Clinical Status and Optimal Use of the Cardioprotectant, Dexrazoxane

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Anthracycline antibiotic use is limited by cardiac toxicity. The risk factors are cumulative dose, radiation to the chest and mediastinum, age, and preexisting myocardial impairment. Dexrazoxane (Zinecard) can prevent

Introduction

The anthracycline antitumor antibiotics are important chemotherapeutic agents for the treatment of leukemias, lymphomas, breast cancer, myeloma, small-cell lung cancer, sarcomas, bladder cancer, and pediatric solid tumors. However, the clinical usefulness of the anthracycline antibiotics is limited by their cardiac toxicity, and clinicians confront a clinical dilemma as they balance the efficacy of longer duration of treatment against the cardiac toxicity associated with cumulative doses.

Clinicians now have an option to prevent cardiac toxicity by using dexrazoxane (Zinecard). Dexrazoxane prevents anthracycline-induced cardiac toxicity and is indicated when anthracycline-induced cardiac myopathy is a clinical concern.

Clinical Features of Cardiac Toxicity

Cancer-Related Cardiac Toxicity
Cardiac complications of cancer are a common clinical problem and can result from underlying cardiac disease and the secondary effects of cancer and cancer treatment. The primary cardiac complications of cancer are arrhythmias due to tumor involvement of the heart or pericardium, pericardial effusion, and/or underlying ischemic coronary artery disease exacerbated by the anemia, hypoxia, and/or stress associated with cancer and cancer treatment.

Cancer Treatment-Related Cardiac Toxicity
The anthracycline antitumor antibiotics are the most common cause of cardiac complications of cancer treatment. Daunomycin (daunorubicin ([Cerubidine]), the first anthracycline antibiotic, was noted to be cardiotoxic in the late 1960s. When doxorubicin was introduced in the early 1970s, Blum et al summarized the data from the initial clinical trials and reported on a cumulative dose-associated congestive heart failure and cardiomyopathy.[1] Von Hoff et al reported a retrospective study of 5,613 patients treated with daunorubicin and 4,018 patients treated with doxorubicin and demonstrated a continuous exponential increase in the incidence of cardiac failure with increasing cumulative doses.[2] Bingham et al reported a progressive endomyocardial structural lesion associated with cumulative doses of doxorubicin.[3] They demonstrated the histology and ultrastructure of an anthracycline-induced cardiac lesion with two distinct types of damage. The first was myofibrillar loss, which, with increasing doses, progressed to complete loss. The second was vacuolar degeneration, which was thought to be a consequence of damage to the sarcoplasmic reticulum. These histopathologic changes could be focal or more widely disseminated.

It was assumed that both types of lesions represented a progressive process of mitochondrial swelling and degeneration, myelin fragmentation, nuclear disintegration, and eventual cell death. These observations led to the histopathologic classification and grading of anthracycline myocardial damage based on a continuum of observable damage, ranging from grade 0 (representing no damage) to grade 4 (associated with maximal myofibrillar loss). The assumption is that histopathologic damage is linearly related to dose, but that functional deterioration is exponential when cardiac compensatory mechanisms can no longer overcome the effects of myocardial dropout.

Anthracycline Cardiac Toxicity
The clinical features of anthracycline cardiac toxicity are acute, subacute, or late. Bristow et al[4] first described an acute toxicity as myopericarditis due to acute myocyte damage and/or the effects
of catecholamine and histamine release induced by the anthracycline. This acute toxicity occurs within the first days after administration and is associated with transient arrhythmias, pericardial effusion, and myocardial dysfunction, which can result in transient congestive heart failure and occasionally, sudden death. Histopathologically, there is acute myocyte disruption and cellular infiltration of the myocardium that is distinguishable from that associated with chronic toxicity. The cardiac toxicity usually associated with anthracyclines tends to be more chronic than acute. The retrospective study by Von Hoff et al described the exponential increase in clinical manifestations of cardiac toxicity with increasing cumulative dose.[2] Other risk factors include age, with patients over 70 at higher risk; chest irradiation, in particular, mediastinal irradiation; and prior cardiomyopathic disease. The impact of coronary artery disease on anthracycline cardiomyopathy is less evident. There is no statistically valid multivariate analysis of cardiac disease factors and the risk of anthracycline-induced cardiomyopathy. If the pathophysiology of anthracycline cardiotoxicity is assumed to be cardiomyopathy, then patients with a history of coronary artery disease, including infarction, and with normal left-ventricular ejection, are not thought to be at higher risk of anthracycline-induced cardiomyopathy and clinical congestive heart failure. On the other hand, it has become standard practice to assume that there is an increased risk of anthracycline cardiomyopathy in patients who have had a myocardial infarction within the past year. The clinical manifestations of cardiotoxicity can be insidious, appearing weeks to months after administration of the last dose. Von Hoff et al described the clinical picture of increasing tachycardia, fatigue, tachypnea, dyspnea, and, in extreme cases, pulmonary edema and right-sided congestive heart failure from low cardiac output.[2]

There is also a delayed anthracycline cardiomyopathy in the pediatric population. Steinherz et al[5-7] described children who, 5 or more years after anthracycline therapy, developed late clinical decompensation with abnormal systolic cardiac function and/or an abdominal cardiac mass. The pathology is different from adults, consisting predominantly of fibrosis and hypertrophy of remaining myocytes with little vacuolization.

Concurrent administration of other cytotoxic drugs has also been associated with an increased incidence of anthracycline cardiomyopathy, but it is not known whether these are additive or synergistic effects on the final common pathway of myocardial damage. For example, Gianni et al reported a higher than expected incidence of cardiac toxicity when doxorubicin was combined with paclitaxel (Taxol).[8] Subsequent studies are underway to confirm this observation.

Mitoxantrone-Related Cardiac Toxicity
Mitoxantrone is an anthracenedione, not an anthracycline, that is structurally similar to doxorubicin. It causes cardiac toxicity by interaction with iron similar to that of doxorubicin, but with little evidence supporting production of free radical pair oxidation. As with doxorubicin, there is increased incidence of myocardial-dysfunction cardiac failure associated with increasing cumulative doses of mitoxantrone. Decreases in ejection fraction have been observed in patients at cumulative doses of more than 110 mg/m², with incidences of cardiac failure in patients who received cumulative doses of more than 160 mg/m².[10] A prior dose of an anthracycline, particularly doxorubicin, increases the probability of congestive failure at lower cumulative mitoxantrone doses.

Monitoring and Treatment of Anthracycline Cardiomyopathy
Alexander et al and others monitored left-ventricular ejection fraction (LVEF) by using multiple-gated radionuclide angiography (MUGA). Serial LVEF measurements reflected changes in myocardial function resulting from anthracycline-induced myocardial damage. Decreases in LVEF of more than 15% and/or an LVEF value less than 45% are predictive of subsequent congestive heart failure and, therefore, can be used to monitor patients who are receiving anthracyclines.

The treatment of anthracycline-induced cardiomyopathy is the same as the treatment of other dilated cardiomyopathies. The primary mode of treatment is supportive care, including diuresis, digitalis and, more recently, the use of angiotensin-converting enzyme (ACE) inhibitors. The Agency for Health Care Policy and Research (AHCPR) recommends the use of ACE inhibitors, which result in improved functional status and reduced morbidity, as initial treatment of congestive heart failure.[11] Although this recommendation is not specifically for anthracycline cardiomyopathy, it does represent a reasonable treatment approach. However, ACE inhibitors are not recommended as the primary modality. A more conservative approach is to use diuretics and digitalis, which may limit the optimum utilization of ACE inhibitors, should the initial treatment not be effective. One possible exception for the treatment of anthracycline-induced cardiomyopathy is that there may be significant tachycardia, which could be catecholamine-mediated. In this case, some advocate the use of beta-blockers in conjunction with ACE inhibitors.
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The clinical outcome of patients with anthracycline-induced cardiomyopathy is variable. Schwartz et al reported on 46 patients who developed congestive heart failure. When doxorubicin was stopped and supportive care initiated, 87% of patients improved and only 2% continued to deteriorate.[12] Moreb et al conducted a retrospective chart review of 19 patients treated with an anthracycline. The outcome was less favorable, with seven patients (37%) dying within a median of 6 weeks after the onset of congestive failure. Twelve patients (63%) survived, three (16%) were weaned from supportive therapy, and eight (42%) improved. Over time, 4 of the initial surviving 12 patients died from cardiac decompensation during periods of secondary illness requiring greater cardiac output, but the authors were unable to identify risk factors for cardiac decompensation.[13]

The management of pediatric patients is a different problem. Arrhythmias are more common and are managed with amiodarone (Cordarone) and mexiletine (Mexitil) and/or a pacemaker and cardioversion. There are several reports of cardiac transplants in this patient population.

Methods of Preventing Anthracycline Cardiotoxicity

**Dose Limitation**
Since clinicians recognize that the most significant risk factor for cardiac toxicity is cumulative dose, they limit the total cumulative dose in two ways. The first is the empiric discontinuation of anthracyclines at a cumulative dose thought to be associated with a relatively low incidence of clinically significant cardiac toxicity. For example, most clinicians limit doxorubicin doses to 450 mg/m², 100 mg less than the 550 mg/m² classically reported in the early 1970s.[1,2] In part, this safe dose level is extrapolated from studies demonstrating a subclinical decrement in LVEF at lower cumulative doses. Another consideration in setting the maximum dose is the use of doxorubicin in adjuvant settings with long-term survival and the unknown impact of long-term anthracycline cardiac damage. Similar empiric dose limitations have been used for other anthracyclines.

The second method of dose limitation is based on guidelines published by Schwartz et al for monitoring doxorubicin-treated patients (Table 1).[12] They recommend that baseline LVEF studies be performed at doses ≤ 100 mg/m²; then, depending on LVEF and anthracycline risk factors, subsequent studies should be performed at doses ≤ 300 mg/m², more than 450 mg/m², and before subsequent doses. With these methods, clinicians have been able to prevent clinically significant cardiac toxicity.

**Schedule Manipulations**
Several studies suggest that dose schedule also influences the risk of cardiac toxicity; eg, weekly administration of doxorubicin was associated with a lower incidence of cardiac toxicity. Since these observations led to the hypothesis that peak drug levels correlated with anthracycline cardiac damage, it was assumed that schedules resulting in lower peak blood levels would then be associated with lower instances of cardiac toxicity. The hypothesis was tested in a number of clinical trials.[14-18] Legha et al conducted pharmacokinetic studies showing that, for the same dose per course, peak blood levels were progressively lower for 24-, 48-, and 96-hour infusions. Using a concurrent, nonrandomized, control study design, they were able to demonstrate less cardiac toxicity measured by lower biopsy scores in the patients receiving prolonged infusion in contrast to the 20-minute bolus infusions.[14] Casper et al reported on a prospective trial of a 72-hour infusion with reduced cardiotoxicity.[15] Dose schedule manipulations continue to be a method used to reduce cardiac toxicity.

**Analogs and Alternative Delivery Systems**
Considerable effort has been invested in finding less cardiotoxic anthracycline analogs. Blum, Israel, et al have been developing AD-32, a more lipophilic and presumably less cardiotoxic agent.[19] To date, no anthracycline antibiotic has proven to be clinically noncardiotoxic, but the search for such agents continues.

Liposomal preparations of anthracyclines have been developed as drug delivery systems that allow the same bioavailable total dose intake, but without the higher peak blood levels of conventional formulations. The encapsulation of doxorubicin into liposomes offers an alternative means for reducing cardiac toxicity. A number of clinical trials support the hypothesis that the distribution pharmacokinetics of the liposomal preparations of both doxorubicin (Doxil) and daunorubicin (DaunoXome) may reduce the incidence of clinically significant cardiac toxicity.[20] With the commercial availability of liposomal preparations of both anthracyclines, clinical data should emerge that support the hypothesis that these preparations are less cardiotoxic.

**Cardioprotective Drugs**
Many agents have been tested for their potential in reducing anthracycline cardiac toxicity. These
investigations, based on various hypotheses of the mechanism of doxorubicin-induced cardiac toxicity, included vasoactive histamine blockers, such as H₁- and H₂-blockers; alpha- and beta-blockers; and cromolyn sodium. Another approach has been the use of agents to block the generation of free radicals and increase the salvage from free radical damage. As an example, free radical scavengers, such as vitamin E (alpha-tocopherol), acetylcysteine, and coenzyme 10, have been tested. None of these has proven to be effective in clinical trials. Only dexrazoxane has emerged as an agent of proven value in preventing anthracycline-induced cardiac toxicity.

Dexrazoxane

Mechanisms of Anthracycline Cardiotoxicity and Prevention With Dexrazoxane

The biochemical mechanisms of anthracycline cardiac toxicity have been extensively studied, leading to a number of hypotheses. Anthracycline cardiomyopathy is thought to be the result of repeated chemical injury to the myocardium after intermittent chemotherapy administration. Over time, there is progressive damage that cannot be repaired by normal cellular defenses, leading to myocyte dropout, decreased contractility, and, ultimately, congestive failure. From a biochemical perspective, the most widely accepted hypothesis is anthracycline-induced free radical formation. The free radical, with its unpaired electron, is highly reactive with other chemicals. The main source of free radicals is from the reduction of molecular oxygen to superoxide. Superoxides then react with themselves to produce hydrogen peroxide, which is highly toxic to the intracellular tissues. Anthracyclines are capable of forming free radicals in reactions that can be catalyzed by flavin reductases, such as NAD hydrogenase, which is widely distributed in mammalian tissues.

Doxorubicin’s anthracycline B ring participates in the reduction of the quinone groups, yielding semiquinone radicals, which then interact with oxygen to form the superoxide. Iron catalyzes this free radical formation through a Fe³⁺-doxorubicin complex. The repetitive doxorubicin-induced free radical damage overwhelms local antioxidant defense mechanisms. For example, glutathione peroxidase declines in the heart but not in the liver. Glutathione peroxidase is especially important in the myocardium, which lacks catalase, an enzyme that serves as a free radical scavenger in other tissues. An alternative hypothesis is that superoxide dismutase is the primary cellular defense mechanism for free radical-induced intercellular damage. The myocardium is associated with a lower superoxide dismutase level that could contribute to the predisposition to anthracycline cardiotoxicity. Other theories include doxorubicin binding to cardiolipin, which, in turn, results in mitochondrial membrane damage through lipid peroxidation.

Dexrazoxane is 1-bis (3,5-dioxopiperazinyl-1-y1) propane. Dexrazoxane, a derivative of EDTA, hydrolyzes to form an open ring, structurally resembling EDTA, that is a potent intercellular chelator. Dexrazoxane also freely penetrates cellular membranes. The mechanism of action of dexrazoxane as a cardioprotector is thought to be due to its intracellular chelation of iron. Gianni and others propose that this dexrazoxane-facilitated intracellular iron chelation decreases doxorubicin-induced free radical formation.[21]

Historical Perspective

The history of dexrazoxane as a cardioprotective agent starts in the 1960s with the preclinical and clinical testing of razoxane (ICRF-159). ICRF-159, which was part of a rational synthesis program of the Imperial Cancer Research Foundation (ICRF) to develop new antitumor agents, underwent clinical trials in the 1970s. The analog ICRF-187 (dexrazoxane), as the (+) enantiomer of the racemic mixture of razoxane, was more water-soluble and easier to formulate for parenteral use. The use of dexrazoxane as a cardioprotector began in the early 1970s when EDTA, the chelating agent, was investigated as a method to prevent cardiac toxicity. Given the structural similarities between EDTA and the ICRF compounds, Feranz and coworkers demonstrated that dexrazoxane was cardioprotective in all species tested.

Clinical trials of dexrazoxane as a cardioprotective drug were initiated in 1984 by investigators at New York University with a randomized trial demonstrating cardioprotection published in 1988. Confirmatory trials were initiated thereafter, with the FDA recommending dexrazoxane for open label use in the context of the ongoing clinical trials. In 1995, the FDA approved dexrazoxane for cardioprotection in women receiving fluorouracil, doxorubicin, and cyclophosphamide (FDC) chemotherapy for breast cancer once they had received a cumulative doxorubicin dose of 350 mg/m².

Clinical Studies of Dexrazoxane Cardioprotection

Pharmacokinetics
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The pharmacokinetics of dexrazoxane in advanced cancer patients with normal renal and hepatic function fit a two-compartment open model with first-order elimination. When dexrazoxane is administered as a 15-minute infusion, followed by doxorubicin, the disposition kinetics of dexrazoxane are dose-independent, with a mean peak plasma dexrazoxane concentration of 36.5 µg/mL, an elimination half-life of approximately 2 hours, a plasma clearance of approximately 7 L/h/m², a renal clearance of 3.35 L/h/m², and a volume of distribution of approximately 22 L/m². Forty-two percent of the dose is excreted in the urine with minimal protein binding apparent in in vitro studies. Dexrazoxane does not perturb doxorubicin pharmacokinetics.[22] Pharmacokinetic data are not available for pediatric patients or patients with impaired hepatic and/or renal function.

New York University Landmark Trial

Most of the evidence of cardioprotection comes from studies of women with breast cancer; in particular, a prospective phase III placebo-controlled landmark clinical trial conducted by the New York University (NYU) group from 1984 to 1989. The NYU trial tested the hypothesis that dexrazoxane could prevent the cardiac toxicity associated with higher cumulative doses of doxorubicin.

Women with advanced breast cancer for whom doxorubicin was the drug of choice were chosen on the assumption that they had a high probability of receiving cumulative doses of doxorubicin that would place them at risk for anthracycline-induced cardiac toxicity. They were eligible if they had received no prior anthracycline treatment, had no active heart disease, and had an LVEF of more than 50%. These patients were treated with fluorouracil (500 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) intravenously every 3 weeks, and were randomly assigned to receive dexrazoxane (1,000 mg/m² immediately prior to chemotherapy) or no dexrazoxane. The ratio of dexrazoxane to doxorubicin was 20:1. The patients were prospectively monitored for signs and symptoms of congestive heart failure by regular clinical examination, and MUGA scans were done at baseline, 300 mg/m², 450 mg/m², and then every 100 mg/m². Endomyocardial biopsies were performed in a subset of patients at cumulative doxorubicin doses of 450 mg/m².[23]

The study end points were either disease progression or evidence of cardiac toxicity. Criteria for cardiac toxicity were clinical evidence of congestive heart failure, an LVEF of less than 45%, a decline in LVEF more than 20% of baseline, and/or endomyocardial biopsy scores of more than 2. The analysis of cardioprotection was based on the primary end point of the doxorubicin dose and cardiac event and the secondary end point of the incidence of congestive heart failure.

In an intent-to-treat analysis, 76 patients were randomized to the experimental group and 74 to the control group. After randomization, there was equal distribution of risk factors, including age, performance status, prior adjuvant treatment, prior hormonal treatment, and prior radiation. There was an unequal distribution of cardiac risk factors, with 54% in the experimental vs 19% in the control group.

Study End Points

In the analysis of the reasons why women went off study (Table 2), a cardiac end point was the primary reason for stopping treatment in 34% of the control group, as compared with 7% of the experimental group. Disease progression accounted for stopping participation in the study in 31% of the control group vs 70% of the experimental group.

An additional end point was the number of cycles of chemotherapy delivered (Table 3). For the control group, the median was 9 cycles (range, 1 to 17); for the experimental group, the median was 11 cycles (range, 1 to 43). The difference in the number of cycles was statistically significant at the P = .001 level.

Cumulative doxorubicin dose delivered was another end point of the study (Table 4). The median dose of doxorubicin in the control group was 440 mg/m² (range, 25 to 850 mg/m²) vs 500 mg/m² in the experimental group (range, 50 to 2,150 mg/m²). There was a significant difference between these two groups at the P < .01 level. Table 4 also shows the percentage of patients at each dose level at the time they went off study, with 39% of those who received dexrazoxane achieving cumulative doses more than 500 mg/m². Another statistical difference between the two groups is the rate of clinical heart failure (Table 5).

Perhaps the most convincing evidence of cardioprotection is presented in a graphic analysis of LVEF. Figure 1 compares the mean percentage decline in LVEF (shown on the ordinate) at increasing dose of doxorubicin. Even at the highest doses, there is near-complete cardioprotection.

Endomyocardial biopsy is another objective measure of cardioprotection. Endomyocardial biopsies were performed at a dose of 450 mg/m² in 32 women (a subset of 40% of the women who, after informed consent, were willing to undergo biopsy). The Billingham myocardial biopsy score for the two groups is shown in Table 6. No patient in the experimental group had a Billingham score more
than 2, while six (38%) in the control had a score more than 2, indicating significant myocardial toxicity.

Dexrazoxane had no effect on the clinical benefits of FDC treatment since the objective response rates for the two groups of patients were the same (Table 7). In an analysis of all toxicity, there was no significant difference between the control and experimental groups, with the single exception of leukopenia. During the second cycle, there was a statistically significant difference in the white blood cell nadir. Although, these data are of borderline clinical significance (Table 8), there were no differences in the incidences of fever, nadir infection, alopecia, stomatitis, gastrointestinal toxicity, or toxic deaths between the experimental and control groups.

**Confirmatory Clinical Trials**

Swain et al have reported on two prospectively randomized, placebo-controlled, double-blind studies conducted from 1988 to 1992 to confirm the efficacy of dexrazoxane as a cardioprotective agent in women with advanced breast cancer.[24] The selection criteria and chemotherapy (FDC given intravenously every 3 weeks) were the same in the two studies and identical to the study conducted by Speyer et al. The two confirmatory studies (clinical studies 088001 and 088006) used computer-generated advice rules that ensured a high degree of protocol compliance. Patients were randomized to either FDC plus dexrazoxane or FDC plus placebo. This study initially used a ratio of study drugs to doxorubicin of 20:1; ie, 1,000 mg/m² of dexrazoxane or placebo with 50 mg/m² of doxorubicin. The dose of study drug (dexrazoxane or placebo) was reduced to 500 mg/m², a drug ratio of 10:1, after the accrual of data for 67 of the total 334 women randomized to dexrazoxane. The reduction was executed on the assumption that the lower dose would provide equivalent cardioprotection and would have less potential for myelosuppression. The second breast cancer study, 088006, tested the 10:1 ratio throughout.

Both studies were amended once it became apparent that dexrazoxane was cardioprotective in the confirmatory studies. A total of 102 patients randomized to the placebo group received dexrazoxane within each subsequent course once they attained a cumulative dose of 300 mg/m² of doxorubicin or beginning with course 7. An analysis of these 102 patients, compared to 99 who received placebo throughout the study, demonstrated that dexrazoxane was protective even when first introduced at a cumulative dose of 300 mg/m². The incidence of congestive failure was 22% in the placebo-only group and 3% in the women who were crossed over to 300 mg/m² of dexrazoxane (P < .001). Cardioprotection was statistically significant between these two groups with respect to the end point of doxorubicin dose to congestive failure and to any cardiac event. In summary, cardioprotection was evident in women who had received a cumulative dose of doxorubicin of 300 mg/m² before starting dexrazoxane. These data led to the recommendation that dexrazoxane was indicated for cardioprotection in patients who reach a potentially cardiotoxic dose of doxorubicin and for whom continued doxorubicin treatment is of potential benefit.

**Toxicity Analyses**

The toxicity analyses of both studies confirmed that there was no significant additive toxicity from dexrazoxane; the incidences of myelosuppression and other toxicities were similar in the experimental and placebo groups. In terms of the efficacy of FDC in the experimental group compared to the control group, there was no statistical difference seen, except in two subset analyses. In the larger study 088001, patients in the dexrazoxane group who received the 10:1 dose ratio had a significantly lower response rate than those who received placebo. The data for measurable objective response were 47% in the dexrazoxane vs 60% in the placebo group (P = .02), but there was no significant difference in this subset in time to progression or survival. In all other subset analyses of therapeutic efficacy in 088001 and 088006, there were no differences between the two groups with respect to objective response rate, time to progression, and overall survival, with one exception. In the subset of women analyzed from the seventh course, there was a significant increase in survival favoring the dexrazoxane-treated women.

To put these data into a broader context, it is difficult to attach clinical significance to the finding of a lower response rate in the single subset analysis. In preclinical studies, no data show a reduction in antitumor efficacy; rather, there are data showing an additive therapeutic benefit for dexrazoxane combinations. None of the clinical studies conducted to date have been designed or sufficiently powered to compare the efficacy of FDC combined with dexrazoxane or placebo, so that analyses of therapeutic end points are of interest, but are not definitive. To summarize, there is ample evidence to support the conclusions that dexrazoxane is cardioprotective, does not add to the toxicity of FDC chemotherapy, and does not adversely affect therapeutic efficacy.

**Pediatric Trials**

Clinicians have great concern about anthracycline-induced cardiac toxicity in the pediatric...
population. Anthracyclines, in particular, doxorubicin, have dramatically reduced the tumor-related morbidity and mortality for many childhood cancers. Several investigators not only have identified the cardiac toxicity described in adults but also have raised the issue of late cardiac effects of anthracycline in the pediatric population. The physiologic evidence for this late cardiac toxicity is evident in changes in preload and afterload volumes of ventricular contractility, as expressed in fraction shortening and changes in ventricular wall thickness in patients treated during childhood and adolescence.[25]

The efficacy of dexrazoxane in preventing these late effects of anthracycline cardiac toxicity is yet to be proven. Also, data are needed to support the assumption that there is no decrease in antitumor efficacy of the anthracyclines when administered with dexrazoxane; this is especially important in a population being treated with curative intent. Further clinical study of anthracycline cardiac toxicity and dexrazoxane cardioprotection in the pediatric population is ongoing.

Ongoing Clinical Trials
Currently, clinical trials are underway to resolve remaining questions about the use of dexrazoxane. The Pharmacia Upjohn Company is sponsoring a multicenter trial to test the hypothesis that prolonged chemotherapy, made safe by dexrazoxane cardioprotection, results in longer freedom from progressive disease and survival. Women with metastatic breast cancer who have stable disease or an objective response to FDC chemotherapy are being randomized to receive continued treatment with doxorubicin and dexrazoxane or no further treatment. The primary end point is time to progression. The study is targeted to complete accrual in 1998. Sparano et al are conducting a multicenter trial to evaluate the cardioprotective effects of dexrazoxane in women with metastatic breast cancer who are receiving a dose-intensive regimen of paclitaxel combined with doxorubicin using granulocyte colony-stimulating factor (G-CSF [Neupogen]) support.
Sallan et al are conducting a prospective phase III trial in pediatric non-T-cell acute leukemia comparing doxorubicin with and without dexrazoxane, using a variety of cardiac end points. The Pediatric Oncology Group is conducting a prospective trial of pediatric T-cell leukemia and lymphoma using a doxorubicin-based regimen, randomly assigning patients to dexrazoxane vs placebo.
Another area of clinical investigation is the use of dexrazoxane with other classes of drugs. As an example, there is evidence that dexrazoxane can prevent organ damage from other iron-dependent reactions, such as bleomycin pulmonary toxicity and cardiac reperfusion injury. Clinical studies of these disease states would be of particular interest.

Dexrazoxane Administration
Dexrazoxane is provided in the United States as Zinecard as 250- or 500-mg single-dose vials that are stable at room temperature. The recommended dose ratio of dexrazoxane to doxorubicin is 10:1; eg., 500 mg/m² of dexrazoxane to 50 mg/m² of doxorubicin. Dexrazoxane must be reconstituted with 0.167 molar sodium lactate injection, USP, supplied with the Zinecard to give a concentration of 10 mg dexrazoxane for each milliliter of sodium lactate. The reconstituted solution is administered as an infusion up to 15 minutes in duration with a 30-minute fixed interval from the completion of dexrazoxane infusion to the initiation of doxorubicin. The reconstituted dexrazoxane is stable for 6 hours from the time of reconstitution when stored at room temperature. Reconstituted dexrazoxane may be further diluted with either 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, to a concentration of 1.3 to 5.0 mg/mL.[6]

Conclusions and Clinical Implications
Dexrazoxane is clearly cardioprotective in prospective phase III, placebo-controlled, randomized trials in women with metastatic breast cancer receiving FDC chemotherapy. Cardioprotection is evident even if dexrazoxane is not initiated until a 300 mg/m² cumulative dose of doxorubicin is reached. Dexrazoxane does not add clinically significant toxicity to the FDC regimen. The therapeutic efficacy of FDC is not affected by the addition of dexrazoxane, with one exception: In a subset analysis of one of the clinical trials described above, the response rate was reduced. The extrapolation of dexrazoxane cardioprotection to other clinical situations is based on limited data. No data from clinical trials are available to demonstrate dexrazoxane cardioprotection with other doxorubicin doses, schedules, and/or intensities; yet, cardioprotection can be assumed from both in vitro and preclinical data. There are some clinical data indicating that dexrazoxane affords cardioprotection when given with other anthracycline antibiotics, such as idarubicin, daunorubicin, and epirubicin, but there are inadequate data to support the use of dexrazoxane to protect against mitoxantrone cardiotoxicity.
The use of dexrazoxane in patients at increased risk for anthracycline cardiac toxicity is unproven but clinically justifiable. There is no reason to assume that the cardioprotective effects seen in breast cancer are disease-specific, and, therefore, the extrapolation of dexrazoxane cardioprotection to other cancers seems logical. For patients who have received prior doxorubicin to the maximal clinically tolerated dose and in whom additional doxorubicin is indicated, it is reasonable to assume that dexrazoxane would prevent additional cardiac damage. Similarly, although there are no data to support the value of dexrazoxane cardioprotection in patients who have preexisting heart disease and/or have received mediastinal irradiation, these uses of dexrazoxane should be clinically evaluated. In summary, the clinician must consider the efficacy of dexrazoxane when assessing the potential clinical benefit of doxorubicin in patients with an increased risk of cardiac toxicity.

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