Effect of Dexrazoxane on Left Ventricular Systolic Function and Treatment Outcomes in Patients With Acute Myeloid Leukemia: A Report From the Children's Oncology Group

Kelly D. Getz, PhD, MPH^{1,2}; Lillian Sung, MD, PhD³; Todd A. Alonzo, PhD⁴; Kasey J. Leger, MD, MS⁵; Robert B. Gerbing, BS, MA⁶; Jessica A. Pollard, MD⁷; Todd Cooper, DO⁵; E. Anders Kolb, MD⁸; Alan S. Gamis, MD, MPH⁹; Bonnie Ky, MD, MSCE²; and Richard Aplenc, MD, MSCE^{1,2}

abstract

PURPOSE To determine whether dexrazoxane provides effective cardioprotection during frontline treatment of pediatric acute myeloid leukemia (AML) without increasing relapse risk or noncardiac toxicities of the chemotherapy regimens.

PATIENTS AND METHODS This was a multicenter study of all pediatric patients with AML without high allelic ratio FLT3/ITD treated in the Children's Oncology Group trial AAML1031 between 2011 and 2016. Median follow-up was 3.5 years. Dexrazoxane was administered at the discretion of treating physicians and documented at each course. Ejection fraction (EF) and shortening fraction (SF) were recorded after each course and at regular intervals in follow-up. Per protocol, anthracyclines were to be withheld if there was evidence of left ventricular systolic dysfunction (LVSD) defined as SF < 28% or EF < 55%. Occurrence of LVSD, trends in EF and SF, 5-year event-free survival (EFS) and overall survival (OS), and treatment-related mortality (TRM) were compared by dexrazoxane exposure.

RESULTS A total of 1,014 patients were included in the analyses; 96 were exposed to dexrazoxane at every anthracycline course, and 918 were never exposed. Distributions of sex, age, race, presenting WBC count, risk group, treatment arm, and compliance with cardiac monitoring were similar for dexrazoxane-exposed and -unexposed patients. Dexrazoxane-exposed patients had significantly smaller EF and SF declines than unexposed patients across courses and a lower risk for LVSD (26.5% v 42.2%; hazard ratio, 0.55; 95% CI, 0.36 to 0.86; $P = .009$). Dexrazoxane-exposed patients had similar 5-year EFS (49.0% v 45.1%; $P = .534$) and OS (65.0% v 61.9%; $P = .613$) to those unexposed; however, there was a suggestion of lower TRM with dexrazoxane (5.7% v 12.7%; $P = .068$).

CONCLUSION Dexrazoxane preserved cardiac function without compromising EFS and OS or increasing noncardiac toxicities. Dexrazoxane should be considered for cardioprotection during frontline treatment of pediatric AML.

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ASSOCIATED CONTENT

Data Supplement

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INTRODUCTION

Anthracycline intensification has played a central role in improving overall survival (OS) for pediatric acute myeloid leukemia (AML).¹⁻⁵ However, anthracyclines increase both early- and late-term cardiotoxicity.⁶⁻²⁰ Anthracyclines generate iron-mediated free radicals when metabolized by the mitochondria, which triggers myocardial cell death and left ventricular systolic dysfunction (LVSD).^{14,21,22} Anthracyclines also intercalate DNA by binding topoisomerase II β , which is abundant in cardiomyocytes, thus inhibiting DNA replication and increasing apoptosis to induce LVSD.^{14,21,22} Anthracycline-associated cardiotoxicity is dose dependent, and approximately 70% of pediatric

patients with AML treated per Children's Oncology Group (COG)-based protocols receive cumulative anthracycline doses > 400 mg/m² during initial treatment. At least 12% of patients with AML experience LVSD within 1 year of initiating therapy and experience significant reductions in 5-year event-free survival (EFS) and OS with higher treatment-related mortality (TRM).¹³

Dexrazoxane interferes with iron-mediated free radical formation and induces rapid degradation of topoisomerase II β to reduce anthracycline-associated cardiotoxicity.^{21,23,24} Despite consistent evidence that has demonstrated cardioprotective benefits in various adult and pediatric cancer populations,²⁵⁻³⁰

CONTEXT

Key Objective

Our primary objective was to evaluate whether dexrazoxane provides effective cardioprotection during frontline treatment of pediatric acute myeloid leukemia without increasing relapse risk or the noncardiac toxicities of the chemotherapy regimens.

Knowledge Generated

Dexrazoxane use prior to anthracycline courses preserved cardiac function with a 45% reduction in left ventricular systolic dysfunction that warranted per-protocol chemotherapy modifications, and a 60% reduction of grade 2 or higher left ventricular systolic dysfunction. Furthermore, addition of dexrazoxane resulted in lower treatment-related mortality with comparable 5-year event-free survival and overall survival without increasing non-cardiac chemotherapy toxicity.

Relevance

Dexrazoxane use should be considered during frontline treatment for pediatric acute myeloid leukemia to mitigate short-term anthracycline-associated cardiac dysfunction.

dexrazoxane historically has been used in < 5% of pediatric patients with AML in the United States.^{31,32} The reluctance to use dexrazoxane may stem from a concern for secondary malignancy,³³ guidance in 2011 by the European Medicines Agency (EMA) that prohibits dexrazoxane in children,³⁴ and an absence of trials that demonstrate protection against clinical heart failure. However, new data that have demonstrated decreased survival in pediatric patients with AML who experience on-therapy cardiotoxicity¹³ and revised EMA guidance for dexrazoxane use in children with high anthracycline exposures^{35,36} suggest that establishment of dexrazoxane as effective cardioprotection in pediatric AML is critical and, if demonstrated, would encourage greater use.

AAML1031, the most recent COG trial for de novo AML, prospectively captured dexrazoxane exposure at each treatment course and longitudinal measures of ejection fraction (EF) and shortening fraction (SF) during therapy and off-protocol follow-up as part of a specific aim to evaluate dexrazoxane effectiveness. We hypothesized that consistent dexrazoxane exposure would result in smaller EF/SF declines and a corresponding reduction in LVSD incidence without increasing rates of relapse or noncardiac toxicities.

PATIENTS AND METHODS

Study Population and Anthracycline Exposure

AAML1031 enrolled patients < 30 years of age without Down syndrome for frontline treatment of de novo AML. Patients were not excluded from the trial on the basis of EF/SF measurements. Course-specific treatment regimens were determined on the basis of risk stratification and random assignment (Data Supplemental, online only). Anthracyclines were administered as intravenous (IV) infusions; daunorubicin (50 mg/m²/dose or 1.67 mg/kg/dose if body surface area [BSA] < 0.6 m²) was administered over 1-15 minutes, and mitoxantrone (12 mg/m²/dose or

0.4 mg/kg/dose if BSA < 0.6 m²) was administered over 15-30 minutes. The current analyses were restricted to patients without high allelic ratio (HAR) FLT3/ITD-positive AML for whom enrollment was open from June 2011 through January 2016. Patients who were HAR FLT3/ITD positive (ie, allelic ratio > 0.4) were excluded because of being under the purview of the COG Data Safety Monitoring Committee at the time of data cutoff. All patients enrolled in AAML1031 provided informed consent for use of trial data for research.

Dexrazoxane Exposure

Dexrazoxane use was at the discretion of the individual treating physician. Exposure to dexrazoxane (yes or no) was captured in the study database for each anthracycline-containing course. Dexrazoxane-exposed patients fell into two categories: patients who received dexrazoxane in every anthracycline-containing course, and patients who received dexrazoxane in at least one but not all anthracycline courses. We were primarily interested in the effectiveness of consistent pretreatment with dexrazoxane; thus, only patients who received dexrazoxane at every anthracycline course were included in primary analyses.

Outcomes

Echocardiogram or multiple-gated acquisition (MUGA) scan was required before each course, at the end of protocol therapy, and every 6-12 months during off-protocol follow-up. The primary outcome of LVSD was defined as SF < 28% or EF < 55% because these were the protocol-mandated thresholds at which anthracyclines were withheld and not restarted unless observed in the context of microbiologically proven bacteremia or sepsis and SF/EF recovery to above those limits. Occurrence of more severe cardiac dysfunction was also evaluated, specifically LVSD grade ≥ 2 (SF < 24% or EF < 50%) and LVSD grade ≥ 3 (SF < 15% or EF < 40%) on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

EFS was defined as the time from study enrollment until death, induction failure, secondary malignancy, or relapse, whereas OS was defined as time to death. Relapse risk was defined as time from enrollment to relapse, secondary malignancy, or induction failure, where deaths without these events were considered competing events. TRM was defined as time from enrollment to death within 30 days after last study-directed chemotherapy or 200 days after study-directed stem-cell transplantation, where relapse, secondary malignancy, or induction failure were considered competing events. Patients were censored at last contact. Noncardiac adverse event (AE) reports for mucositis and microbiologically documented bloodstream infections, course-specific intensive care unit (ICU) requirements, durations of neutropenia, and lengths of hospitalization were obtained from the trial database.

Covariates

Patient demographics and clinical characteristics were obtained from the AAML1031 database. Body mass index percentiles for age and sex were computed on the basis of year 2000 Centers for Disease Control and Prevention (CDC) growth chart data (patients age 2-20 years) and the WHO reference (patients age < 2 years) and were classified into weight categories as follows: obese ($\geq$ 95th percentile), overweight (85th to < 95th percentile), healthy weight (5th to < 85th percentile), and underweight (< 5th percentile). Patients age > 20 years were classified on the basis of CDC body mass index thresholds. Compliance rates for cardiac monitoring were computed for each patient as the proportion of protocol-mandated evaluations documented as completed in the study database.

Statistical Analyses

AAML1031 data used in these analyses were current as of June 30, 2018. Patient characteristics were compared by dexrazoxane exposure using χ^2 or Fisher's exact tests. Echocardiogram compliance was compared using *t* tests. Generalized linear models compared rates of bloodstream infection and mucositis, ICU requirements, duration of neutropenia, and length of hospitalization. Generalized estimating equation methods were used to account for nonindependence of observations from the same patient.

Fine and Gray method was used to compute hazard ratios (HRs) to compare cardiotoxicity incidence by dexrazoxane exposure.^{37,38} Follow-up for cardiotoxicity was defined as time from start of induction I chemotherapy to first occurrence of cardiotoxicity. In secondary analyses, infection-associated cardiotoxicity events were excluded. While the reporting period for each echocardiogram was captured through study case report forms, exact dates were not. Thus, LVSD events were assigned to the midpoint of the corresponding reporting period for time-to-LVSD analyses. Results using the first or last dates of the given reporting period were not meaningfully different. Patients who did not experience cardiotoxicity were censored at relapse, loss to

follow-up, or 4 years after the start of treatment; deaths were considered competing events. Mixed-effects regressions with a heterogeneous autoregressive correlation structure for observations from the same patient were used to compare the longitudinal trends in EF and SF by dexrazoxane exposure.

Kaplan-Meier curves of EFS, relapse risk, TRM, and OS by dexrazoxane exposure were plotted. Because of partial violation of the Cox proportionality assumption, we performed landmark analyses to compare outcomes at 5 years (or 1 year for TRM) by dexrazoxane exposure. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and STATA 14 (StataCorp, College Station, TX) statistical software.

Sensitivity Analyses

Although we were primarily interested in the effectiveness of consistent dexrazoxane pretreatment, our analyses may have excluded patients who initially received dexrazoxane with poor outcomes that led to nonuse with subsequent planned anthracycline courses. To confirm the robustness of our results, we performed intention-to-treat sensitivity analyses in which all patients documented as having received dexrazoxane at induction 1 (first anthracycline course) were considered exposed, and all others were considered unexposed.

Either echocardiogram or MUGA scan was an acceptable modality for cardiac monitoring. Because MUGA scan may provide more accurate measurements, we performed sensitivity analyses restricted to patients monitored with echocardiogram.

RESULTS

Study Population

A total of 1,092 pediatric patients with de novo, non-HAR FLT3/ITD AML were treated in AAML1031. Eighty-four percent were never exposed to dexrazoxane during on-protocol therapy, 9% were consistently exposed to dexrazoxane at each anthracycline-containing course, and 7% (*n* = 78) received dexrazoxane during some but not all anthracycline courses. The majority of the latter group (*n* = 53; 68%) did not receive dexrazoxane before their initial anthracycline exposure and, rather, had it introduced at a subsequent anthracycline course. Primary analyses were limited to comparisons between patients who consistently received dexrazoxane (*n* = 96) and those who never received dexrazoxane (*n* = 918).

Patients were enrolled from 178 institutions; 85% did not administer dexrazoxane for cardioprotection. Among the remaining 26 institutions, the prevalence of consistent dexrazoxane use ranged from 4% to 100%; 65% consistently used dexrazoxane (*n* = 11) or shifted practice toward dexrazoxane use over the study period (*n* = 6). Institutions that used dexrazoxane enrolled a median of 11 patients

TABLE 1. Characteristics of the Study Population Overall and by Dexrazoxane Exposure

Patient Characteristic	Covariate Distribution, No. (%)			P ^c
	AAML1031 Overall ^a	Dexrazoxane Status ^b		
		Exposed	Not Exposed	
Age at diagnosis, years				
0-1	236 (21.6)	19 (19.8)	201 (21.9)	.634
2-10	370 (33.9)	37 (38.5)	311 (33.9)	.360
≥ 11	486 (44.5)	40 (41.7)	406 (44.2)	.631
Sex				
Female	522 (47.8)	49 (51.0)	436 (47.5)	.508
Male	570 (52.2)	47 (49.0)	482 (52.5)	
Race				
White	762 (69.8)	70 (72.9)	638 (69.5)	.488
Black	136 (12.5)	13 (13.5)	118 (12.9)	.848
Other ^d	194 (17.8)	13 (13.5)	162 (17.6)	.311
Ethnicity				
Hispanic or Latino	196 (18.5)	16 (17.2)	158 (17.8)	.895
Not Hispanic or Latino	861 (81.5)	77 (82.8)	732 (82.2)	
Weight status category				
Underweight	63 (5.8)	9 (9.4)	52 (5.7)	.146
Healthy weight	649 (59.5)	63 (65.6)	543 (59.3)	.218
Overweight	189 (17.3)	15 (15.6)	156 (17.0)	.733
Obese	189 (17.3)	9 (9.4)	165 (18.0)	.034
WBC at diagnosis, μL				
≤ 100,000	913 (83.7)	81 (84.4)	764 (83.3)	.791
> 100,000	178 (16.3)	15 (15.6)	153 (16.7)	
Risk classification				
Low ^e	836 (78.4)	72 (79.1)	702 (78.3)	.850
High ^f	230 (21.6)	19 (20.9)	195 (21.7)	
Not documented	26	5	21	
On-protocol stem-cell transplantation	79 (7.2)	8 (8.3)	67 (7.3)	.682
Randomly assigned treatment arm				
Standard	540 (49.5)	47 (49.0)	459 (50.0)	.846
Standard plus bortezomib	552 (50.5)	49 (51.0)	459 (50.0)	
Median duration of follow-up, years (IQR)	3.5 (2.5-4.7)	3.2 (2.4-4.2)	3.6 (2.5-4.8)	.028
Mean compliance rate for cardiac monitoring, % (SD)				
Overall compliance	74.5 (19.6)	73.7 (19.3)	74.6 (19.7)	.653
On-protocol compliance	90.6 (19.5)	92.2 (20.6)	90.5 (19.7)	.422
Off-protocol compliance	58.1 (31.0)	57.5 (25.0)	58.1 (31.4)	.822

Abbreviations: IQR, interquartile range; SD, standard deviation.

^aIncludes all patients enrolled in AAML1031, except those with high allelic ratio FLT3/ITD, regardless of dexrazoxane exposure.

^bExposed indicates patients documented as receiving dexrazoxane at all anthracycline-containing AAML1031 courses; not exposed indicates patients documented as never receiving dexrazoxane during frontline therapy on AAML1031. Patients who received dexrazoxane, but not at all anthracycline-containing courses, were excluded from the current analyses evaluating effects of dexrazoxane exposure.

^cP value for comparison of distributions of given covariate by dexrazoxane exposure status.

^dAsian, American Indian, Alaska Native, and Native Hawaiian or other Pacific Islander and those documented as multiple races or as unknown race.

^eCumulative anthracycline exposure for low-risk patients was 444 mg/m² in daunorubicin equivalents (assuming the daunorubicin equivalents conversion used by Children's Oncology Group at the time of the protocol, 1 mg/m² mitoxantrone = 3 mg/m² daunorubicin).

^fCumulative anthracycline exposure for high-risk patients was 294 mg/m² in daunorubicin equivalents.

(interquartile range [IQR], 5-20 patients), whereas institutions that never used dexrazoxane enrolled a median of 7 patients (IQR, 3-11 patients; $P = .005$).

Distributions of patient demographic and clinical characteristics were comparable between dexrazoxane-exposed and -unexposed patients (Table 1). In addition, compliance with cardiac monitoring was high (ie, 91% during on-protocol therapy, 75% overall) and did not differ by dexrazoxane exposure. Because there was no evidence for meaningful confounding or differential cardiotoxicity detection on the basis of comparability of characteristics between dexrazoxane-exposed and -unexposed patients, unadjusted comparisons are presented.

Impact of Dexrazoxane Use on LVSD

Echocardiogram was the predominant modality for evaluations of cardiac function and represented > 99% of evaluations regardless of dexrazoxane exposure ($P = .359$). Over a median follow-up of 3.5 years (IQR, 2.5-4.7 years), 39% of patients ($n = 397$) experienced protocol-defined LVSD. Median time to LVSD was 3.8 months (IQR, 2.0-6.2 months).

Protocol-defined LVSD incidence was significantly lower among patients consistently exposed to dexrazoxane relative to those who did not receive dexrazoxane (26.5% v 42.2%; HR, 0.55; 95% CI, 0.36 to 0.86; $P = .009$; Table 2). Magnitudes of association were more pronounced for progressively more restrictive definitions of cardiotoxicity. Specifically, dexrazoxane-exposed patients had a 60% lower risk for LVSD grade ≥ 2 (11% v 23%; HR, 0.40; 95% CI, 0.20 to 0.81; $P = .011$) and a 70% lower risk for LVSD grade ≥ 3 (3.8% v 8.5%; HR, 0.30; 95% CI, 0.07 to 1.23; $P = .094$). Results were similar, though modestly attenuated after excluding infection-associated cardiotoxicity events (Data Supplement).

Distributions of maximum LVSD grade differed by dexrazoxane exposure ($P = .012$), with a trend toward worse LVSD among patients not exposed to dexrazoxane. The trend seems to be driven by a combination of more acute LV decline on the basis of higher grade at initial documentation and greater worsening compared with patients exposed to dexrazoxane (Data Supplement).

Dexrazoxane was associated with significant differences in the longitudinal trends in SF and EF (dexrazoxane exposure-reporting period interaction, $P = .005$ for EF and $P < .001$ for SF; Fig 1). Dexrazoxane-exposed patients had a higher mean EF than unexposed patients at all treatment courses after induction II (Data Supplement). Despite some evidence of recovery, EF remained lower among unexposed than exposed patients, even in early off-protocol follow-up. Similar patterns were observed for SF.

Impact of Dexrazoxane Use on Cancer Treatment Outcomes

Patients completed a median of 4 courses regardless of dexrazoxane exposure ($P = .535$). Five-year EFS (49.0% v 45.1%; $P = .534$), relapse risk (42.3% v 47.7%; $P = .337$), and OS (65.0% v 61.9%; $P = .613$) rates among dexrazoxane-exposed patients were comparable to those who were unexposed (Fig 2). However, dexrazoxane-exposed patients had a 53% lower risk for TRM than unexposed patients, a difference that approached statistical significance (5.7% v 12.7%; $P = .068$). Among 42 patients unexposed to dexrazoxane who suffered TRM, 45% ($n = 19$) had documented cardiotoxicity, of whom 26% ($n = 5$) had an AE report that documented death as a result of heart failure. In contrast, among 5 dexrazoxane-exposed patients who suffered TRM, 1 had documented cardiotoxicity but did not have an AE report of death as a result of heart failure. Secondary malignancies were rare over the follow-up ($n = 4$; 1 unknown morphology, 1 myelodysplastic syndrome, 1 glioma, 1 T-cell acute lymphoblastic leukemia [ALL]); only 1 patient was exposed to dexrazoxane.

Impact of Dexrazoxane on Noncardiac Toxicities

There were no observable differences in course length, durations of neutropenia or hospitalization, ICU admissions, or rates of mucositis and bloodstream infection by dexrazoxane exposure (Data Supplement).

Sensitivity Analyses

Results of intention-to-treat sensitivity analyses (Data Supplement) were comparable to the primary analyses. Compared with those unexposed, dexrazoxane-exposed

TABLE 2. Comparison of the Occurrence of Cardiotoxicity by Dexrazoxane Exposure Status

Cardiotoxicity Outcome	Dexrazoxane Status		HR (95% CI)	P
	Consistently Exposed	Never Exposed		
Protocol-defined cardiotoxicity, ^a %	26.5	42.2	0.55 (0.36 to 0.86)	.009
Grade ≥ 2 LVSD, ^b %	10.9	23.4	0.40 (0.20 to 0.81)	.011
Grade ≥ 3 LVSD, ^c %	3.8	8.5	0.30 (0.07 to 1.23)	.094

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 3.0); EF, ejection fraction; HR, hazard ratio; LVSD, left ventricular systolic dysfunction; SF, shortening fraction.

^aSF < 28% or EF < 55%.

^bSF < 24% or EF < 50% per CTCAE.

^cSF < 15% or EF < 40% per CTCAE.

FIG 1. Temporal trends in (A) ejection fraction and (B) shortening fraction by dexrazoxane exposure. Standard errors of the mean ejection fraction and shortening fraction measurements are presented as vertical bars. (*) denotes treatment courses which include an anthracycline.

patients had significantly lower protocol-defined LVSD risk (28.4% v 42.4%; HR, 0.59; 95% CI, 0.40 to 0.87; $P = .008$); similar noncardiac toxicity (Data Supplement), EFS (50.2% v 45.3%; $P = .363$), and OS (67.6% v 62.4%; $P = .323$); but significantly lower TRM (4.6% v 12.6%; $P = .024$). Likewise, analyses that excluded patients assessed with MUGA scans (Data Supplement) were not meaningfully different from primary results.

DISCUSSION

In a preplanned analysis using prospectively captured data on AAML1031, we demonstrate that cardiotoxicity rates were higher than previously described¹³ partly because of more frequent monitoring and the required reporting of EF/SF measurements to the trial database in addition to standard AE reporting. Consistent dexrazoxane exposure before anthracycline courses preserved cardiac function as measured by EF/SF, with a 45% reduction in the cumulative incidence of LVSD that warranted per-protocol chemotherapy modification and a 60% reduction of LVSD grade ≥ 2 . Longitudinal cardiac monitoring revealed that the cardioprotective benefit of dexrazoxane is sustained through early post-treatment follow-up. Furthermore, the addition of dexrazoxane resulted in lower TRM with comparable 5-year EFS and OS without increasing noncardiac chemotherapy toxicity.

These results provide suggestive evidence that dexrazoxane provides cardioprotection during frontline treatment of pediatric AML. While we demonstrate lower TRM, we did not observe a significant improvement in OS with dexrazoxane. This is unsurprising given the greater relative effect of cardiotoxicity on TRM than overall mortality,¹³

the low prevalence of dexrazoxane exposure, and that cardiotoxicity occurs in a minority of patients. On the basis of the current results, the upcoming COG phase III AML trial to test a liposomal anthracycline against standard chemotherapy will mandate dexrazoxane use for all patients randomly assigned to standard chemotherapy.

The low rate of dexrazoxane prophylaxis (< 10% of patients^{31,32}) underscores the potential impact that will be realized should it become standard of care. While liposomal anthracyclines have been available in Europe, a manufacturing shortage has led to the increased use of nonliposomal formulations. Our findings provide treating clinicians in Europe with additional data to support dexrazoxane use in pediatric patients with AML who are receiving nonliposomal anthracyclines.³⁵ Furthermore, these data support approval of dexrazoxane for cardioprotection in countries where its use is limited to anthracycline extravasation.

Our findings of EF/SF preservation with dexrazoxane are consistent with other trials that have demonstrated beneficial effects on intermediate or surrogate markers for cardiac injury in cancer populations treated at lower cumulative anthracycline exposures^{23,25,27-30,39,40} and a single-center study and case series in pediatric AML.^{41,42} The observed reduction in LVSD grade ≥ 2 is comparable to estimates of dexrazoxane effectiveness in preventing clinical and subclinical heart failure obtained from a meta-analysis of children and adults treated for multiple cancers (relative risk, 0.29; 95% CI, 0.20 to 0.41).⁴³ Furthermore, the preservation of EFS and OS is consistent with studies in pediatric ALL,^{25,26,29} non-Hodgkin lymphoma,²⁵ and osteosarcoma³⁰ and a meta-analysis of various pediatric cancers⁴³ that consistently reported no reduction in EFS or

FIG 2. (A) Event-free survival (EFS), (B) overall survival (OS), (C) relapse/treatment failure risk, and (D) treatment-related mortality (TRM) risk by dexrazoxane exposure. SD, standard deviation.

OS and no increase in relapse with dexrazoxane over varying follow-up durations.

To our knowledge, these data are the first demonstration of a potential survival benefit with dexrazoxane, specifically a reduction in TRM (5.7% v 12.7%). The observed TRM rate among dexrazoxane-exposed patients (5.7%) is similar to that previously observed in the absence of LVSD (6.3%),¹³ which suggests that dexrazoxane may directly prevent acute, severe cardiac events that contribute to early deaths. While this finding was not statistically significant in primary analyses, the results of the intention-to-treat analyses were statistically significant and comparable in magnitude. The observed TRM benefit might be explained by residual confounding by other unmeasured supportive care practices; however, the comparable rates of cardiac monitoring, infectious complications, and comparable durations of neutropenia and hospitalization

in dexrazoxane-exposed and -unexposed patients argue against such bias.

As with any observational comparative effectiveness study, our results should be considered in light of potential limitations. First, because dexrazoxane exposure was not formally randomized, our results are susceptible to confounding biases. However, institutions generally used or did not use dexrazoxane uniformly, and patient characteristics, compliance with monitoring, and rates of noncardiac toxicities were comparable for dexrazoxane-exposed and -unexposed patients, which provides reassurance that the likelihood of such bias is modest. Moreover, a randomized clinical trial of dexrazoxane in pediatric AML is not feasible given the rarity of pediatric AML and the extensive resources needed to support such a multicenter trial. Because of resource limitations, echocardiogram images were not obtained and centrally reviewed. This may have caused inconsistencies in EF and

SF measurements, which would be nondifferential with respect to dexrazoxane exposure. Likewise, anthracycline dose modifications and use of cardiac-directed medications after subclinical EF/SF declines were not collected. Thus, we were unable to evaluate whether these factors may have played a role in the observed relationships between dexrazoxane administration and LVSD occurrence, EFS, OS, or TRM. Finally, we are unable to define the relative risk of secondary AML in patients who receive dexrazoxane given the infrequency of this complication and difficulty in differentiating secondary AML from AML relapse. Because the rate of secondary AML would be expected to be much lower than risks for TRM as a result of anthracycline-associated cardiac dysfunction and relapse associated with dose modification in the setting of subclinical cardiac decline, dexrazoxane use would be favored even if it were associated with a modest increase secondary malignancy risk.

In conclusion, our data support dexrazoxane use in pediatric AML to mitigate short-term anthracycline-associated cardiac dysfunction. Temporal trends in EF/SF suggest that dexrazoxane may also decrease later cardiotoxicity,¹⁹ a leading cause of late morbidity and non-relapse-related mortality in pediatric cancer survivors.^{5,7-10} Still, efforts should be made to acquire additional follow-up on cardiac outcomes to fully assess the long-term impacts of dexrazoxane use. While highly effective, dexrazoxane did not provide complete protection against EF/SF declines. Therefore, additional research focused on identifying additional cardioprotective treatment strategies, subpopulations who would realize the greatest benefit from different approaches to prevention, and appropriate cardiac monitoring schedules is warranted. A more complete understanding of the underlying biology of anthracycline-associated cardiotoxicity and effective interventions will improve both the cardiovascular and the oncologic outcomes for children with cancer.

AFFILIATIONS

¹Children's Hospital of Philadelphia, Philadelphia, PA

²University of Pennsylvania, Philadelphia, PA

³The Hospital for Sick Children, Toronto, Ontario, Canada

⁴University of Southern California, Los Angeles, CA

⁵Seattle Children's Hospital, Seattle, WA

⁶Children's Oncology Group, Monrovia, CA

⁷Boston Children's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

⁸Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE

⁹Children's Mercy Hospital and Clinics, Kansas City, MO

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AUTHOR CONTRIBUTIONS

Conception and design: Kelly D. Getz, Lillian Sung, Jessica A. Pollard, E. Anders Kolb, Richard Aplenc

Financial support: Richard Aplenc

Administrative support: Richard Aplenc

Provision of study material or patients: Richard Aplenc

Collection and assembly of data: Kelly D. Getz, Lillian Sung, Todd A. Alonzo, Todd Cooper, Alan S. Gamis, Richard Aplenc

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

CORRESPONDING AUTHOR

Kelly D. Getz, PhD, MPH, Perelman School of Medicine, University of Pennsylvania, 423 Guardian Dr, 909 Blockley Hall, Philadelphia, PA 19106; Twitter: @KDGetzPhD; e-mail: getzk@e-mail.chop.edu.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Effect of Dexrazoxane on Left Ventricular Systolic Function and Treatment Outcomes in Patients With Acute Myeloid Leukemia: A Report From the Children's Oncology Group**

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Kasey J. Leger

Honoraria: Boston Scientific

Consulting or Advisory Role: Jazz Pharmaceuticals, BTG

Research Funding: Abbott Laboratories

Travel, Accommodations, Expenses: Jazz Pharmaceuticals, BTG

Todd Cooper

Employment: Juno Therapeutics (I), Celgene (I)

Stock and Other Ownership Interests: Juno (I), Celgene (I)

E. Anders Kolb

Travel, Accommodations, Expenses: Roche, Genentech

Alan S. Gamis

Consulting or Advisory Role: Novartis

Bonnie Ky

Honoraria: UpToDate

Consulting or Advisory Role: Roche, Bristol-Myers Squibb, Roche, Mateon Therapeutics, Gilead Sciences, Bioinvent, American College of Cardiology

Speakers' Bureau: Bristol-Myers Squibb

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Patents, Royalties, Other Intellectual Property: Patent on the use of neuregulin-1b as a biomarker in heart failure, pending patent application on the use of immunoglobulin E as a biomarker of cardiotoxicity

Richard Aplenc

Honoraria: Sigma-Tau

Expert Testimony: Wiggin and Dana

Travel, Accommodations, Expenses: Sigma-Tau

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