original reports

Dexrazoxane and Long-Term Heart Function in Survivors of Childhood Cancer

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abstract

PURPOSE For survivors of childhood cancer treated with doxorubicin, dexrazoxane is cardioprotective for at least 5 years. However, longer-term data are lacking.

METHODS Within the Children's Oncology Group and the Dana Farber Cancer Institute's Childhood Acute Lymphoblastic Leukemia Consortium, we evaluated four randomized trials of children with acute lymphoblastic leukemia or Hodgkin lymphoma, who received doxorubicin with or without dexrazoxane, and a nonrandomized trial of patients with osteosarcoma who all received doxorubicin with dexrazoxane. Cumulative doxorubicin doses ranged from 100 to 600 mg/m^2 across these five trials, and dexrazoxane was administered uniformly (10:1 mg/m^2 ratio) as an intravenous bolus before doxorubicin. Cardiac function was prospectively assessed in survivors from these trials, plus a matched group of survivors of osteosarcoma treated with doxorubicin without dexrazoxane. Two-dimensional echocardiograms and blood biomarkers were analyzed centrally in blinded fashion. Multivariate analyses adjusted for demographic characteristics, cumulative doxorubicin dose, and chest radiotherapy determined the differences and associations by dexrazoxane status.

RESULTS From 49 participating institutions, 195 participants were assessed at 18.1 ± 2.7 years since cancer diagnosis (51% dexrazoxane-exposed; cumulative doxorubicin dose 297 ± 91 mg/m^2). Dexrazoxane administration was associated with superior left ventricular fractional shortening (absolute difference, +1.4% [95% CI, 0.3 to 2.5]) and ejection fraction (absolute difference, +1.6% [95% CI, 0.0 to 3.2]), and lower myocardial stress per B-type natriuretic peptide (–6.7 pg/mL [95% CI, –10.6 to –2.8]). Dexrazoxane was associated with a reduced risk of having lower left ventricular function (fractional shortening < 30% or ejection fraction < 50%; odds ratio, 0.24 [95% CI, 0.07 to 0.81]). This protective association was primarily seen in those treated with cumulative doxorubicin doses ≥ 250 mg/m^2.

CONCLUSION Among young adult-aged survivors of childhood cancer, dexrazoxane was associated with a cardioprotective effect nearly 20 years after initial anthracycline exposure.

J Clin Oncol 41:2248-2257. © 2023 by American Society of Clinical Oncology

INTRODUCTION

Improvements in the treatment of childhood cancer have been one of the major medical advances of the past 50 years, with 5-year survival increasing from < 60% to more than 85% today.[1] These advances are attributed to refinements in surgery, radiotherapy, and combination chemotherapy, including anthracyclines. Although a newer generation of molecularly targeted agents is receiving much attention, contemporary therapy for most pediatric cancers still relies on anthracyclines and other cytotoxic chemotherapeutics.[2] Anthracyclines are routinely used to treat children and adolescents with newly diagnosed acute lymphoblastic and myeloid leukemias, most lymphomas, neuroblastoma, sarcomas, and advanced-stage liver and kidney tumors.

Cardiomyopathy is the major late toxicity of anthracycline therapy. The cumulative incidence of clinical heart failure in long-term survivors of childhood cancer approaches 25% by age 40 years for some groups.[3] Cumulative anthracycline dose is one of the most important predictors for cardiomyopathy; additional predictors include radiation to the heart, younger age at exposure, female sex, hypertension, and other potentially modifiable risk factors.[4] Although overall late mortality and morbidity have improved in children treated in the 1990s compared with the 1970s, late cardiovascular morbidity has not declined appreciably over this time period.[5,6]

For these reasons, implementation of an effective cardioprotective strategy for newly diagnosed children and adolescents receiving anthracyclines is important. Dexrazoxane is a bisdioxopiperazine that has been

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 6, 2022 and published at ascopubs.org/journal/jco on January 20, 2023: DOI https://doi.org/10.1200/JCO.22.02423

CONTEXT

Key Objective

This multi-institutional cooperative group study sought to determine the long-term efficacy of dexrazoxane in mitigating anthracycline-related cardiotoxicity in survivors of childhood cancer treated on dexrazoxane-containing clinical trials.

Knowledge Generated

We found that among survivors of childhood cancer assessed on average 18 years after cancer diagnosis, those assigned to doxorubicin with dexrazoxane were significantly more likely to have preserved left ventricular function (measured by echocardiography) and lower myocardial stress (measured by serum natriuretic peptide levels) compared with the group assigned to doxorubicin alone. The cardioprotective effect of dexrazoxane was primarily observed in survivors treated with greater cumulative doses of doxorubicin (250 mg/m^2 or greater).

Relevance *(J.W. Friedberg)*

Dexrazoxane should be considered as a standard cardioprotectant in children with cancer receiving a cumulative dose of at least 250 mg/m^2 of doxorubicin.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

tested and used as a cardioprotectant.[7] Randomized trials of dexrazoxane in anthracycline-exposed adult patients with breast cancer have demonstrated its efficacy in minimizing the risk of both clinical and subclinical heart failure.[8] As a result, dexrazoxane is approved by the US Food and Drug Administration for patients with breast cancer who are receiving ≥ 300 mg/m^2 of doxorubicin-based therapy. ASCO and the European Society for Medical Oncology both recommend consideration of dexrazoxane use for any adult patient with cancer expected to receive high-dose anthracycline therapy exceeding 250-300 mg/m^2 (total doxorubicin equivalent dose).[9,10] However, long-term data on the cardioprotective efficacy of dexrazoxane in survivors of childhood cancer are lacking, although short- and medium-term data indicate its potential benefit.[11-13] We addressed this gap in knowledge by conducting a prospective multi-institutional follow-up study (Children's Oncology Group [COG] ALTE11C2; ClinicalTrials.gov identifier: NCT01790152) of childhood cancer survivors previously treated on dexrazoxane-containing clinical trials.

METHODS

Participants

Eligible ALTE11C2 participants included those enrolled on legacy COG protocols P9404, P9425, P9426, and P9754, and Dana Farber Cancer Institute (DFCI) Childhood Acute Lymphoblastic Leukemia Consortium protocol 95-01, all of which assigned patients to doxorubicin doses ranging from 100 to 600 mg/m^2 (Table 1).[14-18] No other anthracyclines were used in these protocols. P9404, P9425, P9426, and DFCI 95-01 were all phase III clinical trials of acute lymphoblastic leukemia/lymphoma or Hodgkin lymphoma that featured upfront random assignment to treatment with or without dexrazoxane. P9754 was a trial for localized osteosarcoma in which all patients received doxorubicin with dexrazoxane. Therefore, for ALTE11C2, a comparison group (non–dexrazoxane-exposed localized osteosarcoma patients treated with ≥ 450 mg/m^2 doxorubicin contemporaneously and who otherwise matched P9754's eligibility criteria) also was recruited from participating sites. Eligible ALTE11C2 participants had to be in remission from their primary cancer and could not have had any subsequent malignant neoplasm treated with a cardiotoxic drug. Primary cancer treatment information, including doxorubicin doses and radiation exposures, was obtained from COG and DFCI. Dexrazoxane was administered uniformly as one intravenous bolus in a 10:1 mg/m^2 dose ratio to doxorubicin in all five trials.

Measurements

Participants were recruited by their treating institution in the United States and Canada for a one-time assessment, which included anthropometric measurements and a ≥ 10-hour fasting blood draw. Serum samples were analyzed for cardiomyocyte injury (high-sensitivity cardiac troponin T) and myocardial stress (B-type natriuretic peptides [BNP] and N-terminal pro-BNP). Other markers of inflammation and heart failure (high-sensitivity C-reactive protein, galectin-3, growth differentiation factor-15, soluble urokinase plasminogen activator receptor, and ST2) were collected for exploratory analyses. Samples were shipped to a Clinical Laboratory Improvement Amendments–certified laboratory and analyzed, with evaluators blinded to dexrazoxane status. Participants' medical histories were updated by research staff, including documenting the presence of cardiovascular and related diseases (hypertension, dyslipidemia, and diabetes).

Participants underwent a standardized two-dimensional, M-mode and Doppler echocardiogram following the ALTE11C2 protocol.[19] Digitized copies of the study echocardiograms were centrally reviewed and remeasured by

TABLE 1. Overview of Legacy Clinical Trials of Children and Adolescents Newly Diagnosed With Cancer Treated With Doxorubicin, With or Without Dexrazoxane

Study	Histology, No. Enrolled, Median Diagnosis Age (range)	Cumulative Doxorubicin Dose (mg/m^2)[a]	Radiotherapy, Gy
P9404[14]	T-cell ALL/lymphoblastic lymphoma, N = 537, 9 years (1-21)	360 (30/dose)	18 (cranial only)
P9425[15]	Intermediate-/high-risk Hodgkin lymphoma, N = 216, 14 years (3-20)	180-300[b] (30/dose; 60/cycle)	21 (regional field)
P9426[16]	Low-risk Hodgkin lymphoma, N = 262, 13 years (2-20)	100-200[b] (25/dose; 50/cycle)	25.5 (involved field)
P9754[17]	Localized osteosarcoma, N = 242, 13 years (3-30)	450-600[b] (37.5/dose; 75/cycle)	None
DFCI 95-01[18]	High-risk precursor B-cell or T-cell ALL, N = 205, 7 years (0-18)	300 (30/dose)	18 (cranial only)

Abbreviations: ALL, acute lymphoblastic leukemia; DFCI, Dana Farber Cancer Institute Childhood ALL Consortium.

[a]Dexrazoxane was given uniformly in all trials, in a 10:1 ratio to doxorubicin, immediately before doxorubicin doses; for P9425, an additional dose of dexrazoxane was also given immediately before each cycle's day 7 bleomycin with doxorubicin being given on days 0 and 1 only; all studies featured 1:1 random assignment to receive or not to receive dexrazoxane, with the exception of P9754, in which all patients were assigned to receive dexrazoxane.

[b]These were risk-adapted trials where rapid or good responders received fewer cycles compared with slower responders.

researchers blinded to dexrazoxane and clinical status (S.A. and N.S.). The primary protocol-specified echocardiographic outcome was end-diastolic wall thickness-to-dimension ratio as a measure of left ventricular (LV) pathologic remodeling.[20] Prespecified secondary outcomes included indices of LV systolic (fractional shortening [FS] and biplane Simpson's ejection fraction [EF]) and diastolic function. In addition to these usual indices of myocardial mechanics, we also measured longitudinal, circumferential, and radial strain with post hoc speckle tracking (by S.A.; TomTec Imaging Systems, Munich, Germany). All study procedures were approved by the Central Institutional Review Board of the US National Institutes of Health and review boards at participating sites. All participants or their legal guardians provided informed consent.

Analyses

T-test, Wilcoxon rank-sum, chi-square, and Fisher's exact tests were used to compare continuous and categorical patient characteristics and outcomes by dexrazoxane status as appropriate. Prespecified subanalyses included comparing outcomes for dexrazoxane- versus non–dexrazoxane-assigned subjects within sex-specific stratum and cumulative doxorubicin dose stratum (< 250 and ≥ 250 mg/m^2 per international consensus recommendations).[21] For continuous outcomes, multivariable linear regression was used to examine differences by dexrazoxane status, adjusting for sex, age at cancer diagnosis, current age, doxorubicin dose, radiation to the heart (yes/no), and history of cardiomyopathy requiring medications or heart transplant. The distribution of outcomes was assessed by residual and Q-Q plots, and log-transformed if there were potential departures from normality. Multivariable logistic regression adjusting for the same covariates assessed the association (odds ratio [OR]) of having lower LV systolic function with dexrazoxane assignment, which was defined as FS $< 30\%$ or EF $< 50\%$. Individuals with a history of cardiomyopathy were coded as having lower LV systolic function regardless of current FS or EF. All analyses were performed using Stata (by D.R.D., version 17, StataCorp, College Station, TX).

RESULTS

Of 488 potentially eligible participants from 49 participating institutions, 201 (41.2%) were enrolled between May 2014 and March 2021. Among nonparticipants, eight declined participation and the remainder were either passive non-responders or assumed to be lost to follow-up (Appendix Fig A1, online only). Among enrolled participants, two were found to be ineligible because of history of relapse, two consented but did not complete any study assessments, and two consented to self-report questionnaire submission only, resulting in 195 participants in the final analysis (50.8% assigned to receive dexrazoxane). When characteristics between nonparticipants and participants were compared, nonparticipants were more likely to be male and to belong to a racial or ethnic minority, and less likely to have had heart radiation exposure (Appendix Table A1, online only). However, characteristics were similar among participants enrolled from institutions that recruited a majority of their participants versus those recruited from sites with $< 50\%$ participation.

Participants had a mean (±standard deviation) attained age of 28.8 ± 5.3 years at study participation and were 18.1 ± 2.7 years since cancer diagnosis. Characteristics between those treated with and without dexrazoxane were similar except that dexrazoxane-assigned participants were slightly younger at time of cancer diagnosis and at study assessment (Table 2). Otherwise, the two groups had similar mean protocol-specified doxorubicin doses (305 ± 92 mg/m^2 *v* 288 ± 90 mg/m^2; $P = .20$) and proportions with heart radiation exposure (22.2% *v* 32.3.%; $P = .11$).

Univariate analyses did not reveal significant differences in the LV structure including the wall thickness-dimension ratio (Table 3). However, the dexrazoxane group had better LV systolic function compared with the no dexrazoxane group, with greater FS (34.7 ± 3.6% *v* 33.4 ± 4.1%; $P = .02$), EF (63.6 ± 5.2% *v* 62.2 ± 5.7%; $P = .08$), and fewer participants with lower LV function (4.1% *v* 12.5%; $P = .04$). Measurements of global longitudinal strain also favored the dexrazoxane group ($P = .03$-$.06$). The dexrazoxane group

TABLE 2. Demographic and Clinical Characteristics of Childhood Cancer Survivors Treated With Doxorubicin, by Dexrazoxane Assignment Status

Characteristic	Dexrazoxane (n = 99)	No Dexrazoxane (n = 96)	*P*
Female sex, No. (%)	45 (45.5)	46 (47.9)	.73
Age at diagnosis, years, median (range)	10.7 (0.9-19.8)	12.3 (0.5-20.7)	.05
Current age, years, median (range)	27.8 (17.3-39.2)	30.9 (16.1-40.5)	.03
White non-Hispanic race/ethnicity, No. (%)	82 (82.8)	81 (84.4)	.77
Original study, No. (%)			
P9404	39 (39.4)	30 (31.3)	.16
P9425	8 (8.1)	19 (19.8)	
P9426	19 (19.2)	15 (15.6)	
P9754[a]	4 (4.0)	6 (6.3)	
DFCI 95-01	29 (29.3)	26 (27.1)	
Original cancer, No. (%)			
ALL	58 (58.6)	43 (44.8)	.29
Lymphoblastic lymphoma	10 (10.1)	13 (13.5)	
Hodgkin lymphoma	27 (27.3)	34 (35.4)	
Osteosarcoma	4 (4.0)	6 (6.3)	
Protocol-specified cumulative doxorubicin dose, mg/m^2 mean (SD)	305 (92)	288 (90)	.20
Cumulative doxorubicin dose ≥ 250 mg/m^2, No. (%)	76 (76.8)	69 (71.9)	.43
Radiotherapy exposure to the heart, No. (%)	22 (22.2)	31 (32.3)	.11
Heart radiotherapy dose, Gy, median (IQR)[b]	25.5 (21.0-25.5)	21.0 (21.0-25.5)	.14

Abbreviations: ALL, acute lymphoblastic leukemia; DFCI, Dana Farber Cancer Institute; IQR, interquartile range; SD, standard deviation.
[a]Four from P9754 and six matched controls.
[b]Among those exposed only.

also had significantly lower BNP and NT-proBNP levels, indicating reduced myocardial stress ($P < .01$); this included a significantly smaller proportion of participants with NT-proBNP levels above an age- and sex-specific 97.5th percentile cutoff ($P = .004$).[22]

In subanalyses, differences in LV systolic function favoring dexrazoxane appear to be more evident in female versus male participants, and among those treated with doxorubicin doses ≥ 250 mg/m^2 versus < 250 mg/m^2 (Table 4). In sensitivity analyses, measurements of LV systolic function did not substantially differ among participants enrolled from sites with ≥ 50% versus < 50% participation (data not shown). Dexrazoxane status also was not associated with differences in conventional cardiovascular risk factors, diastolic function, or other blood biomarkers (Appendix Table A2, online only).

Multivariable analyses confirmed these results, with dexrazoxane assignment associated with better LV systolic function (FS absolute difference: +1.4% [95% CI, 0.3 to 2.5]; EF absolute difference: +1.6% [95% CI, 0.0 to 3.2]), and blood biomarkers consistent with lower myocardial stress (BNP, –6.7 pg/mL [95% CI, –10.6 to –2.8]; NT pro-BNP, –22.1 pg/mL [95% CI, –34.3 to –9.8]; Table 5). The absolute differences in global longitudinal strain, although not statistically significant, also favored dexrazoxane (endocardial, –0.8% [95% CI, –1.7 to 0.1]; myocardial, –0.8% [95% CI, –1.5 to 0.0]). Finally, the risk of reduced LV function was lower in the dexrazoxane group (OR, 0.24 [95% CI, 0.07 to 0.81; Fig 1). Dexrazoxane's protective association was specific to participants treated with ≥ 250 mg/m^2 of doxorubicin (OR, 0.19 [95% CI, 0.05 to 0.76]) and not seen in those receiving < 250 mg/m^2 (OR, 1.17 [95% CI, 0.07 to 20.35]). If a more stringent definition for LV systolic dysfunction was adopted (FS < 28%, EF < 50%), the association with dexrazoxane was similar but less precise—among participants treated with doxorubicin ≥ 250 mg/m^2, OR, 0.29 (95% CI, 0.05 to 1.50).

DISCUSSION

In this prospective multi-institutional study, we found that long-term survivors of childhood cancer treated with dexrazoxane tended to have better LV systolic function and lower blood biomarker levels of myocardial stress compared with those not treated with dexrazoxane. These benefits were accentuated in survivors receiving higher anthracycline (doxorubicin) doses. Most participants had been treated on clinical trials in which they were randomly assigned to dexrazoxane, and all long-term study outcomes were interpreted by assessors blinded to dexrazoxane status.

We detected modest echocardiographic differences in LV systolic function (< 2% absolute difference in either FS or

TABLE 3. Echocardiographic Measurements and Blood Biomarker Concentrations of Childhood Cancer Survivors Treated With Doxorubicin, by Dexrazoxane Assignment Status

Outcomes	No.[a]	Dexrazoxane	No Dexrazoxane	*P*
LV structure, mean (SD)				
End-diastolic dimension, cm	192	4.9 (0.6)	4.9 (0.5)	.75
End-systolic dimension, cm	192	3.2 (0.4)	3.2 (0.4)	.56
Posterior wall thickness, cm	192	0.8 (0.2)	0.8 (0.2)	.85
Interventricular septal thickness, cm	192	0.8 (0.2)	0.8 (0.2)	.29
Thickness-dimension ratio	192	0.17 (0.04)	0.17 (0.04)	.89
LV systolic function, mean (SD)				
FS, %	192	34.7 (3.6)	33.4 (4.1)	.02
EF, %	172	63.6 (5.2)	62.2 (5.7)	.08
Lower function, No. (%)[b]	193	4 (4.1)	12 (12.5)	.04
Myocardial strain, mean (SD)				
Endocardial global longitudinal strain, %	193	–19.9 (2.9)	–19.0 (3.5)	.06
Myocardial global longitudinal strain, %	193	–15.4 (2.4)	–14.6 (2.9)	.03
Blood biomarkers				
Detectable high sensitivity cardiac troponin-T, No. (%)[c]	191	11 (11.1)	14 (15.2)	.40
BNP, pg/mL, median (IQR)	190	10.3 (6.0-16.7)	15.0 (8.0-28.6)	.003
N-terminal proBNP, pg/mL, median (IQR)	193	30.4 (17.4-58.6)	48.2 (24.1-81.5)	.002
Above age- and sex-specific 97.5%tile cutoff, No. (%)	193	9 (9.1)	23 (24.5)	.004

Abbreviations: BNP, B-type natriuretic peptide; EF, ejection fraction; FS, fractional shortening; IQR, interquartile range; LV, left ventricular; SD, standard deviation.

[a]Numbers analyzed, as not all outcomes could be assessed in all participants (n = 195).

[b]Defined as FS < 30% or EF < 50%, or a history of cardiomyopathy (one participant received dexrazoxane, three did not).

[c]If ≥ 6 pg/mL; detectable values ranged from 6.05 to 40.11 pg/mL.

EF). However, the mean age of our participants was only 29 years, and clinical heart failure following treatment for childhood cancer has a long latency period. For example, internationally validated prediction models show that even for survivors at high risk for cardiomyopathy, the cumulative incidence of clinical cardiomyopathy by age 30 years is < 5%, but that it increases to > 10% by age 40 years.[3] As such, the differences we found in this study may become more prominent as survivors age and that any benefit from dexrazoxane could become more evident with further follow-up.[23,24] Mild depression of LV function has been associated with subsequent increased all-cause mortality in other pediatric populations such as HIV-infected children.[25] Finally, it is important to acknowledge that the absolute differences in LV function reported in this study can be within the intra-observer and interobserver variability of measurements at an individual level.[20,26] However, we sought to enhance the rigor of our results by centrally remeasuring all study echocardiograms in blinded fashion. Central remeasurement has been shown to improve the reliability of echocardiographic measurements in cardiac clinical trials, which focus on mean group differences.[27]

Aside from minimizing anthracycline exposure, dexrazoxane is the only other primary cardioprotective strategy available to children and adolescents with cancer. Studies examining potential cardioprotection with other agents (eg, coenzyme-Q10, L-carnitine, and N-acetylcysteine), liposomal formulations of anthracyclines, or prolonged anthracycline infusions have not found those strategies to benefit children and adolescents.[2,8,28,29] Within COG, new liposomal anthracycline formulations (eg, ClinicalTrials.gov identifier: NCT04293562) are being tested, but efficacy data are not yet available. However, although dexrazoxane appears to offer some cardioprotection, this protection is not complete.[30] Periodic echocardiographic surveillance is recommended for all survivors treated with anthracyclines, and if the heart was exposed to radiotherapy.[21] Although our study identified significant differences in serum natriuretic peptide levels, there is no currently accepted role for using this biomarker for post cancer-therapy cardiomyopathy surveillance.[31]

Our findings are consistent with earlier reports from randomized trials of dexrazoxane. Dexrazoxane was associated with significantly reduced serum cardiac troponin concentrations immediately after doxorubicin exposure in the DFCI 95-01 study.[11] Five years after therapy, the dexrazoxane group had less pathologic LV remodeling (a greater wall thickness-dimension ratio) and better LV systolic function; these differences were particularly pronounced in females.[12] In patients treated on protocol P9404, with

TABLE 4. Selected Study Echocardiographic Measurements and Blood Biomarker Concentrations of Childhood Cancer Survivors Treated With Doxorubicin With and Without Dexrazoxane, Stratified by Sex and Cumulative Doxorubicin Dose

	Females (n = 91)			Males (n = 104)			Doxorubicin < 250 mg/m^2 (n = 50)			Doxorubicin ≥ 250 mg/m^2 (n = 145)		
Outcomes	**DRZ**	**No DRZ**	***P***	**DRZ**	**No DRZ**	***P***	**DRZ**	**No DRZ**	***P***	**DRZ**	**No DRZ**	***P***
Thickness-dimension ratio, mean (SD)	0.18 (0.04)	0.16 (0.04)	.03	0.17 (0.04)	0.18 (0.04)	.11	0.18 (0.03)	0.19 (0.04)	.40	0.17 (0.04)	0.17 (0.04)	.41
FS, mean (SD), %	35.6 (3.3)	33.0 (3.6)	< .001	34.0 (3.7)	33.8 (4.5)	.76	35.5 (4.5)	35.0 (4.2)	.71	34.5 (3.3)	32.8 (3.9)	.005
EF, mean (SD), %	64.4 (4.3)	62.3 (5.6)	.06	62.9 (5.7)	62.0 (5.8)	.46	64.3 (7.0)	63.3 (4.8)	.57	63.5 (4.5)	61.7 (6.0)	.06
Lower LV function, No. (%)[a]	2 (4.7)	6 (13.0)	.27	2 (3.7)	6 (12.0)	.15	1 (4.5)	1 (3.7)	> .99	3 (4.0)	11 (15.9)	.02
BNP, median (IQR), pg/mL	13.0 (10.0-21.6)	21.5 (11.1-33.8)	.03	7.9 (4.0-11.7)	11.8 (6.0-16.5)	.02	8.0 (4.0-20.0)	12.5 (6.0-31.0)	.14	11.0 (6.0-16.7)	15.0 (8.0-26.0)	.01
N-terminal proBNP, median (IQR), pg/mL	58.2 (34.3-69.5)	77.4 (47.1-102.8)	.04	19.8 (13.1-31.2)	34.8 (20.2-54.4)	.002	31.2 (12.1-77.1)	45.0 (19.4-81.3)	.40	29.9 (18.9-57.2)	49.2 (25.9-83.6)	.003
High N-terminal pro-BNP, No. (%)[b]	3 (6.7)	10 (22.2)	.07	6 (11.1)	13 (26.5)	.04	3 (13.0)	4 (14.8)	> .99	6 (7.9)	19 (28.4)	.001

Abbreviations: BNP, B-type natriuretic peptide; DRZ, dexrazoxane; EF, ejection fraction; FS, fractional shortening; IQR, interquartile range; LV, left ventricular; SD, standard deviation.

[a]Defined as FS < 30% or EF < 50%, or a history of cardiomyopathy.

[b]If above an age- and sex-specific 97.5 percentile cutoff.

TABLE 5. Multivariable Differences in Selected Echocardiographic Measurements and Blood Biomarker Concentrations of Childhood Cancer Survivors Treated With Doxorubicin With Dexrazoxane Versus Doxorubicin Without Dexrazoxane (referent group)

Outcome	Differences by Dexrazoxane Status (95% CI)[a]
Echocardiographic parameters	
LV thickness-dimension ratio	0.00 (–0.01 to 0.01)
LV systolic function, %	
FS	+1.40 (0.30 to 2.50)
EF	+1.60 (0.00 to 3.20)
Myocardial strain, %	
Endocardial global longitudinal strain	–0.80 (–1.70 to 0.10)
Myocardial global longitudinal strain	–0.80 (–1.50 to 0.00)
Blood biomarkers of myocardial stress, pg/mL	
BNP	–6.70 (–10.60 to –2.80)
N-terminal proBNP	–22.10 (–34.30 to –9.80)

Abbreviations: BNP, B-type natriuretic peptide; EF, ejection fraction; FS, fractional shortening; LV, left ventricular.

[a]Estimates adjusted for sex, age at cancer diagnosis, age at cardiac evaluation, protocol-specified doxorubicin dose, heart radiotherapy exposure, and history of cardiomyopathy.

3 years of follow-up, similar associations were found between dexrazoxane treatment and acute serum troponin concentrations, LV pathologic remodeling, and systolic function.[13] Nonrandomized pediatric data from patients with acute myeloid leukemia treated with daunorubicin and mitoxantrone also suggest that dexrazoxane minimized LV systolic dysfunction during therapy and for several years into follow-up.[32] Finally, the magnitude of the potential risk reduction we observed for lower LV systolic function is nearly identical to those reported in meta-analyses of randomized clinical trials (primarily of older adult patients with breast cancer), where the aggregated risk ratio for clinical heart failure was 0.18 (95% CI, 0.10 to 0.32).[8] In these meta-analyses, when subclinical heart failure also was assessed, the effect associated with dexrazoxane remained highly protective (risk ratio, 0.29 [95% CI, 0.20 to 0.41]). Meta-analyses of nonrandomized studies in children found similar results at a median follow-up < 10 years.[33]

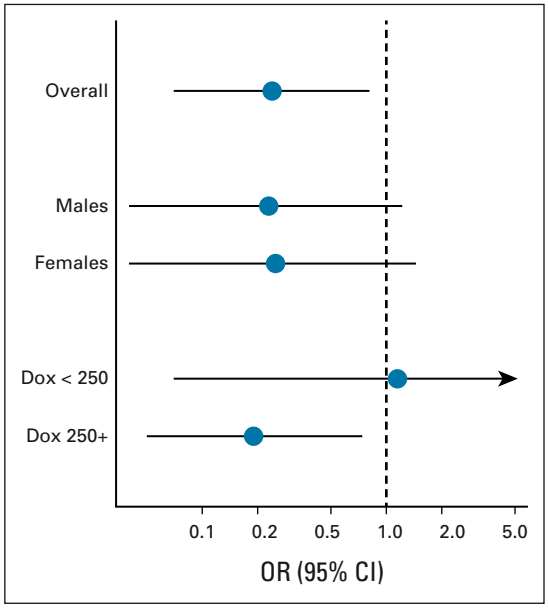

FIG 1. Odds of having lower left ventricular function (fractional shortening < 30% or ejection fraction < 50%) among childhood cancer survivors treated with Dox and dexrazoxane versus Dox without dexrazoxane (referent group). Results overall, by sex, and by lower and greater cumulative Dox doses (< 250 or ≥ 250 mg/m^2). Dox, doxorubicin; OR, odds ratio.

Historically, dexrazoxane use has been limited in children.[34,35] In part, its use was limited because evidence of long-term benefits was lacking, as well as concern about acute toxicities, possible effects on cancer recurrence rates, and induced second cancers. Although concurrent administration of dexrazoxane appeared to be associated with greater hematologic toxicity and infections in children with Hodgkin lymphoma,[15,16] this association was not observed in children with lymphoblastic leukemia and lymphoma, or in pooled summaries of trials in adults.[8,13] In our other long-term follow-up studies of patients in these randomized trials, dexrazoxane was not associated with a difference in overall survival, risk of relapse, or second cancers after nearly 20 years of follow-up.[36] Similarly, dexrazoxane has not been associated with differential relapse rates in randomized trials of adults with cancer.[8]

There are some additional limitations to our results. Although we assessed the impact of dexrazoxane on patients who received a broad range of doxorubicin doses (100-600 mg/m^2), the trials of interest did not use other anthracyclines (eg, daunorubicin and idarubicin) or mitoxantrone (an anthraquinone). As such, our results may not fully apply to patients treated with these other agents.[37] However, nonrandomized data from children with myeloid leukemia treated with daunorubicin and mitoxantrone suggest that dexrazoxane mitigates short-term LV systolic dysfunction.[32] We also were able to prospectively assess only 41% of potential participants. Given the fragmentary nature of health care in the United States (and to a lesser degree, Canada), most nonparticipants were no longer actively seen by the institutions that provided their pediatric cancer treatment, and were likely lost to follow-up.

Although response bias may have influenced our results, the direction of any bias is not obvious. The observation that about half the enrolled participants had received dexrazoxane was reassuring. Nonparticipants were more likely to be male and belong to a racial or ethnic minority, but these characteristics did not differ by dexrazoxane status. As such, although our participation rates could limit generalizability, we do not

believe it affects the internal validity of our results. Nevertheless, to address potential response bias, in a recent publication, we linked patients enrolled in these five clinical trials to multiple administrative data sets: Medicaid, the US National Death Index, the Organ Procurement and Transplantation Network (US registry of solid organ transplantation), and the Pediatric Health Information System (administrative and billing data from 50 children's hospitals).[36] Only one participant (not treated with dexrazoxane) was found to have received a heart transplant.[36] Analysis of these administrative data also indicated that serious cardiovascular outcomes occurred less commonly in the dexrazoxane group compared with the no dexrazoxane group (4% *v* 18%), including cardiomyopathy (4% *v* 8%), findings that are consistent with the direction of our current study.[36]

We believe this study provides evidence that dexrazoxane offers measurable long-term cardioprotection for children and adolescents with cancer receiving anthracycline-based chemotherapy. Per a recently published international consensus guideline, oncology providers should consider administering dexrazoxane to children and adolescents expected to receive ≥ 250 mg/m^2 of cumulative doxorubicin, or an equivalent amount of other anthracyclines.[38] Use of dexrazoxane could be a patient-centered decision in instances where patients are expected to receive lower cumulative anthracycline doses, accounting for other risk factors, including the risk of slow early response or cancer relapse, and whether intensification strategies in these situations may require additional cardiotoxic treatments. However, given the very long time frame for cardiomyopathy development in survivors of childhood cancer, combined with preclinical data that show cardiomyocyte injury following even low doses of doxorubicin exposure, the risk benefits of dexrazoxane use in this situation should be carefully weighed.[39]

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DISCLAIMER

Funders were not involved with the data collection, analysis, or interpretation of the study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the US National Institutes of Health.

PRIOR PRESENTATION

Presented at the 2016 American Society of Hematology annual meeting, San Diego, CA, December 5, 2016; and at the 2020 ASCO annual meeting, virtual, May 29, 2020.

SUPPORT

Supported by National Institutes of Health (P01 CA068484, R01 CA211996, U10 CA098543, U10 CA098413, U10 CA180886, U10 CA180899, U10 CA095861, UG1 CA189955), the St Baldrick's Foundation, and the Leukemia and Lymphoma Society.

CLINICAL TRIAL INFORMATION

NCT01790152

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.02423.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Dexrazoxane and Long-Term Heart Function in Survivors of Childhood Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Research Funding: Abbott

Richard Aplenc
Expert Testimony: Vorys, Sater, Seymour, and Pease LLP

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No other potential conflicts of interest were reported.

APPENDIX

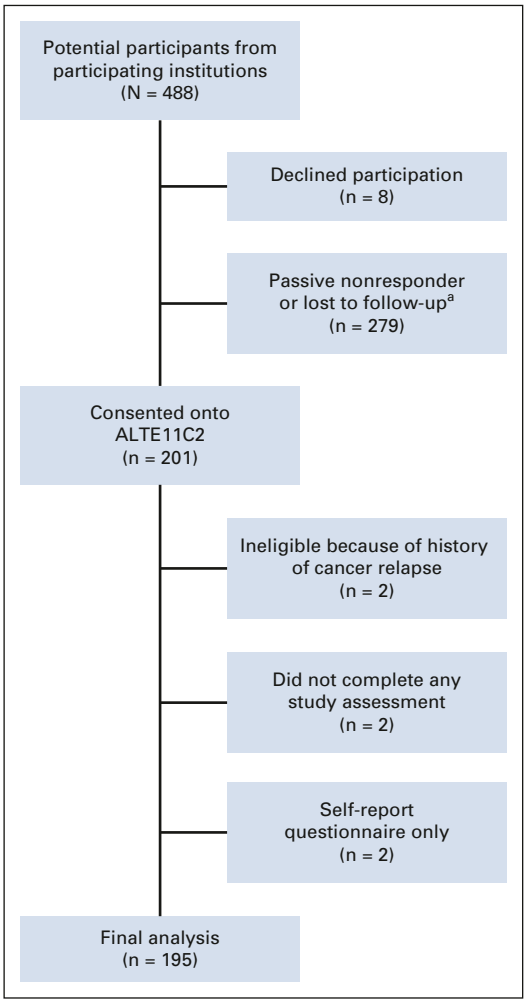

FIG A1. Children's Oncology Group ALTE11C2 study participation flow chart. [a]Institutions did not differentiate between participants who were lost to follow-up versus participants who were felt to be reached but did not respond to study approaches.

TABLE A1. Demographic and Clinical Characteristics of Childhood Cancer Survivors by Children's Oncology Group Protocol ALTE11C2 Participation Status

Characteristic	Participants (n = 195)	Nonparticipants (n = 287)	*P*	From Sites With ≥ 50% Participation (n = 117)	From Sites With < 50% Participation (n = 78)	*P*
Female sex, No. (%)	91 (46.7)	81 (28.2)	< .001	59 (50.4)	32 (41.0)	.20
Age at diagnosis, years, median (range)	11.2 (0.5-20.7)	11.1 (0.2-22.0)	.80	11.3 (0.5-20.7)	10.9 (0.9-18.0)	.28
Current age, years, median (range)	29.4 (16.1-40.5)	28.4 (18.0-41.4)[a]	.82	30.1 (16.1-39.5)	28.3 (17.8-40.5)	.28
White non-Hispanic race/ethnicity, No. (%)	163 (83.6)	203 (70.7)	.001	99 (84.6)	64 (82.1)	.64
Original study, No. (%)						
P9404	69 (35.4)	121 (42.2)	.46	37 (31.6)	32 (41.0)	.58
P9425	27 (13.8)	38 (13.2)		15 (12.8)	12 (15.4)	
P9426	34 (17.4)	49 (17.1)		23 (19.7)	11 (14.1)	
P9754[b]	10 (5.1)	8 (2.8)		6 (5.1)	4 (5.1)	
DFCI 95-01	55 (28.2)	71 (24.7)		36 (30.8)	19 (24.4)	
Original cancer, No. (%)						
ALL	101 (51.8)	153 (53.3)	.56	59 (50.4)	42 (53.8)	.98
Lymphoblastic lymphoma	23 (11.8)	39 (13.6)		14 (12.0)	9 (11.5)	
Hodgkin lymphoma	61 (31.3)	87 (30.3)		38 (32.5)	23 (29.5)	
Osteosarcoma	10 (5.1)	8 (2.8)		6 (5.1)	4 (5.1)	
Cumulative doxorubicin dose, mg/m^2, mean (SD)	297 (91)	298 (85)	.92	289 (95)	309 (85)	.14
Cumulative doxorubicin dose ≥ 250 mg/m^2, No. (%)	145 (74.4)	213 (75.0)	.87	82 (70.1)	63 (80.8)	.09
Radiotherapy exposure to the heart, No. (%)	53 (27.2)	56 (19.5)	.048	33 (28.2)	20 (25.6)	.69
Heart radiotherapy dose, Gy, median (IQR)[c]	24.5 (21.0-25.5)	21.0 (21.0-25.5)	.17	25.5 (21.0-25.5)	21.0 (21.0-25.5)	.17
Dexrazoxane exposure, No. (%)	99 (50.8)	147 (51.2)	.92	62 (53.0)	37 (47.4)	.45

Abbreviations: ALL, acute lymphoblastic leukemia; DFCI, Dana Farber Cancer Institute; IQR, interquartile range; SD, standard deviation.

[a]On the basis of the median enrollment date for participants.

[b]Includes matched controls without dexrazoxane exposure.

[c]Among those exposed only.

TABLE A2. Conventional Cardiovascular Risk Factors, Diastolic Function, and Other Cardiovascular Blood Biomarker Concentrations of Childhood Cancer Survivors Treated With Doxorubicin With and Without Dexrazoxane

Outcomes	No.[a]	Dexrazoxane	No Dexrazoxane	*P*
Blood pressure,[b] mean (SD)				
Systolic, mmHg	195	117.0 (13.0)	116.8 (11.5)	.88
Diastolic, mmHg	195	70.3 (9.9)	70.6 (8.7)	.85
Body mass index, mean (SD)	195	27.4 (6.8)	27.0 (5.8)	.69
Echocardiographic indices of diastolic function, mean (SD)				
Mitral inflow E, cm/s	193	80.7 (13.6)	81.2 (17.4)	.84
Mitral inflow A, cm/s	193	54.3 (15.6)	56.7 (16.0)	.30
Mitral inflow E/mitral inflow A	192	1.6 (0.5)	1.5 (0.5)	.21
Mitral inflow deceleration time, ms	192	186.1 (50.8)	188.6 (60.9)	.76
Septal E′, cm/s	186	11.6 (2.7)	11.0 (2.4)	.09
LV lateral E′, cm/s	192	15.9 (3.5)	15.0 (4.4)	.12
Mitral inflow E/LV lateral E′	190	5.3 (1.5)	5.7 (1.8)	.15
Mitral inflow E/LV septal E′	184	7.2 (1.9)	7.6 (2.2)	.20
Blood biomarker concentrations,[c] median (IQR)				
Total cholesterol, mg/dL	191	178 (154-202)	180 (153-205)	.86
High density lipoprotein, mg/dL	191	51 (42-61)	53 (45-61)	.29
Triglyceride, mg/dL	191	86 (56-124)	83 (62-125)	.78
Glucose, mg/dL	191	86 (82-94)	87 (78-93)	.49
Hemoglobin A1c, %	178	5.0 (4.7-5.3)	5.1 (4.8-5.3)	.32
High-sensitivity C-reactive protein, mg/L	189	1.70 (0.60-4.66)	1.98 (0.88-6.00)	.19
Interleukin-6, pg/mL	194	2.0 (1.0-3.0)	1.9 (1.0-3.0)	.96
Galectin-3, ng/mL	192	6.90 (5.31-8.40)	6.68 (5.23-7.69)	.70
Growth differentiation factor-15, pg/mL	192	409 (320-475)	407 (335-509)	.32
Soluble urokinase plasminogen activator receptor, ng/mL	190	1.90 (1.67-2.18)	1.98 (1.67-2.34)	.26
ST2, ng/mL	192	11.51 (8.42-16.52)	12.37 (8.96-16.93)	.69

Abbreviations: IQR, interquartile range; LV, left ventricular; SD, standard deviation.

[a]Number available for analysis, as not all outcomes could be assessed in all participants (n = 195).

[b]Resting blood pressure (four measurements, first one discarded, average of the remaining three).

[c]Study procedures required a ≥ 10-hour fasting blood draw.