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Dexrazoxane Use in Pediatric Patients With Acute Lymphoblastic or Myeloid Leukemia From 1999 and 2009: Analysis of a National Cohort of Patients in the Pediatric Health Information Systems Database

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Background. Acute lymphoblastic (ALL) and myeloid leukemia (AML) account for approximately 26% of pediatric cancers. Anthracyclines are widely used to treat these leukemias, but dosing is limited by cardiotoxicity. Data support the efficacy of dexrazoxane as a cardioprotectant in children; however, dexrazoxane use in children is not universally accepted due to concerns about toxicity, impact on the antitumor effect of anthracyclines, and risk of secondary malignant neoplasms (SMN). ***Procedure.*** We conducted a retrospective cohort study to describe patterns of dexrazoxane use in pediatric patients with ALL or AML using the Pediatric Health Information Systems (PHIS) database. Patients identified as having *de novo* ALL and AML at these PHIS hospitals were included. ***Results.*** Of 8,733 patients with ALL and 2,556 with AML, 207 (2.4%) and 52 (2.0%) received dexrazoxane, respectively. Dexrazoxane use was greater in older children with ALL and AML and in black patients and males with ALL. Dexrazoxane use varied across time and by region in ALL, but not in AML. Prescribing practices differed across institutions and most patients received the first dose early or late after the start of leukemia treatment. ***Conclusions.*** Dexrazoxane administration is limited in patients with ALL and AML and prescribing practices vary across the country. Further work is necessary to understand how dexrazoxane is used in patients at highest risk of developing cardiotoxicity and to define its true effect on the development of SMNs. Pediatr Blood Cancer 2013;60:616–620.

Key words: acute lymphoblastic leukemia; acute myelogenous leukemia; cardiotoxicity; dexrazoxane; pharmacoepidemiology

INTRODUCTION

Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) account for approximately 26% of pediatric cancers [1]. Currently, with intensive, multidrug therapy, the 5-year event-free survival for children with ALL and AML is approximately 80 [2,3] and 60% [4,5], respectively. Anthracyclines, such as doxorubicin, daunorubicin, idarubicin, and the anthracenedione, mitoxantrone, are widely used in upfront therapeutic regimens for acute leukemia. However, their use is limited by anthracycline-induced cardiotoxicity that may manifest early after treatment or many years after therapy is completed [6]. The risk of cardiotoxicity is clinically significant, as approximately 5% of childhood cancer survivors will develop congestive heart failure over 20 years of follow-up [7]. Furthermore, the standardized mortality ratio (SMR) for cardiac deaths ranged from 3.5 to 9.1 in cohorts of long-term childhood cancer survivors in both the United States and Europe [8–10].

Anthracyclines exert cardiotoxic and anti-cancer effects through different mechanisms. Most evidence suggests that myocardial injury is mediated through the formation of iron-dependent oxygen free radicals, resulting in irreversible myocyte damage and apoptosis [11,12]. This damage may lead to dilated or restricted cardiomyopathy, or a combination of the two, and is dependent on the cumulative dose of anthracycline received [13].

Dexrazoxane (ICRF-187) is an FDA-approved cardioprotective agent that chelates intracellular free iron and iron bound to anthracyclines. Preclinical models show that dexrazoxane is effective at reducing oxygen free radical formation and apoptosis [14,15]. Clinical evidence for the efficacy of dexrazoxane as a cardioprotectant in children is limited, but the available data support both short and long-term cardioprotective effects in patients with ALL and a short-term cardioprotective effect in AML [16,17]. Despite this, dexrazoxane use as a cardioprotectant in pediatric cancer patients at high risk of developing cardiac toxicity remains controversial and is not recommended in any active Children's Oncology Group trials. The lack of support for dexrazoxane use is primarily due to concerns about toxicity, a deleterious impact on the antitumor effect of anthracyclines, and the risk of secondary malignant neoplasms (SMN) [18,19].

In order to describe the rate of dexrazoxane use and to better understand its impact in pediatric patients with leukemia, we assembled a retrospective cohort of ALL and AML patients treated in 43 children's hospitals that contributed data to the Pediatric Health Information Systems (PHIS) database from 1999 to 2009. Our study aims were to define patterns of dexrazoxane use in a national cohort of pediatric leukemia patients treated at academic centers and to determine if these patterns have changed over time as publications regarding dexrazoxane use in pediatric cancer patients have become available.

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METHODS

Study Design

A retrospective study was performed to establish a cohort of patients with *de novo* ALL or AML. Children entered the cohort on the day of admission during which the ALL or AML diagnosis was first reported and were followed through all subsequent admissions until the first dexrazoxane exposure.

Data Source

The PHIS database is an administrative database that contains comprehensive inpatient data from 43 United States tertiary care children's hospitals affiliated with the Child Health Corporation of America (CHCA, Shawnee Mission, KS). Each of the 43 hospitals contributed to the PHIS database between January 1, 1999 and December 31, 2009, although all hospitals did not contribute in every year. Contributing hospitals account for 85% of freestanding children's hospitals in the United States registered by the National Association of Children's Hospitals and Related Institutions and represent 17 of 20 major metropolitan areas in the United States. PHIS data are updated on a quarterly basis. Each individual patient is assigned a unique patient identifier that enables patient tracking across multiple admissions at a particular hospital. PHIS data come from two primary data sources and includes the following: Encrypted patient medical record number, demographics, dates of admission and discharge, up to 41 International Classification of Diseases-9-Clinical Modification (ICD-9-CM) discharge diagnosis codes per hospital admission, ICD-9 procedure codes, and specific billing/resource utilization data, including pharmaceuticals, blood products, laboratory tests, radiology imaging studies ordered, and clinical services utilized. All billing/resource utilization data include date of order and pharmaceutical data includes medication type and route of administration. Laboratory and radiology result data are not available.

Study Cohort

The source population included pediatric patients aged 0–21 years who were admitted to PHIS contributing hospitals between January 1, 1999 and December 31, 2009. Patients were included in the source cohort if they had a diagnosis of *de novo* ALL or AML by review of ICD-9 codes (204.xx-208.xx) and chemotherapy regimens consistent with induction therapy for either type of leukemia [20]. The final cohort of patients deemed to have new onset ALL or AML was then queried to identify patients that were billed for dexrazoxane administration.

Demographic Characteristics

Patient age at admission, gender, race, treating institution, and discharge disposition were collected for all admissions. Gender was coded as a dichotomous variable (male/female) and age was analyzed as a categorical variable (<1 year, 1 to <5 years, 5 to <10 years, 10 to <15 years, 15 to <20 years, and ≥ 20 years). Race (white, black, Asian, Native American, other, and missing) was also analyzed as a categorical variable.

Anthracycline and Dexrazoxane Use

Medication use was determined by pharmacy billing data. The specific anthracyclines and anthracenedione evaluated included doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone. Concomitant dexrazoxane use was defined as having received dexrazoxane within 1 day prior and up to 3 days after receipt of an anthracycline. Additionally, the day-by-day chemotherapy use for each patient who received dexrazoxane was reviewed by one of the study authors (D.W.) to determine an approximate cumulative dose of anthracycline received prior to initiation of dexrazoxane. This anthracycline dose was calculated based on the known anthracycline dose in a patient's particular chemotherapy regimen. All anthracycline doses were converted to doxorubicin equivalents using the formulas published in the Children's Oncology Group Long-Term Follow-Up Guidelines [21].

Statistical Analyses

Baseline and demographic characteristics were summarized by standard descriptive statistics. Demographic characteristics of those patients who received dexrazoxane were compared to those who did not receive dexrazoxane using Pearson's Chi-Square test. The proportion of dexrazoxane use by region was also compared using Pearson's Chi-Square test. Kaplan–Meier analysis was used to describe the time from leukemia diagnosis to dexrazoxane exposure and the log-rank test was used to compare findings between ALL and AML groups. Stata 11.0 (College Station, TX) and SAS 9.2 (Cary, NC) were used for all statistical analyses.

RESULTS

During the period between January 1, 1999 and December 31, 2009, 8,733 patients were identified with *de novo* ALL and 2556 identified with *de novo* AML. From this cohort, we identified 207 (2.4%) patients with ALL and 52 (2.0%) patients with AML who received dexrazoxane during the time period of interest. The demographic data for those patients with and without dexrazoxane exposure in both the ALL and AML cohorts are listed in Table I. The proportion of patients receiving dexrazoxane was higher in older children (>10 years of age) with ALL or AML and in black patients and males with ALL. There was a significant decrease in dexrazoxane use in ALL patients from 2001 to 2005 ($P = 0.0026$) (Fig. 1).

Twenty-two of 43 (51%) PHIS contributing institutions prescribed dexrazoxane for at least one child with AML over the study period of interest, while 28 (65%) institutions prescribed the drug for at least one patient with ALL. Two of 28 (7%) institutions accounted for 50% (104/207) of dexrazoxane exposures in patients being treated for ALL, whereas use in AML patients was more evenly distributed. Eight of 28 (29%) institutions used dexrazoxane exclusively in ALL patients and 3 of 22 (14%) used it only in AML patients with seemingly little consistency in use between ALL and AML. Dexrazoxane use also varied by region, with 13.6% of patients with ALL in the northeast receiving dexrazoxane and only 0.8% of ALL patients in the midwest receiving the drug ($P < 0.0001$). Similarly, in patients with AML, 4.9% of patients in the northeast received dexrazoxane versus only 1.3% of patients in the midwest ($P = 0.0022$) (Fig. 2).

Most patients with ALL and AML either received their first dose of dexrazoxane in the first 30 days (67 and 31%, respectively) or >360 days (23.5 and 31%, respectively) after cohort entry (Fig. 3). The time to dexrazoxane exposure did not differ significantly between patients with ALL and AML ($P = 0.28$). The

TABLE I. Demographic Characteristics of the Patients in the PHIS ALL and AML Cohort

	ALL			AML		
	ALL patients w/o DZX exp (n = 8,526)	ALL patients w/o DZX exp (n = 207)	*P*	ALL patients w/o DZX exp (n = 2,504)	ALL patients w/o DZX exp (n = 52)	*P*
Age, n (%)			<0.001			0.042
<1 year	252 (3)	0 (0)		254 (10)	1 (2)	
1 to <5 years	3,777 (44)	47 (23)		623 (25)	14 (27)	
5 to <10 years	2,211 (26)	45 (22)		426 (17)	4 (7)	
10 to <15 years	1,409 (17)	70 (34)		567 (23)	12 (30)	
15 to <20 years	826 (10)	41 (20)		574 (23)	18 (27)	
≥20 years	51 (0.6)	4 (2)		60 (2)	3 (4)	
Sex, n (%)			0.038			0.600
Male	4,777 (56)	131 (63)		1,353 (54)	30 (58)	
Female	3,749 (44)	76 (37)		1,151 (46)	22 (42)	
Race, n (%)			0.024			0.595
White	6,395 (75)	153 (74)		1,707 (68)	40 (77)	
African American	616 (7)	27 (13)		309 (12)	4 (9)	
Asian	252 (3)	6 (3)		85 (3)	1 (2)	
Native American	42 (0.5)	1 (0.5)		14 (0.5)	0 (0)	
Other	586 (7)	12 (6)		182 (7)	5 (9)	
Missing	631 (7)	8 (4)		207 (8)	2 (4)	
Region, n (%)			<0.001			0.002
Midwest	2,328 (27)	19 (9)		724 (29)	10 (19)	
Northeast	715 (8)	113 (55)		250 (10)	13 (25)	
South	2,876 (34)	38 (18)		870 (35)	13 (25)	
West	2,607 (31)	37 (18)		660 (26)	16 (31)	
Anthracycline						
Doxorubicin		179 (86)			1 (2)	
Daunorubicin		15 (7)			16 (31)	
Mitoxantrone		2 (1)			28 (54)	
Idarubicin		4 (2)			3 (6)	
Epirubicin		0 (0)			0 (0)	
Unknown		7 (3)			4 (8)	
Time to first dexrazoxane exposure, days						
Range		1–2,726			1–1,520	
Mean		245			266	

PHIS, Pediatric Health Information System; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DZX, dexrazoxane.

average anthracycline exposure prior to first dexrazoxane exposure, when estimated as doxorubicin equivalents, was approximately 200 mg/m^2 for patients with AML. Given the greater number and variability of ALL treatment protocols used and the uncertainty of anthracycline doses in each individual's chemotherapy regimen and the fact that the majority of ALL therapy is given in the outpatient setting, we were unable to estimate average anthracycline exposure in patients with ALL.

DISCUSSION

We have analyzed the use of dexrazoxane use in pediatric patients with ALL and AML using data that are nationally representative of children admitted to freestanding, academic pediatric hospitals. Dexrazoxane use in the combined cohort was limited, with 2.3% of patients receiving dexrazoxane at any time in their therapy and no substantial difference in dexrazoxane use was noted by leukemia type. This limited use and the decline in dexrazoxane use in ALL patients between 2001 and 2005 was unexpected, given literature suggesting a cardioprotective benefit in children with leukemias well as solid tumors [22–25]. Continued concerns about dexrazoxane's potential effect on development of SMN may have discouraged physicians from using dexrazoxane in children with ALL and AML. Two randomized trials of dexrazoxane in 239 children with Hodgkin lymphoma reported an increased risk of SMN [19] Based on this information, the European Medicines Agency (EMEA) restricted dexrazoxane use to patients over the age of 18 years in 2011 due to concerns about the secondary AML risk [18]. Additional factors to explain the limited and decreasing use of dexrazoxane over time, including timing of publications about dexrazoxane (shown in Fig. 1), possible dexrazoxane shortages during the study period, and potential periods of PHIS billing inaccuracies were all explored without a plausible explanation for the decline. Other potential explanations include prohibitions against dexrazoxane use in clinical trials or restrictions of dexrazoxane use to clinical trials that provided the

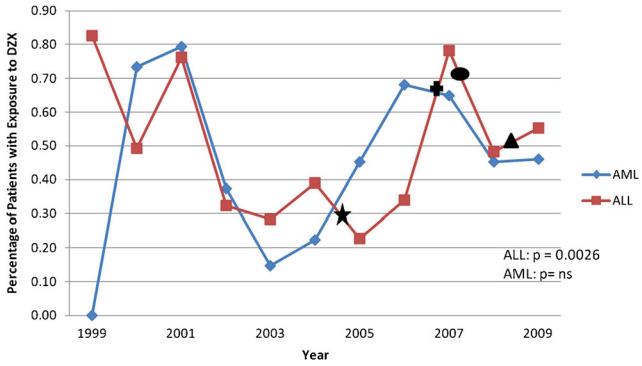

Fig. 1. Trend of dexrazoxane use over time. ★, published results of dexrazoxne use by DFCI in high risk ALL patients in NEJM [25]; ✚ follow-up results of DFCI high risk ALL study in Blood [2]; ●, dexrazoxane use and increased SMNs in patients with Hodgkins lymphoma in JCO [19]; ▲, absence of increased SMN risk in high risk ALL patients in JCO [28]; *P*, statistical significance value comparing dexrazoxane use in 2001 and 2005 in ALL and 2001 and 2003 in AML. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

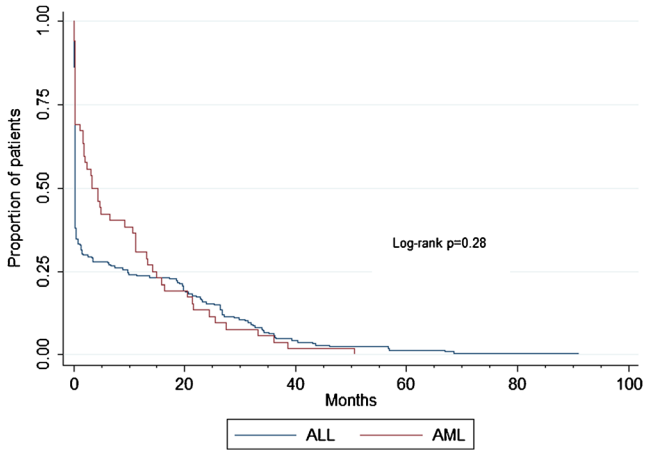

Fig. 3. Time from cohort entry to first dexrazoxane exposure. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *P*, statistical significance value. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

drug, thus preventing the generation of a pharmacy bill for dexrazoxane dispensation. Based on available data in PHIS, we were unable to evaluate either of these potential explanations.

Previous studies have shown that the risk factors associated with the development of anthracycline-induced cardiac toxicity include age <5 years at the time of treatment, female gender, being black or of African descent and cumulative anthracycline dose ≥300 mg/m^2. The current screening recommendations for long-term follow-up of cardiac toxicity are based on many of these factors [26–28]. Interestingly, in our cohort, older children with both ALL and AML and males were more likely to receive dexrazoxane. For patients with ALL, this may be explained by the fact that age ≥10 years places patients in the high-risk category, leading to treatment with higher cumulative doses of anthracyclines than younger patients. Additional pharmacoepidemiology studies will be required to evaluate the cause(s) of the increased use of dexrazoxane in males. However, the increased use of dexrazoxane in black patients is consistent with their increased risk of anthracycline associated cardiac toxicity [27,29].

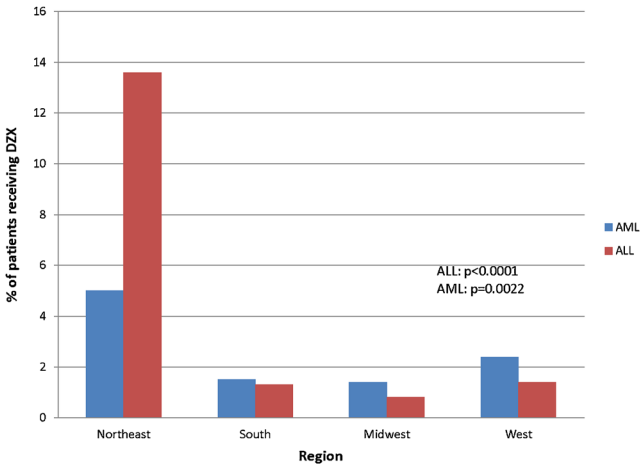

Fig. 2. Dexrazoxane use by region. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DZX, dexrazoxane; *P*, statistical significance value. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

Dexrazoxane prescribing practices varied greatly within and between institutions across the United States. Patients treated in the northeastern U.S. with ALL and AML were more likely to have received dexrazoxane during their treatment. This may, in part, be explained by the results of the Dana-Farber Cancer Institute Childhood ALL Consortium Protocol 95-01 study that was conducted from January 1996 to September 2000 [25]. Many of the institutions in this consortium are centered in the northeastern United States. Short-term results from this study have demonstrated a cardioprotective effect and have failed to show an increase in toxicities or SMNs [16,30]. This consortium continued to use dexrazoxane in patients with high-risk ALL in subsequent trials from 2000 to 2005 and from 2005 to 2010 [31]. However, the relatively modest numbers of ALL patients treated with dexrazoxane indicate that its use is certainly not routine in pediatric patients with ALL even at institutions that more frequently prescribed the medication.

Overall, dexrazoxane use during induction therapy for both AML and ALL was infrequent in all geographic regions of the United States. This may indicate that dexrazoxane use in children with acute leukemia is reserved for patients that have already received or will go on to receive a higher cumulative anthracycline dose (i.e., due to relapse or refractory disease) or for patients with an observed cardiac toxicity rather than administering it as a prophylactic agent.

This PHIS data for pharmacoepidemiology studies has multiple advantages; in particular, it affords the opportunity to establish a large sample size that is representative of practice patterns at free-standing pediatric hospitals in the United States. Nonetheless, we acknowledge several limitations in this analysis. First, this analysis relies on the accuracy of pharmacy billing data. These data may not be reported consistently across PHIS institutions and this could introduce ascertainment bias into the analysis.

However, this would have needed to occur at a number of the PHIS hospitals to cause substantial bias, and multiple other studies have used PHIS data for similar pharmacoepidemiology studies [32–34]. A second limitation of this study is that the diagnoses of ALL and AML were made by use of ICD-9 codes and manual review of chemotherapy received for patients in this cohort. There is the potential that some patients in this cohort have been misclassified as having ALL or AML when in actuality, they had an alternative diagnosis or relapsed leukemia. However, our rigorous approach to manually reviewing chemotherapy should have reduced this risk of misclassification. Finally, the available data were compiled primarily to describe the patterns of dexrazoxane use at the PHIS member institutions. We recognize that this database does not represent all children's hospitals in the United States and that there is no international data. Additionally, the compiled data did not allow for a comprehensive analysis to define the indications for dexrazoxane use, the effectiveness in reducing cardiac toxicities, and the risk for contributing to SMN.

In summary, our results suggest that dexrazoxane exposure is limited in patients with ALL and AML and prescribing practices vary across the country. This limited use of dexrazoxane is potentially related to concerns for SMNs. Currently, we are establishing a dataset to better define the risk of SMNs among pediatric cancer patients exposed to dexrazoxane.

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