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Administration of Dexrazoxane Improves Cardiac Indices in Children and Young Adults with Acute Myeloid Leukemia (AML) While Maintaining Survival Outcomes

Nathan J. Schloemer, M.D.¹, Molly Brickler, APNP¹, Raymond Hoffmann, PhD², Amy Pan, PhD², Pippa Simpson, PhD², Vanessa McFadden, M.D., PhD³, Joseph Block, M.D.⁴, Richard L. Tower II, M.D., M.S.¹, and Michael J. Burke, M.D.¹

¹Division of Pediatric Hematology-Oncology-Blood and Marrow Transplantation, Medical College of Wisconsin, Milwaukee, WI

²Division of Quantitative Health Sciences, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI

³Department of Pediatrics, Children's Hospital of Wisconsin, Milwaukee, WI

⁴Division of Pediatric Cardiology, Medical College of Wisconsin, Milwaukee, WI

Abstract

Anthracycline induced cardiotoxicity remains a significant contributor to late morbidity/mortality in children and young adults with acute myeloid leukemia (AML). The cardioprotectant dexrazoxane can be used as prophylaxis to diminish risk for cardiomyopathy but whether it affects risk of relapse in pediatric AML is unclear.

Our institution adopted the use of dexrazoxane prior to anthracyclines administration for all oncology patients in 2011. We compared patients with AML (ages 0 to 21 years) who received or did not receive dexrazoxane during the years 2008 to 2013.

Forty-four patients with AML (ages 4.5 months to 21.7 years) were included. We identified no statistical difference in 2-year event rate (62% vs. 50%, $p=0.41$) or 2-year overall survival (OS) (69% vs. 69%, $p=0.53$) between patients receiving ($n=28$) or not receiving ($n=16$) dexrazoxane. Ejection fraction ($p=0.0262$) and shortening fraction ($p=0.0381$) trended significantly higher in patients that received dexrazoxane compared to those that did not receive dexrazoxane.

Utilization of the cardioprotectant dexrazoxane prior to anthracycline chemotherapy in pediatric patients with AML demonstrated no significant difference in either event rate or OS relative to institutional controls and appears to improve cardiac function indices. Further studies in this patient population are needed to confirm these findings.

Correspondence to: Nathan J. Schloemer, M.D., Medical College of Wisconsin, Department of Pediatrics, Division of Hematology/Oncology/BMT, 8701 Watertown Plank Road, MFRC 3020, Milwaukee, WI 53226, Phone: 414-955-4170, Fax: 414-955-6543, njschloemer@mcw.edu.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

Keywords

Dexrazoxane; AML; Pediatric; Leukemia; Cardiotoxicity

INTRODUCTION

Acute myeloid leukemia (AML) comprises 5% of pediatric cancers and reports 5-year event free survival (EFS) of approximately 50% with overall survival (OS) approaching 70% following intensive multi-agent chemotherapy.^{1–4} Pediatric cancer survivors who received intensive treatment, such as those with AML, have a 73% incidence of developing a chronic health condition and 42% chance of having a severe, disabling, life-threatening condition or death from a chronic condition.⁵ Importantly the absence of a plateau in chronic condition incidence over 30 years of follow-up is most concerning.⁵ Thus, identifying interventions to minimize the long-term morbidity and/or mortality in pediatric patients with AML remains a priority for the oncology community.

Anthracyclines have been the cornerstone to treatment in AML since the 1960's and continue to be used today for *de novo* AML. The specific anthracyclines used include: daunorubicin, idarubicin, and mitoxantrone. All three of these anthracyclines are cardiotoxic carrying the risk for both acute and late cardiac complications which can include arrhythmias, cardiomyopathy and congestive heart failure (CHF). These risks increase as the cumulative anthracycline dose increases.^{6–10} Nearly 1 in 10 pediatric patients receiving anthracyclines will develop CHF in 20 years with significantly higher incidence when the cumulative dose is $>300 \text{ mg/m}^2$.¹¹ Importantly, current treatment for children with AML includes cumulative anthracycline doses in excess of 300 mg/m^2 which places these children at greater risk for developing CHF.

The predominant mechanism for anti-tumor activity of anthracyclines is DNA intercalation and topoisomerase II inhibition, which interfere with chromatin and inhibit replication of the DNA. The primary cause of anthracycline induced cardiotoxicity is believed to be oxygen free-radical generation.^{12, 13} Dexrazoxane was first developed as a topoisomerase II inhibitor chemotherapy agent but demonstrated poor anti-tumor effects.^{14, 15} However, it also acts as an oxygen free radical chelator, and when given prior to anthracycline chemotherapy, is able to bind to the free radicals and prevent long term cardiac toxicities.^{16–18}

Topoisomerase II inhibitors, including dexrazoxane, have been implicated in higher rates of secondary malignant neoplasm (SMN) development but the association with dexrazoxane has been debated in multiple studies.^{19–22} However, due to the potential for negative anti-leukemic effects as well as the concern for an increased risk of secondary malignancies, dexrazoxane has been utilized in only 2% of *de novo* pediatric AML patients or when patients have received a cumulative anthracycline exposure $>400\text{--}450 \text{ mg/m}^2$.²³ Pediatric leukemia studies incorporating dexrazoxane have demonstrated no increase in relapse risk^{14, 21, 24–27}, and improvement in cardiac indices^{14, 24–28}; however these data are limited to regimens using lower overall anthracycline doses and lack adequate control groups^{14, 21, 23–30}. Due to the known cardiac risk to pediatric patients who receive high

cumulative doses of anthracyclines over their lifetime, we adopted a standardized clinical practice at the Children's Hospital of Wisconsin of administering dexrazoxane prior to any non-liposomal anthracycline beginning in 2011. Here we report the results of our analysis in children and young adults with AML treated with or without dexrazoxane during 2008 to 2013.

MATERIALS AND METHODS

We performed a retrospective chart review of children ages 0 to 21 years who received their therapy for AML at Children's Hospital of Wisconsin (CHW) between January 1, 2008 and December 31, 2013. In 2011, the oncology division at CHW adopted a clinical practice of administering dexrazoxane prior to any non-liposomal anthracycline chemotherapy unless specifically restricted by a clinical trial in which a patient was enrolled. This study was approved by the CHW institutional review board prior to data collection.

Data were collected from the CHW electronic medical record (Sunrise Acute Care, Eclipsys Corporation, Atlanta, GA and EPIC, EPIC Systems Corporation, Verona, WI). Data included patient demographics, date of diagnosis, French-American-British leukemia classification, cytogenetic abnormalities, bone marrow evaluation, complete blood counts, central nervous system (CNS) disease status, presence of chloroma, leukemia treatment plan, anthracycline administration, hematopoietic stem cell transplantation (HSCT) date, echocardiogram date, structural cardiac abnormalities, echocardiogram left ventricular ejection fraction (EF) and shortening fraction (SF), left ventricular (LV) mass (g), LV Mass index (g/m^2), hypertension status, relapse status, treatment related mortality, transplant related mortality, disease related mortality and secondary malignant neoplasms (SMN). Echocardiograms were recorded at time of diagnosis, prior to each cycle of chemotherapy, at completion of therapy and an additional echocardiogram was obtained during off-therapy follow-up.

Cytogenetic risk status was determined based on prior definitions from the Children's Oncology Group.³¹ Anthracycline dose was calculated in daunorubicin equivalents using the formula: Daunorubicin equivalents (mg/m^2) = Daunorubicin (mg/m^2) + 3*Mitoxantrone (mg/m^2) + 0.5*Epirubicin (mg/m^2) + 3*idarubicin (mg/m^2).^{29, 32, 33}

Statistical Methods

Statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) with two-sided p value of 0.05 considered statistically significant. Data was expressed as frequency count and percentage for categorical variables. As the data was not normally distributed, the median with lower and upper quartiles was computed for continuous variables. A Non-parametric Mann-Whitney-Wilcoxon test was used to compare the continuous variables while a Chi-square test or Fisher's exact test was used to compare the categorical variables between dexrazoxane Yes and No groups. Kaplan-Meier Survival Analysis was performed to examine the event rate or overall survival. Event rate was defined as rate of relapse, treatment related death, or relapse related death. A two-sided log rank test was used to detect the difference in survival between patients with dexrazoxane and patients without dexrazoxane. A random coefficient model with unstructured covariance matrix was used to model the changes of cardiac indices over time. Covariance parameters were

estimated using maximum likelihood. RFoundation for Statistical Computing, Vienna, Austria URL <https://www.R-project.org/> was used for the graphs. Based on the number of patients in the two groups, a hazard ratio of 3 would achieve an 85% power to detect a significant difference between the two groups.

RESULTS

Relapse and Survival

A total of 53 patients with AML who received therapy at CHW were identified for this analysis. After exclusion of 9 patients who did not receive their entire *de novo* AML therapy at CHW, a total of 44 patients were included ages 4.5 months to 21.7 years. Of the 44 patients, 64% (n=28) received dexrazoxane as part of their multi-agent chemotherapy regimen and 36% (n=16) did not. The study population demographics and clinical characteristics are summarized in Table 1. There were no differences in rates of HSCT. We identified no statistical difference in 2-year event rate between patients who received dexrazoxane (62%) compared to those that did not (50%; p=0.41) (Figure 1). In addition, there was no difference in 2-year overall survival between groups (69% versus 69%; p=0.53; respectively) (Figure 2). There were 15 (53.6%) relapses, 9 (32.1%) disease related deaths and 1 (3.6%) treatment related death in the dexrazoxane group compared to 7 (43.8%) relapses, 5 (31.3%) disease related deaths, and 1 (6.3%) treatment related death in the non-dexrazoxane group, (p=0.49). No SMNs were diagnosed in either cohort during the study period. The small sample size in this analysis limited further subgroup analysis.

Cardiac Outcomes

Baseline patient cardiac characteristics are summarized in Table 2. Echocardiography data was collected at the time of therapy initiation, during treatment, and following therapy, according to clinical indications and treatment protocols. At presentation there were no patients who underwent prior cardiac surgery or had a diagnosis of hypertension requiring anti-hypertensive medication. We observed a significantly lower presentation SF in patients who received dexrazoxane [34% (31.5 – 36.0)] compared to those who did not [36.5% (35.0 – 39.0); p=0.03].

Changes in cardiac indices over time are demonstrated in Figure 3. There was a significant decrease in both ejection fraction (EF) and shortening fraction (SF) in the group that did not receive dexrazoxane compared to the dexrazoxane recipients (Figure 3A, 3B). One patient in the dexrazoxane group had their anthracyclines held due to a decline in cardiac function which was associated with a fatal sepsis event.

DISCUSSION

In pediatric and young adult patients with AML who received dexrazoxane as a cardioprotectant during their anthracycline therapy, we observed no increase in relapse or decline in overall survival. In addition, patients receiving dexrazoxane demonstrated improved cardiac indices following their anthracycline exposure. This is consistent with other pediatric studies in non-AML diseases where anthracyclines have been used albeit in lower cumulative doses.^{17, 24} Ejection fraction and shortening fraction were preserved

during the study period for patients receiving dexrazoxane immediately prior to anthracycline administration. The decline in shortening fraction observed in the non-dexrazoxane group is consistent with prior adult and pediatric studies of anthracyclines and dexrazoxane as an indicator of long term pathologic LV remodeling.^{34, 35} These trend differences while statistically significant fall within the normal clinical ranges and would not be expected to be clinically detectable. The presentation SF of the dexrazoxane group was significantly lower, but within clinical normal values at presentation. This may be indicative of subclinical cardiac impairment at presentation or act as a confounder of subsequent trends. As well, we observed only a single episode of heart failure in the dexrazoxane group which was temporally associated with a sepsis event. In addition, comparing the incidence of clinically significant cardiac events or heart failure secondary to anthracycline exposure would require a significantly longer follow-up and was not the primary aim of this analysis^{25, 36}.

We observed no episodes of secondary malignancies in either of our cohorts however distinguishing a treatment related AML from a relapse would be challenging. This observation is not surprising given our relatively small patient numbers, relatively short follow-up and the low overall rate of SMN reported in pediatric oncology of 1-2%.^{17, 19, 21, 22, 28, 37} The implementation of dexrazoxane as a cardioprotectant at our institution affords a unique opportunity to study the effect of dexrazoxane on the cardiac toxicities and anti-leukemic effects in children and adolescents with AML. However, the single center and retrospective nature of our study remains a limitation. Despite these limitations, we identified no significant difference in overall survival or rate of relapse in patients receiving dexrazoxane immediately prior to anthracyclines and found improvements in both EF and SF compared to our control non-dexrazoxane group. Based on these findings our center continues to utilize dexrazoxane prior to all non-liposomal anthracycline therapy in patients with AML.

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Figure 1. Event rate unchanged with dexrazoxane administration: Event rate defined as rate of events including relapse, relapse related death, or treatment related death.

Figure 2.
Overall survival unchanged with dexrazoxane administration

Figure 3.

Cardiac indices improved with dexrazoxane administration: 3A. Left Ventricular Ejection Fraction, 3B. Left Ventricular Shortening Fraction. Echocardiogram normal ranges: Left ventricular ejection fraction: 56%–78%; Left ventricular shortening fraction: 28%–44%.

Table 1

Patient characteristic by dexrazoxane administration

Characteristic	Dexrazoxane Yes (n=28)	Dexrazoxane No (n=16)	p-value
Diagnosis Age (Months) Median (IQR)	121.2 (17.9 – 185.9)	38.8 (17.8 – 145.0)	0.20
Gender, n (%)			
Female	14 (50)	10 (62.5)	0.42
Male	14 (50)	6 (37.5)	
Trisomy 21, n (%)	0	2 (12.5)	0.13
Risk Status, n (%)			
Low	5 (18.5)	1 (6.3)	0.59
Intermediate	19 (70.4)	13 (81.3)	
High	3 (11.1)	2 (12.5)	
Chloroma, n (%)	6 (21.4)	2 (12.5)	0.69
CNS disease, n (%)	11 (39.3)	9 (56.3)	0.50
WBC >100K at Diagnosis, n (%)	7 (25)	5 (31.3)	0.65
HSCT in CR1, n (%)	2 (7.1)	4 (25)	0.17
Median Anthracycline Dose mg/m ² (IQR)	382.8 (300 – 444)	444 (300 – 444)	0.21
Anthracycline Dose Reduction	1 (3.6)	0	>0.99

IQR, interquartile range; CNS, central nervous system; WBC, White blood count; CR1, Complete Remission 1; HSCT, hematopoietic stem cell transplantation

Table 2

Initial cardiac characteristics by dexrazoxane administration

Characteristic	Dexrazoxane Yes (n=28)	Dexrazoxane No (n=16)	p-value
Ejection Fraction %, Median (IQR)	65.0 (64.0 – 67.5)	68.0 (64.0 – 71.0)	0.10
Shortening Fraction %, Median (IQR)	34.0 (31.5 – 36.0)	36.5 (35.0 – 39.0)	0.03
LV Mass Index, Median (IQR)	40.0 (32.0 – 47.0)	35.0 (28.0 – 47.0)	0.61
Patent Foramen Ovale, N (%)	3 (10.7%)	3 (18.8%)	0.65
Atrial Septal Defect, N (%)	1 (3.6%)	0	>0.99
Left Ventricular Hypertrophy, N (%)	0	1 (6.3%)	0.36
Dilated Cardiomyopathy, N (%)	1 (3.6%)	0	>0.99

IQR, interquartile range; LV, Left Ventricular; LV Mass Index = $0.8 \times (1.04 \times [(LV \text{ end-diastolic diameter} + \text{diastolic posterior wall thickness} + \text{diastolic septal wall thickness})^3 - (LV \text{ end-diastolic diameter})^3] + 0.6) / m^2$