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Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane®) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy

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Background: Anthracycline-induced cardiotoxicity has led to the adoption of empirical dose limits that may restrict continued use of anthracyclines among patients who might benefit. Dexrazoxane, a cardioprotective agent, has been shown to reduce the risk of anthracycline-associated cardiotoxicity when given from first dose of anthracycline. This study sought to confirm the benefit of dexrazoxane in patients at high risk of cardiotoxicity due to prior anthracycline use.

Patients and methods: A total of 164 female breast cancer patients, previously treated with anthracyclines, received anthracycline-based chemotherapy either with (n = 85) or without (n = 79) dexrazoxane for a maximum of six cycles.

Results: Compared with those receiving anthracycline alone, patients treated with dexrazoxane experienced significantly fewer cardiac events (39% versus 13%, $P < 0.001$) and a lower and less severe incidence of congestive heart failure (11% versus 1%, $P < 0.05$). Tumor response rate was unaffected by dexrazoxane therapy. The frequency of adverse events was similar between groups and there were no significant between-group differences in the number of dose modifications/interruptions.

Conclusion: Dexrazoxane significantly reduced the occurrence and severity of anthracycline-induced cardiotoxicity in patients at increased risk of cardiac dysfunction due to previous anthracycline treatment without compromising the antitumor efficacy of the chemotherapeutic regimen.

Key words: anthracycline, breast cancer, cardioprotection, clinical trial, dexrazoxane

introduction

Anthracyclines, used alone or in combination with other chemotherapeutic agents, are the mainstay of treatment for a number of cancers. However, their clinical usefulness is limited by cardiotoxicity. This is characterized by myocardial injury, markers of which can be detected in some patients from the first dose of anthracycline [1]. Endomyocardial biopsies and measurements of left ventricular ejection fraction (LVEF) have also revealed that subclinical cardiac abnormalities are evident from very low doses of anthracycline [2–4]. The cardiac damage is irreversible and potentially progressive with each subsequent dose of anthracycline. Impaired cardiac function can result in clinically overt disease manifest as congestive heart failure (CHF), which can occur in adult patients at any stage during or following treatment. The development of clinical signs of heart failure may result in severe, disabling morbidity and increased mortality.

To date, it has proved impossible to predict which patients are at risk of progressing to clinical CHF. Retrospective analyses estimate the overall incidence of CHF as 3%–5% at a total cumulative doxorubicin dose of 400 mg/m^2, increasing to 7%–26% at 550 mg/m^2 and up to 48% at 700 mg/m^2 [5, 6]. As the risk of developing CHF dramatically increases above a cumulative dose of 450–550 mg/m^2, this dose range is usually considered the maximum 'safe' cumulative dose for doxorubicin treatment (equivalent to a maximum cumulative epirubicin dose of 900–1100 mg/m^2). However, CHF has been reported at much lower doses, even following the first dose of doxorubicin [5], so the concept of a 'maximum safe dose' is a misnomer.

Several strategies have been investigated in an attempt to minimize anthracycline-induced cardiotoxicity: lowering total

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cumulative dose, altering the schedule of anthracycline administration, using less cardiotoxic analogs and the development of liposomal delivery systems. As outlined above, current practice involves discontinuing treatment with doxorubicin or epirubicin at a total cumulative dose of 450–550 mg/m^2 or 900–1100 mg/m^2, respectively. Consequently, clinicians may have to stop a treatment to which the tumor is responding. Furthermore, relapsed patients previously treated with anthracyclines may have to be treated with alternative, potentially less effective or less well-tolerated treatment regimens omitting anthracyclines. As the role of anthracyclines is expanding due to their effectiveness in combination with newer antitumor drugs (e.g. taxanes, trastuzumab) [7], the oncologist is faced with the dilemma of having to exclude one of the most effective anti-tumor agents in order to avoid potentially disabling and life-threatening cardiotoxicity.

The co-administration of the cardioprotective agent dexrazoxane (Cardioxane®, ICRF-187) with each dose of anthracycline has been shown to significantly reduce cardiotoxicity in several randomized controlled studies [3, 4, 8–14]. Dexrazoxane is thought to exert its cardioprotective effect through the chelation of iron, preventing the formation of anthracycline-iron complexes and the subsequent generation of free radicals that lead to oxidative damage to surrounding cardiac tissue. Unlike most other organs, the heart lacks adequate levels of scavenging mechanisms making it particularly susceptible to free-radical attack [15–17]. The mode of action of dexrazoxane is not tumor-specific and cardioprotection has been demonstrated in a number of tumor types [8, 12–14], including pediatric populations who are particularly prone to anthracycline-induced cardiotoxicity.

As advanced/metastatic breast cancer accounts for the largest population of patients treated with anthracyclines, the bulk of the evidence demonstrating cardioprotection with dexrazoxane has been obtained in this group [3, 4, 8–11]. With the exception of a subset of patients in one report [11], dexrazoxane was co-administered from the first dose of anthracycline in all of the previous randomized studies. However, patients with advanced/metastatic breast cancer who have received prior anthracycline-based chemotherapy are at an elevated risk of developing cardiotoxicity with further anthracycline treatment. A previous retrospective analysis suggested that dexrazoxane may still be effective as a cardioprotectant if administered following a previous cumulative dose of >300 mg/m^2 doxorubicin [9]. The patients in this retrospective analysis received dexrazoxane during the same course of treatment as the preceding cumulative dose of doxorubicin. The current prospective randomized controlled study was designed to confirm that patients who had received anthracyclines months or years previously would benefit from the cardioprotective effect of dexrazoxane on repeated exposure to anthracyclines.

patients and methods

patient eligibility

Women over the age of 18 years with confirmed advanced/metastatic breast carcinoma and a history of prior anthracycline exposure were enrolled in the study provided they: had progressive disease; had been anthracycline-free for at least 6 months prior to the start of the study; and had a LVEF considered normal according to the lower limit of the normal range in use in the center. Patients were excluded if they had experienced a myocardial infarction in the previous year, a history of uncontrolled angina pectoris, CHF, or symptomatic valvular heart disease. Prior treatment with androgens, progestins, estrogens, anti-estrogens (e.g. tamoxifen), corticosteroids or aromatase inhibitors was allowed, provided treatment was discontinued at least 2 weeks prior to study entry. Written informed consent was obtained for all patients.

This study was approved by the institutional review boards or ethics committees at each participating institution and was conducted in accordance with local regulations, the Declaration of Helsinki (1964 and subsequent revisions) and Good Clinical Practice according to the International Conference on Harmonization guidelines.

study design

In this multicenter, international, open-label, randomized, controlled phase III study, patients treated with anthracycline (doxorubicin or epirubicin)-based combination chemotherapy were randomly assigned either to receive or not receive concomitant dexrazoxane therapy. Randomization was performed centrally using a permuted-block design, which was stratified by center (and thus by type of anthracycline used and dose of dexrazoxane). Dexrazoxane was given from the first dose for a minimum of two cycles. Patients with stable disease, or better, continued their assigned treatment for a maximum of six cycles. Dexrazoxane was then administered on a compassionate basis to patients who, in the investigators opinion, benefited from the continuation of the anthracycline-containing chemotherapy. Appropriate supportive therapies, including hematopoietic growth factors, were given according to each institute's routine. All patients at each individual institution received the same chemotherapy regimen, as approved by the institute's treatment review committee.

treatment

Thirty minutes before infusion of the anthracycline, dexrazoxane was infused intravenously over approximately 15 min at a 20:1 dexrazoxane:doxorubicin dose ratio, or at a 10:1 dexrazoxane: epirubicin dose ratio. Treatment cycles were repeated every 3 weeks provided the neutrophil count was $\geq 1.5 \times 10^9$/l and the platelet count was $\geq 100 \times 10^9$/l, otherwise both dexrazoxane and anthracycline treatment were delayed until hematological recovery. If the neutrophil and platelet count was $<1 \times 10^9$/l and $<75 \times 10^9$/l, respectively, treatment was withheld. The doses were reduced by 50% in case of a bilirubin value between 1.5 and 3.0 mg/dl and by 75% for a value more than 3.0 mg/dl. Treatment was discontinued if patients developed progressive disease, clinical signs of CHF, experienced a cardiac event or unacceptable toxicity.

Dexrazoxane was provided by Chiron BV (Amsterdam, The Netherlands). Each vial contained 500 mg lyophilized powder and was reconstituted with 25 ml sterile water. The dexrazoxane solution was diluted by a further 25–100 ml per vial with either Ringer's lactate or sodium lactate solution according to the manufacturer's instructions.

monitoring

Prior to starting therapy, all eligible patients underwent cardiac assessment, tumor assessment, physical examination, evaluation of medical history and performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) criteria, and routine hematology and serum chemistries. Hematology, serum chemistries, performance status and adverse events graded according to Common Toxicity Criteria (CTC) version 2.0 were also assessed before each cycle and at the first follow-up visit (within 30–45 days after treatment completion).

Cardiac evaluation consisted of physical examination, multiple-gated acquisition (MUGA) scan or echocardiography (both confirmed by

a repeated measurement), blood pressure measurements, ECG and chest X-rays (the latter two at the discretion of the investigator). Cardiac assessments were performed every other cycle during treatment up to a cumulative dose of 500 mg/m^2 doxorubicin or 900 mg/m^2 epirubicin inclusive; thereafter, a cardiac evaluation was performed with every cycle. Cardiac assessments were also performed at the first follow-up visit and during long-term follow up (3 monthly during first 2 years and 6 monthly during the next 3 years).

Tumor assessment was performed using X-rays, CT scan, MRI, echography or scintigraphy. Whenever possible, a bidimensional measurement was performed. Tumor status was assessed every 6–8 weeks during treatment, at the first follow-up visit and during long-term follow up.

evaluation of a cardiac event

The primary efficacy parameter was the incidence of cardiac events. A cardiac event was defined as: a reduction in LVEF by 10% absolute percentage points or more as measured by MUGA scan or 15% or more as measured by echocardiography; reduction in absolute LVEF, as measured by MUGA scan or echocardiography, to a value below 45%; or the appearance of clinical signs of cardiac insufficiency (graded according to the New York Heart Association classification of cardiac status) [18]. For each individual patient, the same method (MUGA scan or echocardiography) was used throughout the study; echocardiography was performed by the same operator on each occasion.

Cardiac event-free survival was defined as the time from the date of first study treatment until the date a cardiac event was first noted. An independent adjudication committee, who were blinded to treatment, evaluated the primary end point.

evaluation of tumor response

Tumor response was assessed according to disease presentation (measurable disease, bone metastasis) and/or tumor markers. In case of a difference in response, the most conservative outcome determined the overall response. Tumor response was measured and assessed according to standard WHO criteria for measurable and evaluable disease [19]. Overall survival was defined as the time from first date of study treatment to death or the date of last contact for living patients. Progression-free survival was defined as the time from first date of complete response (CR), partial response (PR) or stable disease (SD) until the date progressive disease (PD) was first noted.

statistical analysis

All analyses were conducted at the two-sided 5% significance level. The primary end point was the incidence of cardiac events as defined above. The study had an 80% power to detect a decrease of at least 20% in the proportion of patients with a cardiac event between the control and dexrazoxane groups. Secondary analyses included the incidence of CHF, response, cardiac event-free survival, progression-free survival, overall survival and adverse events. All of the randomized patients received at least one dose of assigned study treatment and were included in the exposure and safety analysis. Efficacy analyses were based on the intent-to-treat (ITT) population (all randomized patients who had at least one post-baseline echocardiography or MUGA scan or had at least one evaluable cardiac event assessment performed by the adjudication committee) and the per-protocol (PP) population (patients who received at least two cycles of chemotherapy and were treated without any major protocol violations).

Statistical comparison between the two treatment groups for categorical variables was made with the Pearson's chi-square test or the Fisher's exact test, as appropriate. Changes from baseline LVEF were summarized by cycle and tested using ANOVA with treatment arm as the independent factor. For all survival times and the total doxorubicin-equivalent dose until occurrence of cardiac event, distributions were estimated from pooled data across centers by the Kaplan–Meier method and treatment differences were assessed using the log-rank test. Where appropriate, the 95% confidence interval for proportions was calculated by the Clopper–Pearson formula. Adverse events were coded using MedDRA, version 2.4 or higher.

The total cumulative anthracycline dose was calculated by adding the total cumulative dose before study entry to the cumulative dose administered during the study until the time a cardiac event occurred (or the end of the study for patients who did not have a cardiac event). The dose of epirubicin was converted to doxorubicin-equivalent dose: 50 mg doxorubicin ≡ 90 mg epirubicin.

results

Thirty-six centers in the Czech Republic, France, Germany, Poland, South Africa and Spain enrolled 164 breast cancer patients between December 2000 and September 2003. All of the patients were randomized to receive either anthracycline (doxorubicin or epirubicin)-based combination chemotherapy with ($n = 85$) or without ($n = 79$) concomitant dexrazoxane. No post-baseline cardiac assessment was available for 11 patients, therefore 153 patients were included in the ITT analysis. The results of the per-protocol analysis ($n = 140$) were similar and have not been shown.

patients

Demographic factors and disease status of patients in both groups were comparable at baseline (Table 1). The median age of all patients was 52 years (range 30–76 years), and the majority of patients were Caucasian, non-smokers and had an ECOG PS of 0–1. The median time between relapse and start of treatment was 4.8 months (range 0.1–200 months). All patients had received prior systemic therapy, and the median cumulative anthracycline dose received before study entry was similar in both groups. The proportion of patients receiving doxorubicin or epirubicin in either group exceeded 100% indicating that some patients received both types of anthracycline during the course of their treatment.

All six cycles of study treatment were administered to 49 patients (58%) in the dexrazoxane group and 36 patients (46%) in the control group. Primary reasons for premature withdrawal from the study are listed in Table 2. Fewer patients discontinued treatment due to adverse events in the dexrazoxane group than in the control group (11% versus 19%, respectively). In most cases, the adverse event causing study discontinuation was a decrease in LVEF (dexrazoxane group, 5% versus control group, 13%).

evaluation of cardiac protection

Significantly fewer cardiac events occurred in the dexrazoxane group compared with the control group ($P < 0.001$). Ten patients (13%, 95% CI 6% to 22%) receiving dexrazoxane experienced a cardiac event versus 29 patients (39%, 95% CI 28% to 51%) in the control group, translating into a relative risk reduction of 68% (Figure 1A).

Significantly fewer cases of CHF occurred in the dexrazoxane group ($P = 0.015$) and these cases were less severe than those experienced by the control group. One patient (1%, 95% CI 0.032% to 7%) in the dexrazoxane group developed CHF (NYHA grade 2) versus eight patients (11%, 95% CI 5% to

Table 1. Patient characteristics

Characteristic	Control group (n =79)	Dexrazoxane group (n = 85)
Age, years		
Median (range)	52 (30–71)	50 (31–76)
Weight, kg		
Median (range)	68 (36–118)	65 (44–100)
Race, n (%)		
Caucasian	69 (87)	73 (86)
Black	5 (6)	7 (8)
Other	1 (1)	2 (2)
Smoker, %		
Yes/No	9/90	12/84
ECOG PS, n (%)		
0	38 (48)	35 (41)
1	35 (44)	43 (51)
2	5 (6)	7 (8)
RTI (months)		
Median (range)	6.9 (0.2–200)	3.7 (0.1–158)
Primary tumor[a], n (%)		
T1	15 (19)	17 (20)
T2	37 (47)	47 (55)
T3	9 (11)	12 (14)
T4	13 (16)	5 (6)
Stage at first diagnosis[b], n (%)		
I	11 (14)	11 (13)
II	42 (53)	48 (56)
III	13 (16)	19 (22)
IV	11 (14)	5 (6)
Prior surgery, n (%)	72 (91)	82 (96)
Prior radiotherapy, n (%)	62 (78)	74 (87)
Prior systemic therapy, n (%)	79 (100)	85 (100)
Prior anthracycline therapy, n (%)		
Doxorubicin	44 (56)	46 (54)
Epirubicin	38 (48)	42 (49)
Prior cumulative anthracycline dose (mg)		
Doxorubicin, median (range)	243 (60–480)	290 (30–650)
Epirubicin, median (range)	360 (94–599)	421 (231–599)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; RTI, time interval between relapse and start of treatment.
[a]T0 for two patients in the DEX + chemotherapy group; not available or not assessable for two patients in the DEX + chemotherapy group and for five patients in the chemotherapy-only group.
[b]Not available for four patients, two in each group.

Table 2. Summary of premature withdrawal from study

Reason for premature withdrawal	Control group, n (%) (n = 79)	Dexrazoxane group, n (%) (n = 85)
Total	43 (54)	36 (42)
Death	3 (4)	5 (6)
Adverse event	15 (19)	9 (11)
Withdrawal of consent	3 (4)	4 (5)
Unsatisfactory therapeutic response	2 (3)	0
Disease progression	13 (16)	14 (16)
Other	7 (9)	4 (5)

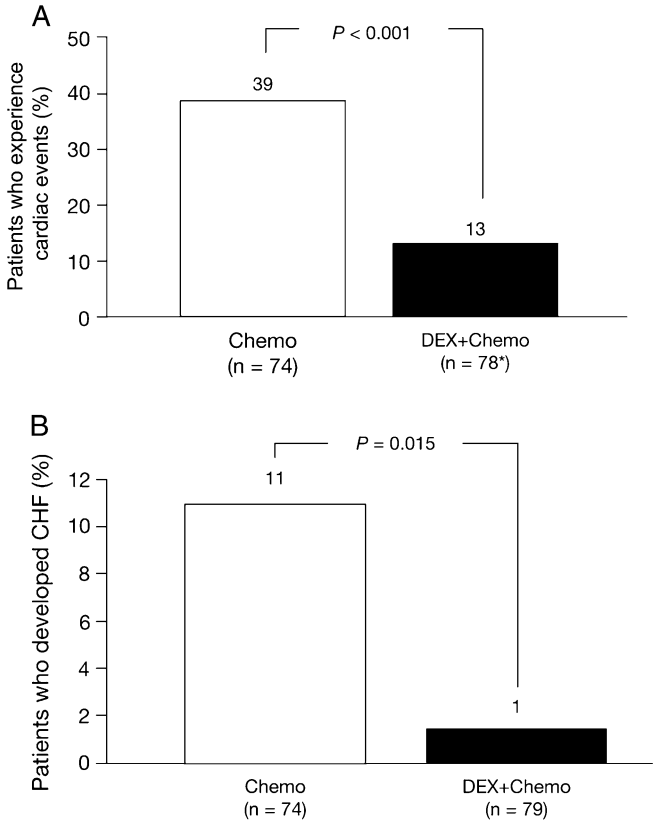

Figure 1. (**A**) Incidence of cardiac events. (**B**) Incidence of CHF. *One patient did not have evaluable data.

20%,) in the control group (one NYHA grade 2, three NYHA grade 3 and four NYHA grade 4), a relative risk reduction of 88% (Figure 1B). At the time of developing CHF, the cumulative doses that patients had received were 346 mg/m^2 doxorubicin in the dexrazoxane group versus 255, 550, 600, 612 and 661 mg/m^2 doxorubicin and 892, 1195 and 1200 mg/m^2 epirubicin in the control group. Furthermore, patients in the dexrazoxane group had a significantly longer cardiac event-free survival time [median, not reached for dexrazoxane (range 0.8–28+ months) versus 7.1 months (range 1.3–13.4+ months) for control, P = 0.004; Figure 2A] and received significantly higher total cumulative anthracycline doses prior to the occurrence of a cardiac event [median, not reached for dexrazoxane (range 294–936+ mg/m^2) versus 833 mg/m^2 (range 298–900+ mg/m^2) for control, P = 0.001; Figure 2B] compared with those receiving chemotherapy only.

A sub-group analysis was performed on those patients receiving either doxorubicin or epirubicin (Table 3). While this was not planned as part of the primary analysis and should be interpreted accordingly, the results were similar for both groups.

response and survival to chemotherapy

Overall response rates (CR + PR) were similar in both treatment groups: 35% (95% CI 25% to 46%) for the dexrazoxane group compared with 35% (95% CI 25% to 47%) for the control group (Table 4). There was also no statistically significant

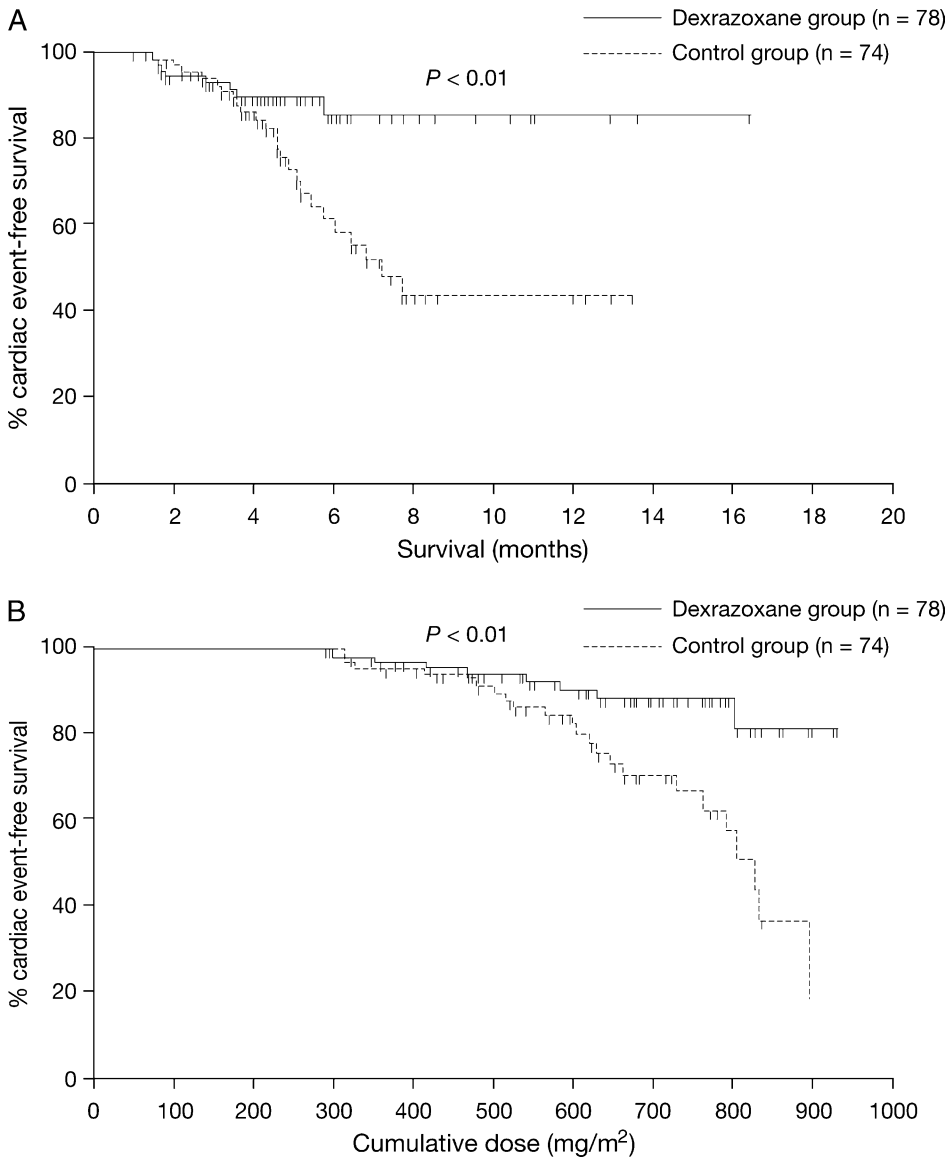

Figure 2. Kaplan–Meier analysis of (**A**) cardiac event-free survival and (**B**) total cumulative anthracycline dose until occurrence of a cardiac event.

difference in either progression-free survival or overall survival (Table 4, Figure 3).

exposure to study treatment

Patients in the two groups received a similar number of treatment cycles, although the proportion of patients completing six cycles was higher in the dexrazoxane group (58% versus 46%). The median number of treatment cycles, days spent on study and the doses of anthracycline received were comparable between groups (Table 5). Overall, 27 (32%) patients in the dexrazoxane group and 21 (27%) patients in the control group required dose modifications/interruptions; the difference was not statistically significant ($P = 0.47$). Where the dose was modified, this was due to hematological toxicity in 25% and 16% of cases in the dexrazoxane and control groups, respectively ($P = 0.19$). Neutropenia was the most frequent cause of dose modification/interruption in the dexrazoxane group.

evaluation of safety

The main adverse events are listed in Table 6. The majority of patients experienced at least one adverse event, with the most common being alopecia, nausea, neutropenia, vomiting, leukopenia and anemia. The incidence of adverse events was comparable between the two groups with the possible exceptions of anemia, which appeared more frequent in the dexrazoxane group, and asthenia and mucosal inflammation, which appeared more frequently in the control group. Neutropenia was the most common grade 3/4 toxicity, occurring in approximately one-third of patients in either group. Twenty-two patients (28%) in the control group and 31 patients (36%) in the dexrazoxane group also experienced

Table 3. Doxorubicin and epirubicin subgroup analysis: cardiac evaluation (intent-to-treat population)

	Treatment group			
	Doxorubicin + dexrazoxane	Doxorubicin (control)	Epirubicin + dexrazoxane	Epirubicin (control)
Incidence of cardiac events				
Number	6	17[a]	4	12[b]
Percentage	12%	37%	14%	43%
95% CI	5%–25%	23%–52%	4%–32%	24%–63%
N	49	46	29	28
Incidence of clinical congestive heart failure				
Number	1	5[c]	0	3[d]
Percentage	2%	11%	0%	11%
95% CI	0.051%–11%	4%–24%	0%–12%	2%–28%
N	50	46	29	28

CI, confidence interval.

P values for testing the difference between the active and control arms: [a]$P = 0.005$; [b]$P = 0.015$; [c]$P = 0.10$; [d]$P = 0.11$.

Table 4. Antitumor response in all patients randomized to treatment

Variable	Control group ($n = 79$)	Dexrazoxane group ($n = 85$)
	No. (%)	
Complete response	3 (4)	6 (7)
Partial response	25 (32)	24 (28)
Stable disease	30 (38)	25 (29)
Progressive disease	16 (20)	21 (25)
Not evaluable	5 (6)	9 (11)
	Median (range)	
PFS, months	7.0 (0.7–9.3)	7.8 (0.7–12.7+)
OS[a], months	16.0 (0.5–25.3)	13.5 (0.2–27.8+)

PFS, progression-free survival; OS, overall survival.

[a]Control group, $n = 63$; dexrazoxane group, $n = 68$.

at least one serious adverse event; the incidence was similar for both groups, although febrile neutropenia appeared to be slightly higher among dexrazoxane-treated patients (16% versus 11%, respectively).

Six deaths occurred within 28 days of the final administration of chemotherapy: four in the dexrazoxane group and two in the control group. None of the deaths were considered to be dexrazoxane-related by the investigator. Underlying causes in the dexrazoxane group included one case each of pulmonary embolism, metastatic disease, respiratory insufficiency and deep vein thrombosis. The deaths in the control group were due to respiratory insufficiency and septicemia with cardiac failure. There were no differences between groups with respect to biochemical or hematological laboratory measurements.

discussion

Randomized controlled studies in various cancers have clearly demonstrated that dexrazoxane is effective in reducing cardiotoxicity associated with anthracycline use [3, 4, 8–14]. However, in nearly all of these studies, dexrazoxane was administered from the first dose of anthracycline onwards. The current study confirms the cardioprotective effect of dexrazoxane in a group of patients with existing subclinical myocardial damage secondary to prior anthracycline exposure. It builds upon the previous work of Swain et al. [9, 10], who demonstrated the advantage of administering dexrazoxane after a cumulative doxorubicin dose of >300 mg/m^2 rather than administering doxorubicin alone. Although an important study, the analysis was retrospective, and therefore less authoritative than the current study. In addition, the patients in the current study had a gap of months or years between previous anthracycline exposure and the use of dexrazoxane as a cardioprotectant.

Dexrazoxane significantly decreased the incidence of cardiac events ($P < 0.001$), including CHF ($P < 0.05$), in this high-risk group of patients. The addition of dexrazoxane resulted in an approximately three-fold decline in the risk of developing a cardiac event while the risk of developing CHF was reduced by nearly 90%. This benefit is comparable with the 76% overall risk reduction in CHF that was estimated in a recent meta-analysis [20] of several large controlled randomized studies of patients treated with doxorubicin or epirubicin where dexrazoxane was given from the first dose of anthracycline.

Not only was the incidence of CHF significantly lower in the dexrazoxane group, but the CHF was also less severe than that in the control group. Although one patient receiving dexrazoxane developed CHF, it was milder (NYHA grade 2) in comparison with the CHF experienced by patients in the control group. Seven of eight patients in the control group had CHF of NYHA grade 3 or 4 severity. Similar results have been reported previously [4, 11]. Identifying which patients will develop CHF is difficult to predict and this has resulted in conventional dose limits being adopted in clinical practice. However, this study clearly demonstrates that CHF occurs even in patients who have received anthracycline doses below conventional limits. Furthermore, while not the focus of this study, examination of the LVEF measurement prior to the CHF event suggests that LVEF is a poor indicator of CHF onset; only one patient showed a substantial reduction from baseline in LVEF prior to developing CHF, while it was inconclusive in two patients because of non-compliance with the cardiac monitoring protocol.

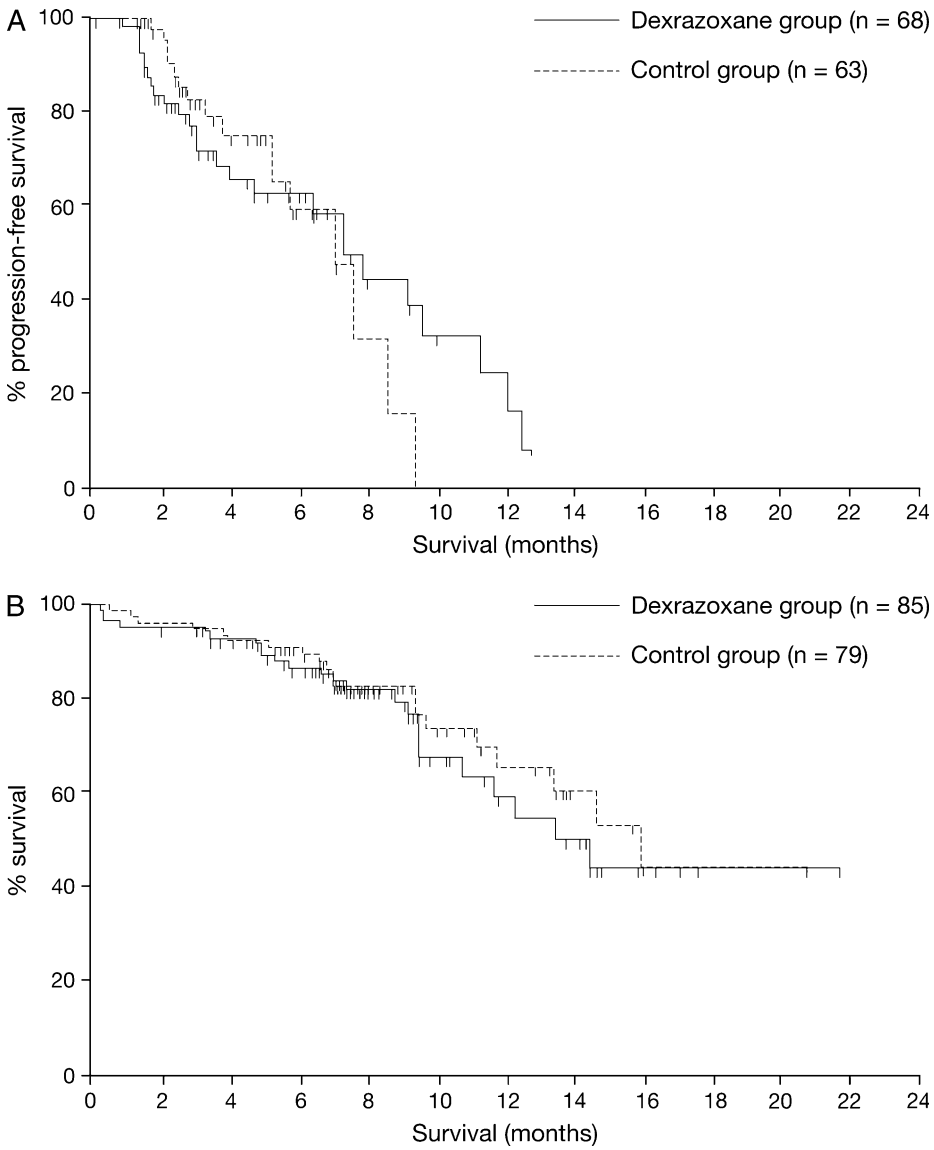

Figure 3. Kaplan–Meier analysis of (**A**) progression-free survival and (**B**) overall survival.

Table 5. Patient exposure to treatment during study

Patient exposure	Control group (n = 79)	Dexrazoxane group (n = 85)
	Median (range)	
Days on study	118 (15–252)	133 (7–211)
No. of cycles received	5.0 (1–6)	6.0 (1–6)
Total cumulative anthracycline[a,b] dose (mg)	608 (244–900)	669 (247–936)
Average anthracycline[b] dose per day (mg)	80 (40–120)	80 (37–116)

[a]Includes pre-study cumulative anthracycline dose.
[b]The epirubicin dose is converted to doxorubicin-equivalent dose: 50 mg doxorubicin ≡ 90 mg epirubicin.

Longer-term follow up of the current study will enable the outcome of the patients with CHF to be determined. However, it is widely accepted that quality of life is greatly impaired in people with CHF compared with the general population, as well as people with other chronic conditions, such as chronic lung disease and arthritis [21, 22]. Moreover, deterioration in quality of life increases with the severity of heart failure; patients with more severe heart failure have greater limitation of social functioning and more severe impairment of the measures of mental health than those with mild heart failure [21, 22]. Thus, dexrazoxane can potentially improve daily functioning and the quality of life of patients treated with anthracyclines. By decreasing cardiotoxicity, dexrazoxane may also alleviate the burden on medical resources, as treatment of cardiac events induced by anthracycline therapy results in substantial healthcare costs, especially if hospitalization is required. A preliminary pharmacoeconomic analysis in the US [23]

Table 6. Adverse events

Adverse event	% of patients			
	Control group (n = 79)		Dexrazoxane group (n = 85)	
	All	Grade 3/4	All	Grade 3/4
Anemia	24	6	34	7
Febrile neutropenia	15	14	19	18
Leukopenia	28	18	34	20
Neutropenia	39	35	40	38
Thrombocytopenia	13	0	16	1
Constipation	18	0	14	1
Diarrhoea	20	1	18	1
Stomatitis	11	3	9	0
Nausea	43	6	44	1
Vomiting	32	8	35	1
Asthenia	29	3	16	2
Fatigue	18	1	16	3
Mucosal inflammation	28	1	14	0
Pyrexia	18	0	14	2
Ejection fraction decreased	19	1	13	0
Alopecia	57	18	49	21
Bone pain	10	5	1	0
Febrile bone marrow aplasia	1	1	5	5

indicated that dexrazoxane is cost effective: the cost of dexrazoxane therapy per life-years gained was low ($US2809 per life-year gained) in comparison with other standard life-saving medical interventions ($US19 000 per life-year gained) [24].

This study also showed that dexrazoxane enabled the safe administration of anthracycline-based chemotherapy in patients previously exposed to anthracyclines. Dexrazoxane may, therefore, support optimal anthracycline therapy by facilitating both the completion of the full schedule, as well as retreatment with anthracycline-based therapy among patients who relapse. There is data suggesting that the use of higher doses of anthracyclines may improve survival in some cancers [25–28]; the addition of dexrazoxane could enable the use of higher doses with these treatments. Of particular interest is the possible combination of anthracyclines with newer agents (e.g. taxanes, herceptin etc.). These combinations are associated with high response rates, but also increased cardiotoxicity [29]. Dexrazoxane could potentially improve the risk/benefit ratios of these treatments; the results of this study support the rationale for further investigation of these combinations.

The addition of dexrazoxane did not reduce the efficacy of the anthracycline regimen in this study; there was no significant difference in tumor response rates with an overall rate of 35% observed in both groups. Although progression-free survival and overall survival appeared to favor the dexrazoxane group and control group, respectively, the between-group differences did not reach statistical significance. These data need to be confirmed in longer-term follow-up. These findings are consistent with those of other studies [4, 8, 10, 11] and a recent meta-analysis of previous randomized trials (n = 818) [16], which all show that dexrazoxane does not interfere with the efficacy of anthracyclines. Only one study has reported a diminished response rate to anthracyclines with the addition of dexrazoxane [10]. The current data add to the body of evidence that the results of this single study were an anomalous statistical finding, especially as the progression-free and overall survival in this study were not affected. The lack of effect of dexrazoxane on the efficacy of anthracyclines confirms expectations arising from the understanding of their mechanisms of action, as well as findings in *in vitro* and animal models [30, 31]. In addition, while the overall tumor response rates were relatively low in both arms (35%) compared with previous published studies [3, 8–10], this may be explained by the fact that some patients were receiving the selected regimen as a second (or subsequent)-line treatment for metastatic disease. All of the patients had been previously treated with anthracyclines, either at the adjuvant or metastatic stage.

Administration of dexrazoxane did not produce any new toxicity and did not exacerbate anthracycline-induced toxicities, except for a slight increase in the incidence of anemia and aggravation of febrile neutropenia. In most cases, these toxicities were mild-to-moderate and manageable with appropriate treatment when required. There was no difference in anthracycline dose reductions or delays between the two groups. More patients in the dexrazoxane group than the control group completed the maximum of six cycles of therapy stipulated by the protocol.

A limitation of this study could be that the licensed doses of doxorubicin and epirubin differ; therefore, different (prospectively defined) doses of dexrazoxane had to be administered according to the anthracycline treatment regimen (20:1 dexrazoxane: doxorubicin or 10:1 dexrazoxane:epirubicin dose ratio). However, as shown in Table 3, a doxorubicin and epirubicin subgroup analysis of cardiac events and CHF incidence confirms that the differing treatment regimens had no apparent effect on the results.

In conclusion, this study confirms that dexrazoxane is cardioprotective, not only when given from the first dose of anthracycline, but also in patients with advanced/metastatic breast cancer who are at high risk of cardiotoxicity due to previous anthracycline treatment. Dexrazoxane allows the safe administration of anthracyclines without compromising their efficacy. By allowing the safe and optimal use of anthracycline therapies, dexrazoxane can potentially offer oncologists broader therapeutic options and cancer patients an improved quality of life.

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references

1. Lipshultz SE, Rifai N, Sallan SE et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997; 96: 2641–2648.
2. Ewer MS, Ali MK, Mackay B et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving adriamycin. J Clin Oncol 1984; 2: 112–117.
3. Speyer JL, Green MD, Kramer E 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.
4. Speyer JL, Green MD, Zeleniuch-Jacquotte A et al. ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol 1992; 10: 117–127.
5. Von Hoff DD, Layard MW, Basa P et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91: 710–717.
6. Swain SM, Whaley FS, Ewer MS et al. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003; 97: 2869–2879.
7. Swain SM, Vici P. The current and future role of dexrazoxane as a cardioprotectant in anthracycline treatment: expert panel review. J Cancer Res Clin Oncol 2004; 130: 1–7.
8. Lopez M, Vici P, Di Lauro K et al. Randomized prospective clinical trial of high-dose epirubicin and dexrazoxane in patients with advanced breast cancer and soft tissue sarcomas. J Clin Oncol 1998; 16: 86–92.
9. Swain SM, Whaley FS, Gerber MC et al. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. J Clin Oncol 1997; 15: 1333–1340.
10. Swain SM, Whaley FS, Gerber MC et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997; 15: 1318–1332.
11. Venturini M, Michelotti A, Del Mastro L et al. 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.
12. Lipshultz SE, Rifai N, Dalton VM et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med 2004; 351: 145–153.
13. Wexler LH, Andrich MP, Venzon D et al. Randomized trial of the cardioprotective agent icrf-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 1996; 14: 362–372.
14. Feldmann JE, Jones SE, Weisberg SR et al. Advanced small cell lung cancer treated with CAV (cyclophosphamide + Adriamycin® + vincristine) chemotherapy and the cardioprotective agent dexrazoxane (ADR-529, ICRF-187, Zinecard®). Proc Ann Meet Am Soc Clin Oncol 1992; 11: AA93.
15. Herman EH, Ferrans VJ. Amelioration of chronic anthracycline cardiotoxicity by icrf-187 and other compounds. Cancer Treat Rev 1987; 14: 225–229.
16. Green MD, Alderton P, Gross J et al. Evidence of the selective alteration of anthracycline activity due to modulation by ICRF-187 (ADR-529). Pharmacol Ther 1990; 48: 61–69.
17. Hasinoff BB. The interaction of the cardioprotective agent ICRF-187 [+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane); its hydrolysis product (ICRF-198); and other chelating agents with the Fe(iii) and Cu(ii) complexes of adriamycin. Agents Actions 1989; 26: 378–385.
18. Criteria Committee of New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels (8th edn). Boston, MA: Little Brown 1979.
19. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–214.
20. Seymour L, Bramwell V, Moran LA. Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer. The provincial systemic treatment disease site group. Cancer Prev Control 1999; 3: 145–159.
21. Juenger J, Schellberg D, Kraemer S et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 2002; 87: 235–241.
22. Hobbs FD, Kenkre JE, Roalfe AK et al. Impact of heart failure and left ventricular systolic dysfunction on quality of life: A cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. Eur Heart J 2002; 23: 1867–1876.
23. Bates M, Lieu D, Zagari M et al. A pharmacoeconomic evaluation of the use of dexrazoxane in preventing anthracycline-induced cardiotoxicity in patients with stage iiib or iv metastatic breast cancer. Clin Ther 1997; 19: 167–184.
24. Tengs TO, Adams ME, Pliskin JS et al. Five-hundred life-saving interventions and their cost-effectiveness. Risk Anal 1995; 15: 369–390.
25. Stockler M, Wilcken N, Coates A. Chemotherapy for metastatic breast cancer–when is enough enough? Eur J Cancer 1997; 33: 2147–2148.
26. Fumoleau P, Kerbrat P, Romestaing P et al. Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positive breast cancer patients: 10-year follow-up results of the french adjuvant study group 01 trial. J Clin Oncol 2003; 21: 298–305.
27. Ejlertsen B, Pfeiffer P, Pedersen D et al. Decreased efficacy of cyclophosphamide, epirubicin and 5-fluorouracil in metastatic breast cancer when reducing treatment duration from 18 to 6 months. Eur J Cancer 1993; 29A: 527–531.
28. Biganzoli L, Piccart MJ. The bigger the better? Or what we know and what we still need to learn about anthracycline dose per course, dose density and cumulative dose in the treatment of breast cancer. Ann Oncol 1997; 8: 1177–1182.
29. Gianni L, Munzone E, Capri G et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 1995; 13: 2688–2699.
30. Pearlman M, Jendiroba D, Pagliaro L et al. Dexrazoxane in combination with anthracyclines lead to a synergistic cytotoxic response in acute myelogenous leukemia cell lines. Leuk Res 2003; 27: 617–626.
31. Imondi AR. Preclinical models of cardiac protection and testing for effects of dexrazoxane on doxorubicin antitumor effects. Semin Oncol 1998; 25 (4 Suppl 10): 22–30.