

ORIGINAL ARTICLE

The Effect of Dexrazoxane on Myocardial Injury in Doxorubicin-Treated Children with Acute Lymphoblastic Leukemia

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ABSTRACT

BACKGROUND

Doxorubicin chemotherapy is very effective in children with acute lymphoblastic leukemia (ALL) but also injures myocardial cells. Dexrazoxane, a free-radical scavenger, may protect the heart from doxorubicin-associated damage.

METHODS

To determine whether dexrazoxane decreases doxorubicin-associated injury of cardiomyocytes, we randomly assigned 101 children with ALL to receive doxorubicin alone (30 mg per square meter of body-surface area every three weeks for 10 doses) and 105 to receive dexrazoxane (300 mg per square meter) followed immediately by doxorubicin. Serial measurements of serum cardiac troponin T were obtained in 76 of 101 patients in the doxorubicin group and 82 of 105 patients in the group given dexrazoxane and doxorubicin. A total of 2377 serum samples (mean, 15.1 samples per patient) were obtained before, during, and after treatment with doxorubicin. Troponin T levels were evaluated in a blinded fashion to determine whether they were elevated (>0.01 ng per milliliter) — the primary end point — or extremely elevated (>0.025 ng per milliliter).

RESULTS

Elevations of troponin T occurred in 35 percent of the patients (55 of 158). Patients treated with doxorubicin alone were more likely than those who received dexrazoxane and doxorubicin to have elevated troponin T levels (50 percent vs. 21 percent, $P<0.001$) and extremely elevated troponin T levels (32 percent vs. 10 percent, $P<0.001$). The median follow-up was 2.7 years. The rate of event-free survival at 2.5 years was 83 percent in both groups ($P=0.87$ by the log-rank test).

CONCLUSIONS

Dexrazoxane prevents or reduces cardiac injury, as reflected by elevations in troponin T, that is associated with the use of doxorubicin for childhood ALL without compromising the antileukemic efficacy of doxorubicin. Longer follow-up will be necessary to determine the influence of dexrazoxane on echocardiographic findings at four years and on event-free survival.

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THE FIVE-YEAR SURVIVAL RATE AMONG children who receive a diagnosis of cancer during the first 14 years of life is 77 percent.¹ There are more than 250,000 survivors of childhood cancer in the United States, and an estimated 1 in 570 such young adults will be 20 to 34 years old by 2010.¹ This success brings a new challenge: understanding and minimizing the late effects of therapies for cancer administered to children. More than 50 percent of long-term survivors of childhood cancer were treated with doxorubicin or another anthracycline.² Many of those who were treated with doxorubicin have long-term problems,³⁻¹¹ such as impaired left ventricular contractility, late congestive heart failure, or high-grade ectopy, and an increased risk of sudden death and death from cardiac causes. One study estimated that the risk of death from cardiac causes was 8.2 times that of the normal population even 25 years after therapy.¹² A second study found that the risk of death from cardiac causes increased by a factor of 5.8 and that of sudden death, presumably from cardiac causes, by a factor of 3.9.¹³ These sequelae were related, in part, to the use of doxorubicin, and the incidence has not decreased during more recent treatment eras.¹⁴

Doxorubicin is an effective therapy for acute lymphoblastic leukemia (ALL),¹⁵ the most common cancer in children. A doxorubicin-containing protocol for children with high-risk ALL has resulted in the highest five-year event-free survival rate: 81 percent.¹⁶ In long-term survivors of childhood ALL, doxorubicin-associated cardiotoxic effects are pervasive, persistent, and often progressive.³⁻⁹

The serum level of cardiac troponin T is an accurate surrogate for acute myocardial injury in children,^{9,17-19} specifically that related to doxorubicin,²⁰⁻²³ and the maximal cardiac troponin T level during doxorubicin therapy is significantly correlated with the cumulative dose of doxorubicin²⁴ and with subsequent structural abnormalities of the left ventricle seen on echocardiograms in these patients.¹⁷ A continuous 48-hour infusion of doxorubicin was not found to be more cardioprotective than bolus administration in patients with childhood ALL.²⁵ Enalapril therapy delayed but did not prevent progressive, late cardiotoxic effects in long-term survivors of childhood cancer who had received doxorubicin.²⁶

The only effective way to avoid late cardiotoxic effects appears to be to prevent cardiac injury during chemotherapy.²⁷ A promising possibility in-

volves treatment with dexrazoxane, a free-radical scavenger that is cardioprotective in adults receiving anthracycline therapy.²⁷⁻³² Dexrazoxane may also be useful in children, although there is concern that this agent may protect tumor cells from chemotherapy.^{27,33-41} We conducted a multicenter, randomized, controlled trial to determine whether dexrazoxane therapy reduces myocardial injury, as measured by serum cardiac troponin T levels, in children with newly diagnosed ALL who are being treated with doxorubicin.

METHODS

PATIENTS

This study was part of the multiagent chemotherapy regimen in the Dana-Farber Cancer Institute childhood ALL consortium protocol 95-001. The study was approved by the institutional review board of each participating institution, and informed consent was obtained before treatment from all participants or their families or guardians. Between January 1996 and September 2000, all children in the consortium who were under 18 years of age and had newly diagnosed and previously untreated high-risk ALL (excluding known mature B-cell ALL) were invited to enroll in this study. Patients with standard-risk disease, as defined by an age between 1 and 10 years, a white-cell count of less than 50,000 cells per cubic millimeter at presentation, and the absence of T-cell markers, an anterior mediastinal mass, and central nervous system disease, were excluded. All other patients were classified as being at high risk, including infants and patients with T-cell disease.

RANDOMIZATION

Randomization involved a permuted-block design and was carried out centrally at the Dana-Farber Cancer Institute's Quality Assurance Office for Clinical Trials before patients received doxorubicin or dexrazoxane. In addition to receiving multiagent chemotherapy and central nervous system radiation, patients with high-risk ALL received two doses of doxorubicin (30 mg per square meter of body-surface area per dose) during remission induction, followed by eight more doses (30 mg per square meter every three weeks) during induction therapy (cumulative dose, 300 mg per square meter). No doxorubicin was given after nine months of therapy. Patients at high risk were randomly assigned to receive doxorubicin alone or dexrazoxane (300 mg per square meter) immediately followed by doxorubi-

cin. Local centers and patients were not blinded to the assignment with respect to dexrazoxane therapy, but central investigators performing troponin T measurements and echocardiographic evaluations and providing summary study results remained blinded throughout the study. An independent data-monitoring committee reviewed data on enrollment, adverse effects, and troponin T levels every six months and released the troponin T results when all patients had completed doxorubicin therapy.

CARDIAC TROPONIN T

The protocol included the collection of serum at standardized times — at diagnosis (before doxorubicin therapy), daily after induction doses of doxorubicin, seven days after a dose of doxorubicin during induction therapy, and at the completion of therapy — for the measurement of cardiac troponin T. Serum collected at clinical sites was immediately frozen and stored at -70°C until it was assayed for cardiac troponin T at a central core laboratory with the use of the Elecsys Troponin T STAT Immunoassay (Roche Diagnostics), which has a sensitivity of 0.01 ng per milliliter.¹⁷ Hemolyzed samples were excluded. The members of the central laboratory for the measurement of cardiac troponin T remained unaware of the patients' treatment status. Serum cardiac troponin T results were entered directly into the central data base and were not reported to the various centers.

ECHOCARDIOGRAMS

Echocardiograms were available for a subgroup of patients who underwent randomization, since cardiac troponin T was the primary marker of cardiac injury during therapy. Echocardiograms were required before the initiation of doxorubicin therapy and recommended at the end of induction therapy, after cumulative doses of 150 and 300 mg of doxorubicin per square meter had been received, and at the completion of all therapy. Echocardiography is also being performed at four years after diagnosis, and the resulting information will provide the primary measure of cardiac function. Patients with the most severely impaired cardiac function had the most echocardiograms, and thus, including all echocardiograms in the analysis could have biased the results. Therefore, we analyzed the latest echocardiogram obtained from each patient in each period: before, during, and after doxorubicin therapy. All echocardiograms were reevaluated by a single sonographer, who was unaware of the pa-

tients' clinical data.⁴ Each study consisted of two-dimensional echocardiography and Doppler evaluation.^{1,2,5} We measured fractional shortening, an index of left ventricular systolic performance influenced by heart rate, preload, afterload, and contractility, and the stress-velocity index, a load-independent index of contractility that incorporates preload and heart rate and varies with afterload.^{1,2,5} Diastolic function was not assessed.

STATISTICAL ANALYSIS

Fisher's exact test and the Kruskal–Wallis test were used to compare baseline characteristics and the frequency of elevated cardiac troponin T levels (defined as those above 0.01 ng per milliliter) — the primary end point of this analysis — and of extremely elevated levels (defined as those above 0.025 ng per milliliter) between treatment groups.⁴² Repeated-measures analysis of cardiac troponin T samples was used. Logistic regression was used to identify covariates associated with elevated cardiac troponin T levels.⁴³ The time to event was either zero for patients with induction failure or those who died during induction or the time from complete remission to relapse, death during remission, or the last follow-up visit, whichever occurred first. Event-free survival was estimated according to the Kaplan–Meier method, with data on the time to event censored for patients who were in complete continuous remission at the time of data analysis.⁴⁴

To adjust echocardiographic data for changes associated with growth, we calculated the z score (the number of standard deviations a measurement is above or below the predicted value) by dividing the difference between a child's observed cardiac outcome and the normal predicted value by the standard deviation of a distribution of normal values. We used data from 285 children evaluated at the same center and in the same manner as the study patients to calculate the normal predicted value according to a regression model.^{1,2,5} The z scores for left ventricular dimension were adjusted for body-surface area, and those for fractional shortening were adjusted for age. Echocardiographic data were analyzed with the use of t-tests and repeated-measures analysis. All reported P values are two-sided.

RESULTS

STUDY COHORTS

A total of 219 children with high-risk ALL were enrolled, but 13 eligible patients did not undergo ran-

domization (11 because of the parents' or patient's refusal and 2 because of logistical problems). The randomized cohort of 206 patients was used for the analysis of event-free survival and adverse effects. Nine patients (5 in the doxorubicin group and 4 in the group given dexrazoxane and doxorubicin) did not have a complete remission, and 39 others (20 and 19, respectively) did not have data on cardiac troponin T values because specimens were not available at the time of analysis. The percentage of patients without samples available varied according to the study center but was evenly divided according to treatment group. The remaining 158 patients formed the cohort used for the cardiac troponin T analyses. The randomized cohort and the cardiac troponin T cohort were similar with respect to age, sex, the cumulative dose of doxorubicin, and the absence of reported congestive heart failure or symptomatic arrhythmias. No patient who had undergone randomization refused to participate, failed to receive or discontinued dexrazoxane as assigned, or was excluded from the analysis.

The treatment groups did not differ significantly with respect to baseline characteristics (Table 1). There were no cases of congestive heart failure or other symptomatic cardiac disease. Transient cardiomyopathy developed 16 months after the completion of doxorubicin therapy in one patient treated with doxorubicin alone. Figure 1 shows the Kaplan–Meier estimates of event-free survival, with a median follow-up of 2.7 years; the event-free sur-

vival rates at 2.5 years were 83 percent in both groups ($P=0.87$).

CARDIAC TROPONIN T

A total of 2377 serial measurements of cardiac troponin T were obtained (mean, 15.1 samples per patient). As compared with the patients in the doxorubicin group, significantly fewer patients in the group given dexrazoxane and doxorubicin had any elevations in cardiac troponin T (21 percent vs. 50 percent, $P<0.001$), any extreme elevations in cardiac troponin T (10 percent vs. 32 percent, $P<0.001$), or multiple elevations in cardiac troponin T (12 percent vs. 37 percent, $P<0.001$) (Table 2).

TIMING OF ELEVATIONS IN CARDIAC TROPONIN T

Figure 2 shows the percentage of patients in each group who had an elevated cardiac troponin T level at least once, overall, before treatment, and during doxorubicin therapy. Differences between the groups in the percentage of patients with at least one elevated cardiac troponin T level began to emerge between 61 and 120 days after the start of therapy, and these differences persisted throughout the rest of the treatment period, becoming significant during the interval between 121 and 180 days ($P<0.001$). Patients in the doxorubicin group also had a higher rate of elevation over time in comparison with those in the group given dexrazoxane and doxorubicin ($P=0.003$). Figure 3 shows that the same pattern was evident for differences in the incidence of extremely elevated cardiac troponin T levels. Analyses including only the 86 patients with at least one measurement of cardiac troponin T during days 181 to 240 of doxorubicin therapy yielded results over time that were very similar to those shown in Figures 2 and 3.

PATIENTS WITH PRETREATMENT ELEVATIONS IN CARDIAC TROPONIN T

Ten percent of the children in whom cardiac troponin T was measured before the initiation of doxorubicin therapy had an elevated cardiac troponin T level (12 of 119), indicating the presence of myocardial injury unrelated to the chemotherapy. As compared with patients who did not have an elevated cardiac troponin T level before doxorubicin treatment, those who did had a higher rate of elevated levels (73 percent vs. 27 percent, $P=0.004$) and of extremely elevated levels (58 percent vs. 17 percent, $P=0.003$) after doxorubicin treatment began. Children who had elevated levels before treatment had higher

Table 1. Characteristics of the Patients.*

Characteristic	Doxorubicin (N=101)	Dexrazoxane + Doxorubicin (N=105)
Sex — no.		
Male	56	64
Female	45	41
Median age at diagnosis — yr	7.3	7.5
Doxorubicin		
Median cumulative dose — mg/m ²	300	300
Received less than the median of 300 mg/m ² — no./total no. (%)	26/96 (27)	19/101 (19)
Troponin T samples		
Median no./patient	15.0	15.1
Total no. that could be evaluated	1139	1238
No. with doxorubicin- or dexrazoxane- associated dose-limiting adverse effects	0	0

* There were no significant differences between groups.

baseline white-cell counts (median, 300,300 vs. 27,200 cells per cubic millimeter; $P < 0.001$) and a higher percentage of blasts (median, 89.0 percent vs. 57.5 percent; $P = 0.003$). Differences between these two groups in the extent of T-cell disease or central nervous system disease, morphologic findings, sex, or age were not significant. When the children who had elevated cardiac troponin T levels before treatment were excluded from the analysis, treatment with dexrazoxane remained a significant cardioprotective factor (Table 2).

PROGNOSTIC FACTORS

We used a logistic-regression analysis to determine whether covariates other than treatment group were associated with elevated cardiac troponin T levels. Covariates were sex (male vs. female), race (white vs. nonwhite), age (< 10 vs. ≥ 10 years), and the cumulative dose of doxorubicin (< 300 vs. ≥ 300 mg per square meter). None of these covariates were significant (data not shown).

ECHOCARDIOGRAPHIC DATA

A total of 462 echocardiograms were obtained in eligible patients who underwent randomization, for whom cardiac troponin T data were available, and who had a complete remission (median, 2.5 echocardiograms per patient [2.0 per patient in the doxorubicin group and 3.0 per patient in the group given dexrazoxane and doxorubicin]). Echocardiograms obtained before doxorubicin therapy showed normal left ventricular fractional shortening (84 echocardiograms; mean z score, 0.19; $P = 0.51$) and contractility (22 echocardiograms; mean z score, -0.02 ; $P = 0.96$) but slight left ventricular dilatation, as reflected by the left ventricular dimension (79 echocardiograms; mean z score, 0.28; $P = 0.03$). A total of 162 echocardiograms were obtained during doxorubicin therapy, and 164 were obtained a median of 198 days after the completion of therapy. After treatment, fractional shortening (91 echocardiograms; mean z score, -1.06 ; $P < 0.001$) and contractility (29 echocardiograms; mean z score, -0.82 ; $P = 0.02$) were depressed and the left ventricular dimension was normal (89 echocardiograms; mean z score, 0.01; $P = 0.92$). There were no significant differences between the children who received doxorubicin alone and those who received dexrazoxane and doxorubicin with respect to the mean left ventricular dimension, fractional shortening, or contractility before, during, or after doxorubicin therapy. Fractional shortening was significantly de-

pressed in both randomized groups during and after doxorubicin therapy.

DISCUSSION

Dexrazoxane therapy was associated with a large and statistically significant reduction in the incidence of myocardial injury, as indicated by troponin T elevations, in doxorubicin-treated children with high-risk ALL. Dexrazoxane reduced the percentage of patients with any elevation in cardiac troponin T, multiple elevations, and extreme elevations. Because dexrazoxane reduces free-radical injury, our findings suggest that doxorubicin-associated myocardial injury in children may be related, at least in part, to oxidative damage. Doxorubicin forms a complex with iron that is thought to facilitate the formation of toxic oxygen radicals in tissues.⁴⁵ The attenuating effect of dexrazoxane on doxorubicin-induced cardiotoxicity may be attributable to its intracellular conversion to its active metal ion-binding form (ADR-925), which either removes iron from the doxorubicin-iron complex or binds free iron, thus preventing the formation of oxygen radicals.⁴⁶

Troponins are sensitive and specific markers of myocardial injury. In the absence of injury, troponin levels are usually below the limit of detection of cur-

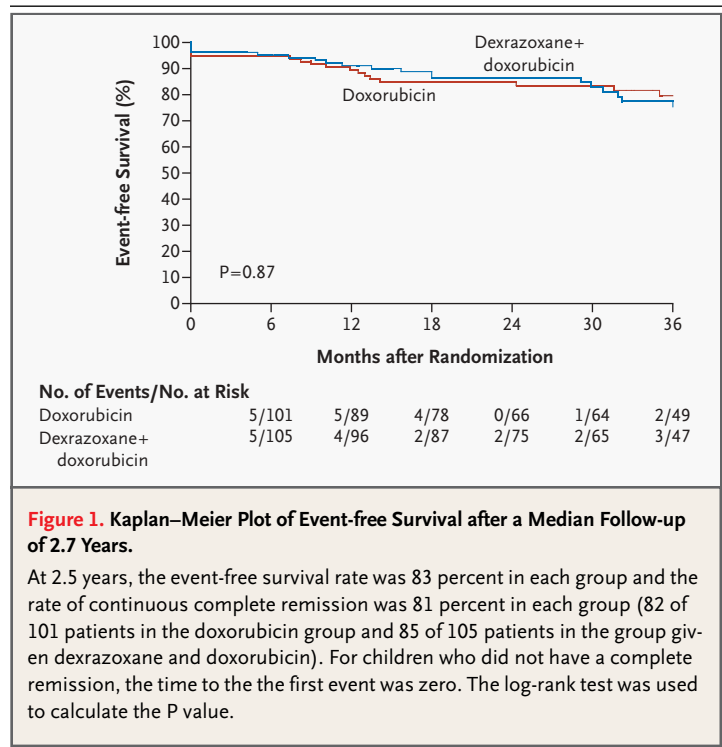


Figure 1. Kaplan-Meier Plot of Event-free Survival after a Median Follow-up of 2.7 Years.

At 2.5 years, the event-free survival rate was 83 percent in each group and the rate of continuous complete remission was 81 percent in each group (82 of 101 patients in the doxorubicin group and 85 of 105 patients in the group given dexrazoxane and doxorubicin). For children who did not have a complete remission, the time to the the first event was zero. The log-rank test was used to calculate the P value.

Table 2. Frequency of Elevations in Serum Cardiac Troponin T.*

Subgroup	Doxorubicin (N=76)		Dexrazoxane + Doxorubicin (N=82)		P Value
	No. with Finding/ Total No.	% (95% CI)	No. with Finding/ Total No.	% (95% CI)	
Any elevation in troponin T	38/76	50 (38–62)	17/82	21 (13–31)	<0.001
During doxorubicin therapy	35/76	46 (35–58)	12/80	15 (8–25)	<0.001
After doxorubicin therapy ended	11/29	38 (21–58)	5/29	17 (6–36)	0.14
Multiple elevations in troponin T	28/76	37 (26–49)	10/82	12 (6–21)	<0.001
Any extreme elevation in troponin T	24/76	32 (21–43)	8/82	10 (4–18)	<0.001
Multiple extreme elevations in troponin T	15/76	20 (11–30)	6/82	7 (3–15)	0.03
No pretreatment elevations in troponin T	71/76		75/82		
Any subsequent elevation	33/71	46 (34–58)	10/75	13 (7–23)	<0.001
Any elevation during doxorubicin therapy	32/71	45 (33–57)	9/74	12 (6–22)	<0.001
Any elevation after doxorubicin therapy ended	10/27	37 (19–58)	4/26	15 (4–35)	0.12
Multiple elevations	24/71	34 (23–46)	5/75	7 (2–15)	<0.001
Any extreme elevation	21/71	30 (19–42)	4/75	5 (1–13)	<0.001
Multiple extreme elevations	15/71	21 (12–32)	4/75	5 (1–13)	0.006

* An elevated troponin T level was one that exceeded 0.01 ng per milliliter, and an extremely elevated level was one that exceeded 0.025 ng per milliliter. CI denotes confidence interval.

rent analytical methods. Low-level elevations have significant prognostic value in patients with unstable angina and myocardial infarction but without ST-segment elevation,⁴⁷ since those with baseline cardiac troponin T levels between 0.01 and 0.05 ng per milliliter are at higher risk for death and myocardial infarction at one and six months than are patients with levels below 0.01 ng per milliliter.⁴⁸ We have previously demonstrated that low-level elevations of cardiac troponin T induced by doxorubicin are associated with histologic evidence of myocardial injury and are clinically meaningful.²¹ Our current findings are similar to our finding that dexrazoxane-treated rats had less frequent elevations in cardiac troponin T and less severe cardiac injury on histologic analysis and were in better health than rats that did not receive dexrazoxane.⁴¹

The degree of cardiac injury identified after the first dose of doxorubicin treatment is related to the likelihood of subsequent echocardiographic abnormalities on the completion of therapy.¹⁷ Now, we have shown that the incidence of doxorubicin-associated elevations in cardiac troponin T increases substantially during doxorubicin therapy, persists throughout treatment, and is dramatically reduced by dexrazoxane therapy. Pretreatment with dexrazoxane reduces the late cardiotoxic effects of doxorubicin. Low-level elevations of cardiac troponin T

are meaningful predictors of late cardiotoxic effects and may be used to guide preventive and therapeutic strategies to reduce these adverse effects. Children with higher percentages of leukemic blasts in the peripheral blood at baseline were more likely than those with lower values to have cardiac injury at diagnosis that was unrelated to doxorubicin.

We used cardiac troponin T instead of echocardiographic measurements as an indicator of myocardial injury because of the poor sensitivity and specificity of echocardiography in identifying subclinical abnormalities of left ventricular structure and function in children with cancer who are receiving doxorubicin.^{49,50} Our results suggest that echocardiographic measurements are not valid surrogates for subclinical myocardial injury in this setting. Other factors, such as abnormal heart rate, abnormal loading conditions, and the presence of cytokine-mediated myocardial depressants, may affect these echocardiographically derived measurements and result in values that may misrepresent the extent of subclinical doxorubicin-associated myocardial injury. These confounders of active myocardial injury are likely to be transient, a finding that may have implications with respect to the accuracy of echocardiographic monitoring for low-level myocardial injury during doxorubicin therapy.

Our findings demonstrate the efficacy of a car-

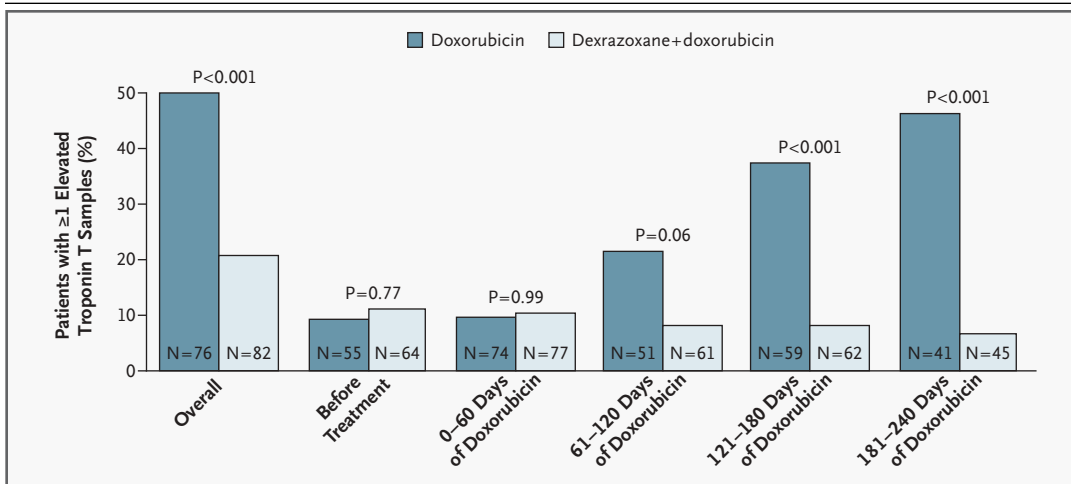


Figure 2. Percentage of Patients with at Least One Elevated Cardiac Troponin T Level Overall, before Treatment with Doxorubicin, and during Treatment.

An elevated level of troponin T was defined as one that exceeded 0.01 ng per milliliter. The number of patients in whom troponin T was measured at least once during the specified intervals is shown in each bar.

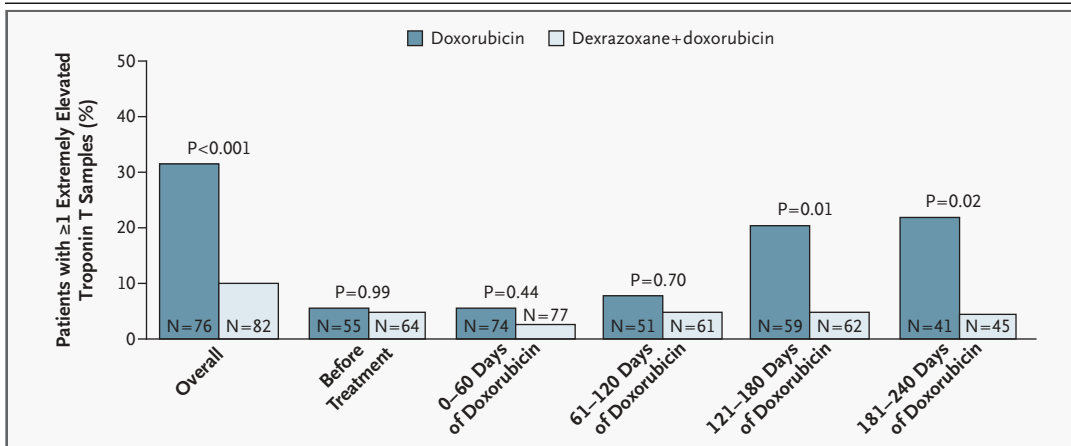


Figure 3. Percentage of Patients with at Least One Extremely Elevated Cardiac Troponin T Level Overall, before Treatment with Doxorubicin, and during Treatment.

An extremely elevated level of troponin T was defined as one that exceeded 0.025 ng per milliliter. The number of patients in whom troponin T was measured at least once during the specified intervals is shown in each bar.

dioprotectant agent in children.⁹ Free-radical damage is a common mechanism of cardiac injury in children during the perinatal period, as well as in children with myocarditis, those with hypoxia and reoxygenation related to myocardial infarction or stroke,⁵¹ and those undergoing cardiopulmonary bypass or hemodialysis.^{9,17-19} Because children are still growing, minor myocardial injury has a greater

chance of producing subsequent myocardial impairment in children than in adults.^{3,4,13}

The optimal dose of dexrazoxane is unknown.⁹ Dexrazoxane has a short half-life, and repeated doses⁵² or continuous infusions⁵³ may provide additional cardioprotection in patients with persistent elevations of cardiac troponin T. Further echocardiographic follow-up of this cohort is needed to

identify any long-term cardioprotective effects of dexrazoxane.²⁻⁵ Continued monitoring of event-free survival in these patients will allow us to confirm that the cardioprotective effects of dexrazoxane do not reduce the antileukemic efficacy of doxorubicin.

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