorubicin dose of between 800 and 1000 mg/m$^2$ in 33 of 35 patients given dexrazoxane (dosage ratio 20 : 1; 2 patients had a

**Table III.** Summary of the largest studies evaluating the protective effect of dexrazoxane (DRZ) against anthracycline-induced cardiac toxicity in patients with advanced breast cancer. Unless stated otherwise, dexrazoxane was administered about 30 minutes prior to each cycle of chemotherapy

| Reference | Study design | No. of patients (% with risk factors for cardiac disease) | Treatment regimen (dosage of DOX, EPI or DRZ in mg/m$^2$) once every 3 weeks [dosage ratio] | Overall incidence of cardiac events[a] | Incidence of CHF (% pts) | Objective response rate (% pts)[b] | Median overall survival | Comments |
|---|---|---|---|---|---|---|---|---|
| **Comparisons with placebo** | | | | | | | | |
| Swain et al.[7] | r,db,mc | 181 (NR) | FAC (50) + PL | 31 | 15 | 60.5 | 551 days | Risk of cardiac events significantly higher in PL recipients according to log rank test (no LVEF data presented) |
| | | 168 (NR) | FAC (50) + DRZ (500) [10 : 1] | 15*** | 0*** | 46.8* | 598 days | |
| Swain et al.[7] | r,db,mc | 104 (NR) | FAC (50) + PL | 31 | 7 | 49.3 | 553 days | Risk of cardiac events significantly higher in PL recipients according to log rank test (no LVEF data presented) |
| | | 81 (NR) | FAC (50) + DRZ (500) [10 : 1] | 14** | 2 | 53.7 | 458 days | |
| Swain et al.[59]c | mc, ic | 99 (NR) | FAC (50) + PL | 60 | 22 | NR | 460 days | Delayed administration of DRZ still cardioprotective (no LVEF data presented) |
| | | 102 (NR) | FAC (50) + PL then DRZ (500)[d] [10 : 1] | 25*** | 3*** | NR | 882 days*** | |
| **Comparisons with patients who received only chemotherapy** | | | | | | | | |
| Lopez et al.[57] | r,nb | 49 (NR) | EPI (160) | NR | 4 | 67 | 19mo | Mean reduction in LVEF significantly less in patients given DRZ (1.2%) than in controls (12.6%; p < 0.001) |
| | | 43 (NR) | EPI (160) + DRZ (960) [6 : 1] | NR | 0 | 69 | 29mo | |
| Speyer et al.[58] | r | 45 (58) | FAC (50) | NR | 11 | 45 | NR | Mean reduction in LVEF in controls and doxorubicin recipients: 7 *vs* 1% (cumulative DOX 250 to 399 mg/m$^2$; p = 0.02), and 16 *vs* 1% (cumulative DOX 400 to 499 mg/m$^2$; p = 0.001). Increase in Billingham biopsy score ≥2 in 5/13 controls and 0/13 DRZ recipients (p < 0.05) |
| | | 47 (62) | FAC (50) + DRZ (1000) [20 : 1] | NR | 2* | 48 | NR | |
| Speyer et al.[61]e | r | 74 (58) | FAC (50) | NR | 27 | 41 | 16.7mo | Clinically significant reduction in LVEF[a] in 43% of controls *vs* 6.6% of DRZ recipients ( p < 0.001) |
| | | 76 (54) | FAC (50) + DRZ (1000) [20 : 1] | NR | 2.6*** | 37 | 18.3mo | |
| Venturini et al.[60] | r | 78 (38.5) | EPI (120) or FEC (60)[f] | 23.1 | 5.1 | 47.6 | NR | Cumulative probability of developing cardiac toxicity significantly lower in DRZ recipients *vs* the no-DRZ group (p < 0.01) [LVEF data presented in fig. 3] |
| | | 82 (38.1) | EPI (120) or FEC (60) + DRZ (1200 or 600) [10 : 1] | 7.3** | 2.4 | 46.2 | NR | |
| **Noncomparative trial** | | | | | | | | |
| Kolaric et al.[56] | nc | 212 (63) | FAC (50) + DRZ (1000) [20 : 1] | NR | 3 | 49.5 | NR | 68 of 134 patients (51%) with cardiac risk factors received cumulative DOX at 450 to 900 mg/m$^2$ without significant cardiac toxicity |

a Including clinical signs of CHF; a reduction in the LVEF to <45% or a ≥20% reduction in LVEF from baseline; and/or a ≥2-point increase in the Billingham biopsy score.
b Antitumour activity determined by Eastern Cooperative Oncology Group (ECOG)[49] and WHO[50] criteria. Objective response rate included complete and partial tumour responses.
c This study compared the outcome of patients (enrolled in the 2 phase III studies[7]) who received placebo throughout the study duration (≤13 cycles of chemotherapy) with patients initially randomised to receive placebo and then switched to open-label dexrazoxane after 6 chemotherapy cycles (i.e. after protocol amendment because of evident cardioprotection by dexrazoxane).
d Dexrazoxane administration delayed until a cumulative doxorubicin dose of ≥300 mg/m$^2$ had been given.
e Updated analysis including some patients from an earlier study by Speyer et al[58]
f Dependent on prior anthracycline exposure.

**CHF** = congestive heart failure; **controls** = dexrazoxane-untreated or placebo recipients; **db** = double-blind; **DOX** = doxorubicin; **EPI** = epirubicin; **FAC** = fluorouracil + doxorubicin + cyclophosphamide; **FEC** = fluorouracil + epirubicin + cyclophosphamide; **ic** = indirect comparison of patients enrolled sequentially rather than concurrently (see footnote 'c'); **LVEF** = resting left ventricular ejection fraction; **mc** = multicentre; **nb** = nonblind; **nc** = noncomparative; **NR** = not reported; **PL** = placebo; **r** = randomised; *p < 0.05; **p < 0.01; ***p < 0.001 *vs* controls.

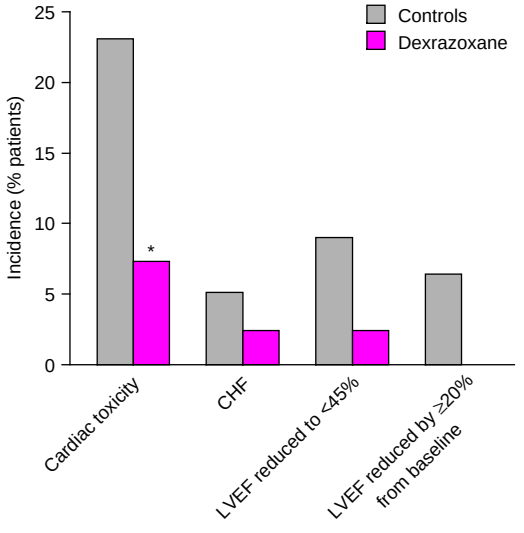


**Fig. 3.** Cardioprotective efficacy of dexrazoxane. Incidence of cardiac events in patients receiving epirubicin (60 or 120 mg/m$^2$)-based chemotherapy with (n = 82) or without (n = 78) dexrazoxane (10 : 1 dose ratio) for advanced breast cancer.[60] Cardiac toxicity included CHF, a reduction in the resting LVEF to <45% or a ≥20% reduction in LVEF from baseline. **CHF** = congestive heart failure; **LVEF** = resting left ventricular ejection fraction; * $p < 0.01$ *vs* control group.

20% reduction in LVEF from baseline after a cumulative dose of 250 mg/m$^2$).[62] Larger studies, in which >35% of patients had risk factors for cardiac toxicity, found dexrazoxane to provide cardiac protection regardless of cardiac risk factors.[56,58,60,61]

As a consequence of reduced cardiac toxicity, patients receiving dexrazoxane could tolerate a significantly higher number of cycles and a higher cumulative dose of anthracycline than controls. In one study,[61] the median number of cycles and the cumulative dose of doxorubicin in control and dexrazoxane treatment groups were 9 *vs* 11 and 441 *vs* 500 mg/m$^2$, respectively. 26 of 76 patients treated with dexrazoxane received cumulative doxorubicin doses of ≥700 mg/m$^2$ (11 of these patients received ≥1000 mg/m$^2$). In comparison, only 3 of 74 patients in the control group received doxorubicin ≥700 mg/m$^2$. Whether an increase in the cumulative dose of anthracycline will translate into an increase in time to disease progression or improved survival remains unclear. Current evidence with dexrazoxane does not clarify this issue (see section 3.1.2).

#### *3.1.2 Effect on Clinical Outcome*

In most studies, objective response rates were similar in dexrazoxane-untreated or placebo-treated patients to those in dexrazoxane recipients (ranging from 37 to 69%) and no significant difference in time to disease progression or median duration of survival was evident when dexrazoxane was initiated at the same time as anthracycline therapy. However, in the largest study, a significantly higher response rate was observed in placebo versus dexrazoxane recipients (60.5 *vs* 46.8%; $p < 0.05$), but time to disease progression and median survival duration did not differ significantly between treatment groups.[7] Response rates were similar between treatment groups in another study of similar design conducted by the same investigators (49.3 *vs* 53.7%).[7]

In general, clinical trials to date have failed to detect any significant survival advantage in patients given dexrazoxane versus controls. Although the median duration of survival appeared longer in the dexrazoxane treatment group in most studies, the difference was not statistically significant. Only Swain et al.[59] reported a significant difference in survival in favour of dexrazoxane versus placebo (median duration 882 *vs* 460 days; $p < 0.001$) in their retrospective analysis of patients enrolled to receive placebo before or after protocol amendment in the 2 placebo-controlled phase III studies.[7] The survival advantage may be explained, in part, by the finding that more dexrazoxane-treated patients were able to continue treatment with doxorubicin beyond standard cumulative doses (15 courses of chemotherapy were administered to 26% of dexrazoxane recipients versus 5% of placebo recipients). However, the median number of cycles of chemotherapy received did not differ significantly between the treatment groups. In addition, time to disease progression did not differ significantly between treatment groups in this study.

### 3.2 Childhood Malignancy

Children and adolescents appear to be particularly susceptible to the cardiotoxic effects of anthracyclines. Up to 70% of long term survivors of childhood cancer have evidence of cardiac dysfunction, despite cumulative doxorubicin doses being limited to ≤450 mg/m$^2$.[9,63-65]

Although only a few small studies have been conducted (n ≤33 patients with a range of malignancies), available data indicate that dexrazoxane can protect against anthracycline-induced cardiac toxicity in this high-risk group of patients.[66-69] In a nonblind randomised trial, which included 33 patients aged 4 to 24 years undergoing doxorubicin therapy for sarcomas [70 mg/m$^2$ in chemotherapy cycles 1, 3 and 5 or 50 mg/m$^2$ in cycles 9, 11, 13 and 15 (doxorubicin was not given in the other cycles)], the incidence of cardiac toxicity was significantly lower in patients given dexrazoxane [1000 mg/m$^2$; n = 18] than in the control group (n = 15; 22 *vs* 67%; $p < 0.01$).[67] The mean reduction in LVEF per 100 mg/m$^2$ doxorubicin was 2.7% in controls versus 1% in dexrazoxane recipients ($p = 0.02$). The median cumulative dose of doxorubicin in dexrazoxane recipients and controls was 410 and 310 mg/m$^2$, respectively ($p < 0.05$). There was no significant difference between treatment groups in objective response rates or overall survival (median follow-up 39 months). Furthermore, Rubio et al.[68] observed that the incidences of CHF or clinically significant reductions in LVEF were lower in patients given dexrazoxane than in a historical control group who received a similar chemotherapy regimen without dexrazoxane. Indeed, CHF did not occur in any patients given dexrazoxane (n = 14), whereas 3 of 30 controls (10%) developed CHF during chemotherapy or within 1 year of stopping treatment.

Further long term clinical experience with dexrazoxane in this patient group will determine the benefits of the drug in terms of preventing late-onset cardiac toxicity.

## 4. Tolerability

Clinical trial data from patients receiving anthracycline-based therapy for advanced breast cancer indicate that coadministration of dexrazoxane does not compromise tolerability in most patients. The incidence and nature of adverse events was generally the same in patients treated with dexrazoxane as in controls (given placebo or nothing in addition to chemotherapy).[7,57,58,60] Table IV summarises the incidence of all adverse events occurring in patients who received dexrazoxane or no additional treatment in a large randomised study, and figure 4 shows the overall incidence of severe (ECOG grade 3/4 toxicity) adverse events occurring in 2 placebo-controlled studies.

Although haematological toxicity occurred to some extent in most patients as a result of chemotherapy, it appeared to be more common in dexrazoxane treatment groups.[7,58,60] Indeed, severe (ECOG grade 3/4) leucopenia at nadir (days 1 to 18) was significantly more common in dexrazoxane recipients than placebo recipients (78 *vs* 68%; $p < 0.01$) in pooled results from 2 placebo-controlled studies.[7] However, the incidence of grade 3/4 granulocytopenia did not differ significantly between treatment groups (88 *vs* 86%) nor did that of thrombocytopenia (9 *vs* 10%). Platelet counts were

**Table IV.** Incidence of all adverse events occurring in patients receiving doxorubicin-based chemotherapy with or without dexrazoxane for advanced breast cancer[60]

| Adverse event | Incidence (% patients) | |
|---|---|---|
| | dexrazoxane (n = 82) | controls (n = 78) |
| **Haematological** | | |
| Leucopenia | 30.5 | 24 |
| Thrombocytopenia | 2 | 4 |
| Anaemia | 17 | 13 |
| **Other** | | |
| Diarrhoea | 13 | 15 |
| Fatigue | 38 | 27 |
| Fever | 7 | 10 |
| Nausea | 72 | 64 |
| Phlebitis | 12 | 4 |
| Stomatitis | 49 | 59 |
| Vomiting | 54 | 44 |

usually lower in dexrazoxane recipients, but toxicity was generally grade 1 (incidence 47 *vs* 29%; p < 0.01).[7]

Of the nonhaematological adverse events, only pain on injection was more frequent in patients treated with dexrazoxane versus placebo, but this was generally mild to moderate (grade 1 or 2 severity).[7] Severe nausea appeared more common with placebo (fig. 4).

Other adverse events, including mucositis, infection, fever with neutropenia, alopecia, diarrhoea, vomiting, fatigue, anaemia, haemorrhage, sepsis and stomatitis, appeared to have a similar incidence in patients treated with dexrazoxane to that in untreated controls or placebo recipients.[7,58,60]

The incidence of treatment withdrawal due to noncardiac adverse events was similar in dexrazoxane and placebo treatment groups: 6.8 versus 6.3%.[7]

There were no statistically significant differences between the treatment groups in laboratory parameters indicative of hepatic or renal function.[7,59]

Limited data indicate that dexrazoxane has a similar tolerability profile in children and adolescents to that observed in women with advanced breast cancer.[66,67] However, further investigation in these patient groups is warranted.

## 5. Pharmacoeconomic Analysis

Pharmacoeconomic analyses conducted in the US and Canada indicate that the benefit of cardiac protection offered by dexrazoxane outweighs the cost of the drug.[70,71] These analyses used data from a retrospective study of breast cancer patients enrolled in 2 phase III trials who received placebo (in addition to doxorubicin-based chemotherapy) for the entire study period or placebo for the first 6 cycles of chemotherapy (cumulative doxorubicin dose ≥300 mg/m$^2$) then dexrazoxane (as a consequence of protocol amendment, see section 3.1).

The primary end-point was the cost per cardiac event avoided over a 1-year period. The cost per life-year gained (over the 150-week observation period) was also determined, although survival data required confirmation at the time of analysis. A Markov model was used to quantify the economic costs in 1995 of therapy with and without dexrazoxane: these included the direct medical costs associated with treating patients with metastatic breast cancer and the costs associated with treating any cardiac events that occurred.

Therapy with dexrazoxane was found to cost $US5662 per cardiac event prevented. The cost per CHF event prevented was $US12 992. The authors observed that this compared favourably with the cost for each case of heart failure prevented using invasive cardiac monitoring, and was a small percentage of the total lifetime treatment cost of breast cancer.[70]

The cost of dexrazoxane therapy per life-year gained, $US2809, was considered to be low in comparison with other interventions.

Sensitivity analysis showed that the results of the model did not change when parameters were varied (these included varying the price of drugs, tests, procedures, hospitalisations and cardiology visits, varying the difference in survival time between the 2 groups and varying the difference in the number of cardiac and CHF events between the 2 groups).

A similar result was found when costs were determined in Canadian dollars ($Can5745 per cardiac event prevented, $Can2856 per life-year gained), dexrazoxane appearing slightly more cost-effective in Canada.[71]

These investigators concluded that the cost-effectiveness ratio of using dexrazoxane to prevent anthracycline-induced cardiac toxicity falls within the range of other generally accepted medical interventions in both the US and Canada.

## 6. Dosage and Administration

Dexrazoxane is a cardioprotective agent which is recommended for use in patients receiving anthracycline-based chemotherapy for malignancy.

Dexrazoxane solution should be given intravenously by slow push or by rapid drip infusion from a bag, starting approximately 30 minutes before anthracycline infusion.

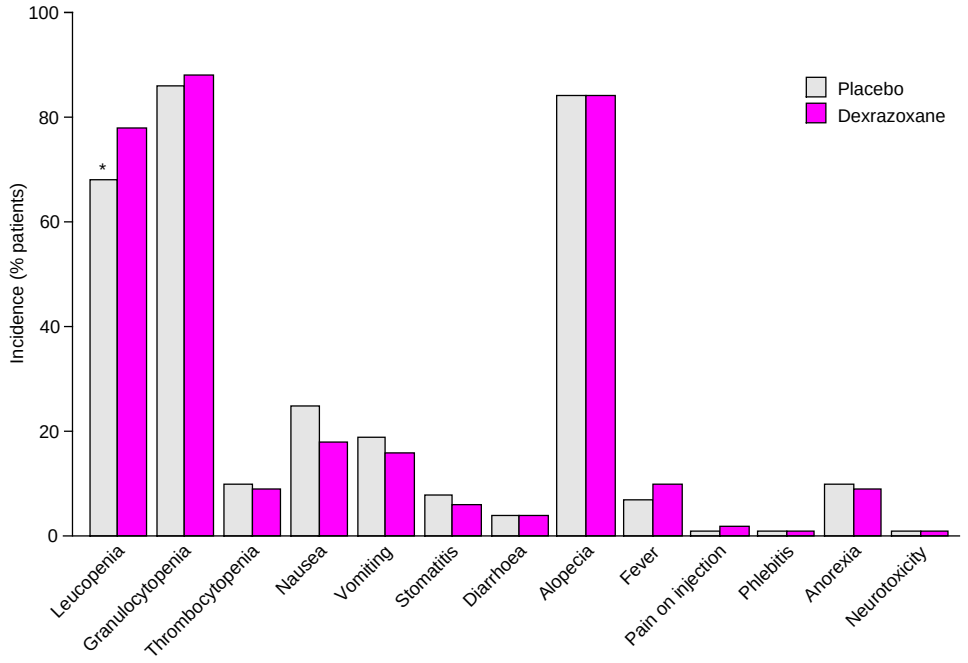


**Fig. 4.** Overall incidence of severe adverse events (ECOG grade 3/4) occurring in patients receiving doxorubicin-based chemotherapy with dexrazoxane [n = 249 (1 : 10 dosage ratio)] or placebo (n = 285) for advanced breast cancer.[7] The incidences shown for leucopenia, granulocytopenia and thrombocytopenia were at nadir. * $p < 0.01$ *vs* dexrazoxane.

In the US, the recommended dexrazoxane to doxorubicin dosage ratio is 10 : 1 (i.e. if 50 mg/m$^2$ doxorubicin is used, 500 mg/m$^2$ of dexrazoxane should be given). Dexrazoxane should be initiated once patients have received a cumulative dose of 300 mg/m$^2$ doxorubicin.[42] In Europe, the recommended dosage ratio is 20 : 1, dexrazoxane therapy being initiated at the time of the first dose of doxorubicin and with subsequent doxorubicin doses once every 3 weeks.[11] The maximum dose of dexrazoxane given in each cycle should not exceed 1000 mg/m$^2$.

Monitoring of haematological parameters is required during the first 2 treatment cycles as dexrazoxane may potentiate haematological toxicity induced by chemotherapy or radiation. The drug should not be given to pregnant or breast-feeding women, and caution is required in patients with renal or liver impairment.

## 7. Place of Dexrazoxane as a Cardioprotective Agent in Patients Receiving Anthracycline-Based Chemotherapy

Anthracycline-based chemotherapy has been widely used to treat malignancies in adults and children; however, the cardiac toxicity which occurs in 20 to 40% of patients receiving a cumulative dose >600 mg/m$^2$ significantly limits the use of this class of drugs (see section 1). Patients at high risk of cardiac toxicity include those aged >65 years, smokers, those with previous irradiation to the heart, mediastinum or chest wall, a history of hypertension, cardiac failure, diabetes mellitus, angina, rheumatic heart disease, an abnormality on ECG or those exposed to anthracyclines as children.

Attempts to avoid or delay the onset of cardiac toxicity have included modification of the administration schedule (including limiting the cumula-

tive dose to <450 mg/m$^2$, prolonging administration over 96 hours or weekly rather than 3-weekly administration), development of anthracycline analogues with the same antitumour activity, but devoid of cardiac toxicity (e.g. altered lipophilicity, use of a liposomal delivery system), and development of cardioprotective drugs. To date, only the cardioprotective agent dexrazoxane has been consistently shown to reduce anthracycline-induced cardiac toxicity.

Large well-controlled clinical trials have found that patients treated with dexrazoxane have a significantly lower incidence of cardiac events than placebo recipients. This appears to be true for patients with or without pre-existing cardiac risk factors. Cardiac protection was evident when dexrazoxane was initiated either before the first dose of anthracycline or when administration was delayed until after a cumulative doxorubicin dose ≥300 mg/m$^2$ had been given. In addition, dexrazoxane to doxorubicin dosage ratios of 20 : 1 and 10 : 1 have both proved effective in preventing anthracycline-induced cardiac toxicity. Thus, the optimal treatment regimen remains to be established. At present, the 10 : 1 dosage ratio is recommended in the US, whereas a ratio of 20 : 1 is recommended in Europe.

Preliminary results indicate that dexrazoxane is also beneficial in protecting against cardiac toxicity in children and adolescents receiving anthracycline-based chemotherapy for malignancy. However, it remains unclear whether the drug will be of benefit in the long term in terms of preventing late-onset cardiac toxicity.

Whether dexrazoxane is able to protect against late-onset cardiac toxicity is of particular importance given that anthracyclines are widely used to treat diseases that occur in young patients (i.e. sarcoma, lymphoma and acute leukaemia) in whom cardiac deterioration has the potential to cause significant impairment of quality of life and increased mortality.

Investigation of the cardioprotective effect of dexrazoxane in patients receiving high-dose chemotherapy regimens (e.g. in the treatment of soft tissue sarcomas where dose intensity of doxorubicin is directly related to patient outcome[72]) is warranted, as is its use in patients undergoing combination therapy with doxorubicin and paclitaxel in whom cardiac toxicity appears to be exacerbated.[73-75] In addition, it remains to be determined whether dexrazoxane will protect the myocardium from anthracyclines (other than doxorubicin and epirubicin) and anthracenediones.

An important property of chemoprotective agents is that they do not negate the clinical outcome of chemotherapy. Dexrazoxane was shown to significantly reduce the antitumour activity of doxorubicin in the largest placebo-controlled study but not in any other study (including one by the same investigators). Other measures of clinical outcome, including time to disease progression and median duration of survival were similar in dexrazoxane and placebo treatment groups.

Indeed, one would expect dexrazoxane administration to improve clinical outcome as the drug permits patients to continue anthracycline treatment beyond standard cumulative doses; however, further clinical experience is needed to determine whether longer term treatment with doxorubicin will translate into improved survival.

Another important property of chemoprotective agents is that they are well tolerated. Clinical trial data indicate that, with the exception of severe leucopenia, dexrazoxane does not increase the incidence of adverse events in patients receiving anthracycline-based chemotherapy. The incidence of severe leucopenia (ECOG grade 3/4) is significantly higher in dexrazoxane recipients than in those receiving placebo; however, the incidence of all other adverse events, including haematological and nonhaematological, is generally the same as that in patients receiving anthracycline-based chemotherapy alone.

Cardiac events resulting from anthracycline therapy are associated with significant additional healthcare costs, especially if the patient requires hospitalisation. Preliminary pharmacoeconomic analyses indicate that dexrazoxane is cost effective in patients with advanced breast cancer at risk of anthra-

cycline-induced cardiac toxicity. However, these findings, which were based on data from a retrospective analysis, require confirmation.

Thus, dexrazoxane is a unique agent that has been shown to significantly reduce anthracycline-induced cardiac toxicity whether administered at the beginning of chemotherapy or delayed until a cumulative dose of ≥ 300 mg/m$^2$ doxorubicin has been given. In addition to its efficacy in women with advanced breast cancer, dexrazoxane also appears effective in children and adolescents receiving anthracycline-based chemotherapy. Further clinical experience will determine its long term benefits in this patient group in terms of preventing late-onset cardiac toxicity. Further investigation is required to confirm that it does not adversely affect clinical outcome and that it is a cost-effective option. In addition, the optimal treatment regimen remains to be determined as well as its usefulness in preventing cardiac toxicity induced by other chemotherapy regimens.

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