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ORIGINAL REPORT

Absence of Secondary Malignant Neoplasms in Children With High-Risk Acute Lymphoblastic Leukemia Treated With Dexrazoxane

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ABSTRACT

Purpose
Dexrazoxane is a drug used to prevent anthracycline-induced cardiotoxicity. A recent report found an association between the use of dexrazoxane and the risk of developing secondary malignant neoplasms (SMNs) in children with Hodgkin's disease. We report the absence of an association of SMNs in children with acute lymphoblastic leukemia (ALL) treated on Dana-Farber Cancer Institute ALL Consortium Protocol 95-01.

Patients and Methods
Two hundred five children with high-risk (HR) ALL were randomly assigned to receive doxorubicin alone (n = 100) or doxorubicin with dexrazoxane (n = 105) during the induction and intensification phases of multiagent chemotherapy. We compared incidence of SMNs in these two groups.

Results
With a median follow-up of 6.2 years, no differences in the incidence of SMNs were noted between the group that received dexrazoxane and the group that did not ($P = .66$). One SMN (a melanoma located outside of the cranial radiation field) occurred in a patient who was randomly assigned to doxorubicin alone. No SMNs were observed in patients randomly assigned to receive dexrazoxane.

Conclusion
Dexrazoxane was not associated with an increased risk of SMNs in children treated for HR ALL. Given the potential importance of dexrazoxane as a cardioprotectant, we recommend that dexrazoxane continue to be used and studied in doxorubicin-containing pediatric regimens.

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INTRODUCTION

Anthracyclines, such as doxorubicin, have broad activity against a variety of cancers.[1-7] However, such drugs have been associated with toxic effects on the myocardium.[8,9] One approach to prevent anthracycline-induced cardiac damage has been the use of cardioprotective agents, such as dexrazoxane.

Dexrazoxane, a bisdioxopiperazine compound introduced in the 1970s as an anticancer agent, acts by inhibiting topoisomerase II, scavenging free radicals, and chelating heavy metals.[10-12] Dexrazoxane binds to intracellular iron and prevents the formation of free radicals.[12,13] As a result, the myocardial free iron pool is reduced and iron is prevented from complexing with anthracyclines and causing cellular damage.[14]

The first clinical trials examining the role of dexrazoxane as a cardioprotectant were conducted in women with advanced breast cancer.[15] Dexrazoxane had a marked cardioprotective effect in preventing deterioration in cardiac ejection fraction and also prevented the development of clinical congestive heart failure. Subsequent studies in other adult cancer patients confirmed that dexrazoxane reduced anthracycline-associated cardiotoxicity and allowed higher cumulative doses of anthracyclines to be used without having an adverse impact on antitumor activity.[16,17]

Between 1996 and 2000, we conducted one of the first randomized studies of the cardioprotective effects of dexrazoxane in pediatric patients. On Dana-Farber Cancer Institute (DFCI) Acute Lymphoblastic Leukemia (ALL) Consortium Protocol 95-01, children with high-risk (HR) ALL were randomly assigned to receive either doxorubicin alone or dexrazoxane before each dose of doxorubicin.[18] We have previously reported that dexrazoxane

significantly reduced elevations of troponin-T, a marker of acute cardiomyocyte injury.[19] On the basis of these results, since 2000, we have administered dexrazoxane to all HR children with ALL receiving high cumulative doses of doxorubicin.

Recently, the Children's Oncology Group reported that dexrazoxane was associated with a higher risk for developing secondary malignant neoplasms (SMNs), including acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), in children treated for Hodgkin's disease (HD).[20] That study was the first to report such an association. As a result, we have updated our outcome results from Protocol 95-01 and present evidence that dexrazoxane, used as a cardioprotectant in children with ALL, is not associated with SMNs.

PATIENTS AND METHODS

Patients

DFCI-ALL Consortium Protocol 95-01 enrolled patients between January 1996 and September 2000. Participating institutions included DFCI and Children's Hospital Boston (Boston, MA), University of Rochester (Rochester, NY), McMaster University (Hamilton, Ontario, Canada), San Jorge Children's Hospital/University of Puerto Rico (San Juan, Puerto Rico), Hospital Sainte-Justine (Montreal, Quebec, Canada), Maine Children's Cancer Program (Portland, ME), Ochsner Clinic (New Orleans, LA), Mount Sinai Medical Center (New York, NY), and Le Centre Hospitalier de L'Universite (Laval, Quebec, Canada). Institutional review board approval was obtained at all participating institutions, and informed consent was obtained for each patient before initiation of therapy.

A total of 498 children, 0 to 17.99 years of age, with newly diagnosed ALL were enrolled. Informed consent was obtained from parents and/or guardians before initiation of therapy. Three patients were deemed ineligible after enrollment, one due to HIV positivity, one due to prior steroid treatment, and one due to a diagnosis of Burkitt lymphoma. Three patients withdrew consent for further treatment, and one patient was withdrawn as a result of inadequate consent. Therefore, a total of 491 assessable patients were available for analysis.

Patients were stratified into two risk groups, standard risk (SR) and HR, according to NCI-recommended criteria on the basis of characteristics at the time of diagnosis.[21] HR was defined as age younger than 1 year or older than 10 years; WBC $\geq$ 50,000/μL; and the presence of T-cell immunophenotype, the Philadelphia chromosome, a radiologic mediastinal mass, or evidence of CNS leukemia (defined as CNS-2 or CNS-3).[22] All other patients were classified as SR.

Among the 491 assessable subjects, 219 were classified as HR. Fourteen HR patients declined random assignment and were directly assigned to receive doxorubicin without dexrazoxane. Of the remaining 205 HR patients, 100 (49%) were randomly assigned to receive doxorubicin alone, and 105 (51%) were randomly assigned to receive doxorubicin with dexrazoxane during the induction and intensification phases of therapy. As of April 2007, median follow-up for this group of patients was 6.2 years.

Treatment

Details of the treatment regimen have been previously published.[18] Briefly, therapy for the HR arm consisted of four phases: (1) a five-drug induction regimen (vincristine, prednisone, doxorubicin, high-dose methotrexate, and asparaginase); (2) a 2-week CNS-intensification phase (consisting of four doses of intrathecal chemotherapy and 18 Gy cranial radiation); (3) a 30-week intensification phase consisting of weekly asparaginase and cycles once every 3 weeks of vincristine, prednisone, mercaptopurine, and doxorubicin 30 mg/m^2/dose to a cumulative dose of 300 mg/m^2; and (4) a continuation phase consisting of cycles once every 3 weeks of vincristine, prednisone, mercaptopurine, and methotrexate. Therapy was continued until 24 months of complete continuous remission. For the patients randomly assigned to receive dexrazoxane, a dose of 300 mg/m^2 was administered by rapid intravenous infusion immediately before each dose of doxorubicin during the induction and intensification phases.

Statistical Methods

Differences in baseline characteristics between groups were compared using Fisher's exact tests for categoric data and Kruskal-Wallis tests for continuous data. Outcome events included death during induction, failure to achieve complete remission (CR), death during remission, relapse, and occurrence of SMN. Event-free survival (EFS) was defined as the time from CR to the first outcome event. Induction failures and induction deaths were considered events at time zero. Leukemia-free survival (LFS) was defined as the time from CR to relapse, and overall survival (OS) was defined as the time from the start of treatment to death from any cause. The Kaplan-Meier method was used to estimate the distribution of EFS, LFS, and OS, and univariate associations between groups were tested using log-rank tests.[23,24] All tests conducted were two-sided at the .05 significance level. There were no corrections for multiple comparisons.

Competing Risks Analysis

We estimated the cumulative incidence of SMNs among HR patients on Protocol 95-01 who achieved CR. A total of 195 patients were included in this analysis after excluding induction failures and deaths during induction (n = 9), as well as one patient for whom the date of CR was not available. The primary event of interest was defined as the occurrence of any SMN, and competing events were defined as relapse and death in remission from any cause. Time to event was calculated from the date of CR to the date of the first event, and patients who did not experience one of the events were censored at the last date of follow-up. All calculations, including treatment comparisons, were made using the competing risks methodology of Gray.[25]

RESULTS

Patient Characteristics

The presenting characteristics of the 205 randomly assigned HR patients are listed in Table 1. Patients assigned to either doxorubicin alone or doxorubicin plus dexrazoxane did not differ in the presenting features, including age at diagnosis, sex, immunophenotype, and presenting WBC count.

Response to Therapy and Survival by Randomization Group

As listed in Table 2, the two groups did not differ in terms of the rate of CR, number and type of relapses, rate of remission deaths, EFS, LFS, or OS. The two randomly assigned groups did not differ significantly in the occurrence of death in remission (P = .53) or relapse (P = .68). Among the 195 randomly assigned HR patients who achieved CR, observed events included 35 relapses, three remission deaths, and one SMN.

Figure 1 illustrates the 5-year EFS in the two groups. With a median follow-up of 6.2 years, EFS $\pm$ SE was 77% $\pm$ 4% for patients randomly assigned to doxorubicin alone, and 76% $\pm$ 4% for patients randomly assigned to doxorubicin plus dexrazoxane (P = .95).

Secondary Malignant Neoplasms

In total, two SMN events occurred on Protocol 95-01. One SMN, a malignant melanoma, was diagnosed 9.4 years after ALL diagnosis in a patient randomly assigned to doxorubicin alone (no dexrazoxane). The patient was 2 years of age at the time of ALL diagnosis, and 11 years of age when diagnosed with melanoma. Another SMN, also a malignant melanoma, occurred 3.1 years after ALL diagnosis in one of the 14 HR patients directly assigned to receive doxorubicin alone. This patient was diagnosed with ALL at 14 years of age, and developed melanoma at age 17. Neither of these cases of melanoma occurred in the cranial radiation field. No cases of secondary AML or MDS were

Table 1. Presenting Characteristics of Children With HR ALL Treated on DFCI-ALL Consortium Protocol 95-01

Characteristic	Total		Doxorubicin Alone		Doxorubicin and Dexrazoxane		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Total patients	205		100	49	105	51	
Age at diagnosis, years							.90
< 1	14	7	6	6	8	8	
1-9.99	107	52	52	52	55	52	
≥ 10	84	4	42	42	42	40	
Median	7		7		7		.75
Range	3 days to 17 years		3 days to 17 years		21 days to 17 years		
Sex							.48
Male	120	59	56	56	64	61	
Female	85	41	44	44	41	39	
WBC, per μL							.44
< 20,000	88	43	48	48	40	38	
20,000-49,999	26	13	13	13	13	12	
50,000-99,999	40	20	16	16	24	12	
≥ 100,000	51	25	23	23	28	27	
Median	29,500		23,650		47,300		.51
Range	1,300-1,175,000		1,300-740,400		1,900-1,175,000		
Immunophenotype							.85
B lineage	155	76	77	77	78	75	
T cell	49	24	23	23	26	25	
Unknown	1				1		
Anterior mediastinal mass							.85
No	171	85	84	86	87	84	
Yes	30	15	14	14	16	16	
Unknown	4		2		2		
CNS disease stage							.95
1	134	65	65	65	69	66	
2	46	22	24	24	22	21	
3	12	6	6	6	6	6	
Traumatic tap	11	5	5	5	6	6	
Unknown	2	1	0		2	2	

Abbreviations: HR, high risk; ALL, acute lymphoblastic leukemia; DFCI, Dana-Farber Cancer Institute.

observed. No SMNs were observed in patients randomly assigned to receive dexrazoxane. There were no SMNs observed in SR patients.

With 6.2 years median follow-up, the 5-year cumulative incidence of SMN was 0.2% (95% CI, 0% to 0.65%) for all 491 patients enrolled onto Protocol 95-01, and was 0.5% (95% CI, 0% to 1.5%) for all HR patients. The 5-year cumulative incidence of SMN for HR patients randomly assigned to receive dexrazoxane was zero. There was no significant difference in the occurrence of SMN based on dexrazoxane randomization ($P = .56$).

DISCUSSION

Dexrazoxane is a cardioprotective agent that has been shown to prevent anthracycline-induced cardiotoxicity.[15-17] The DFCI-ALL Consortium has been studying the cardioprotective effects of dexrazoxane since 1996. In addition to documenting the short-term prevention of cardiac injury, as evidenced by reduction of troponin-T elevations,[19] we have demonstrated that no difference exists in the 5-year EFS between children who received doxorubicin and dexrazoxane and those who received doxorubicin alone (76% *v* 77%; $P = .99$).[18] We now report the absence of an association between the use of dexrazoxane and the development of SMNs in these patients.

The latter finding differs from that of Tebbi et al,[20] who reported the results of a randomized study of the cardioprotectant dexrazoxane in pediatric patients with HD. Patients with low-risk HD received treatment with doxorubicin, bleomycin, vincristine, and etoposide; HR patients received similar therapy that was further intensified with prednisone and cyclophosphamide. Patients were randomly assigned to receive dexrazoxane (300 mg/m^2 intravenously, given on any day that doxorubicin or bleomycin was administered), to evaluate its cardiopulmonary protective effect. All patients received low-dose, involved-field or regional-field radiation. Investigators found an increased incidence of SMNs in the dexrazoxane-treated recipients, after a median follow-up time of 4.8 years. Specifically, among 478 HR and low-risk patients with HD, a total of 10 SMNs were noted: eight occurred in the dexrazoxane-treated group and two occurred in the group treated without dexrazoxane. Of the 10 SMNs, eight patients developed either AML or MDS, and two others developed solid tumors (a thyroid papillary carcinoma and an osteosarcoma). Of note, two of the SMNs occurred after relapse of HD and salvage therapy.

Table 2. Outcome Events Among Children With HR ALL Treated on the DFCI-ALL Consortium Protocol 95-01

Event	Total			Doxorubicin Alone			Doxorubicin and Dexrazoxane			
	No. of Patients	%	SE	No. of Patients	%	SE	No. of Patients	%	SE	*P*
Total No. of patients	205			100			105			
Induction deaths	2			1			1			
Induction failure	7			4			3			
CR	196	96		95	95		101	96		
Relapse	35	17		16	16		19	18		
BM only	27			12			15			
CNS only	1			1			0			
Testis only	2			0			2			
BM/CNS	5			3			2			
Remission deaths	3			2			1			
CCR	158	77		76	76		81	77		
SMN, 5 years	1			1	1		0			
EFS		76	3		77	4		76	4	.95
LFS		79	3		79	4		78	4	.85
OS		85	3		86	4		84	4	.81

Abbreviations: HR, high risk; ALL, acute lymphoblastic leukemia; DFCI, Dana-Farber Cancer Institute; CR, complete remission; BM, bone marrow; CCR, complete continuous remission; SMN, second malignant neoplasms; EFS, event-free survival; LFS, leukemia-free survival; OS, overall survival.

The 4-year cumulative incidence rate of SMNs was 3.43% ± 1.2% in the dexrazoxane arm and 0.85% ± 0.6% in the arm without dexrazoxane ($P = .06$).

Our findings, specifically the absence of SMNs in the dexrazoxane-treated patients, serve as a note of caution in the interpretation and generalization of the results from Tebbi et al.[20] Their overall number of events was small, and the direct comparison of cumulative incidence of SMNs between the two groups was only of borderline statistical significance. Only after adjusting their results by standardizing against the general population did they reach a significant *P* value.

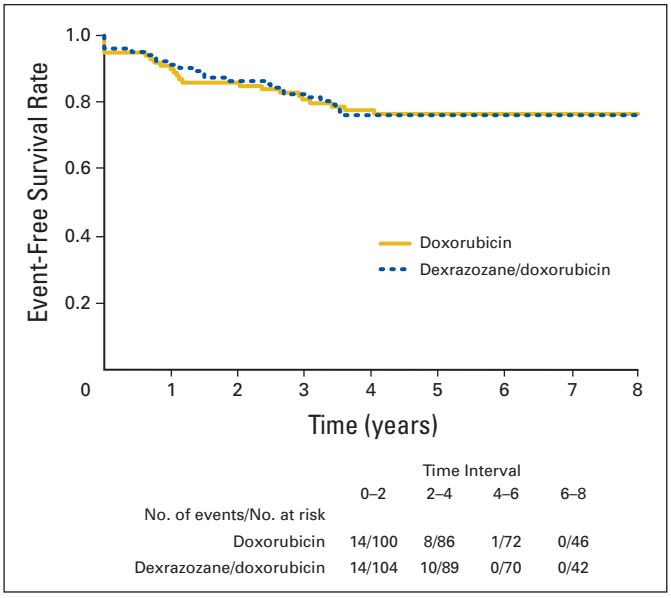

Fig 1. Event-free survival (EFS) among 205 children with high-risk (HR) acute lymphoblastic leukemia (ALL) treated on Dana-Farber Cancer Institute–ALL Consortium Protocol 95-01. The 5-year EFS ± SE was 77% ± 4% for patients randomly assigned to doxorubicin alone, and 76% ± 4% for patients randomly assigned to doxorubicin plus dexrazoxane. The difference was not statistically significant ($P = .95$).

Several facts may explain the differences between our results and those of Tebbi et al.[20] First, the pediatric HD and childhood ALL patient populations differ with regard to underlying demographics, such as age at diagnosis. The median age at diagnosis in the DFCI cohort was 7 years compared with approximately 13 years in the HD cohort. Second, in our analysis, we treated relapse of leukemia as a competing event with SMNs, whereas Tebbi et al did not. We believe our method more accurately reflects the potential impact of dexrazoxane administered during initial therapy, because relapse therapy likely has an impact on the subsequent risk of SMNs. Of note, however, we are unaware of any SMNs occurring after relapse in our patients treated on Protocol 95-01.

In addition, although an excess of subsequent neoplasms has been reported in survivors of childhood ALL and HD, survivors of childhood and adolescent HD are recognized as having a higher incidence of SMNs.[26-31] Indeed, the cumulative incidences of SMNs after childhood ALL have been reported from 1.18% to 3.99% after 10 to 15 years, and 6.27% at 30 years of follow-up.[27,30,32] In childhood and adolescent HD, however, the cumulative incidence ranges from 3.82% to 18.7% at 10 to 15 years, and 26.3% at 30 years of follow-up.[26,29,33,34] In a report from the Childhood Cancer Survivor Study, SMNs of any type were independently associated with a childhood cancer diagnosis of HD in multivariate regression models adjusted for radiation exposure.[31] In that cohort, onto which 1,815 HD patients and 4,581 leukemia patients were enrolled, 111 (6.1%) of HD patients reported an SMN, compared with only 64 (1.4%) of the leukemia patients. The difference in the distribution of SMNs between these two groups was statistically highly significant ($P < .001$).

In addition, treatment exposures differed between our population and that described in the study by Tebbi et al.[20] Of importance, etoposide was used in both arms of the pediatric HD study but not on Protocol 95-01. Treatment with etoposide has been associated with an increased risk of secondary AML/MDS.[35,36] Tebbi et al reported that

the doses of etoposide (75 to 125 mg/m^2/dose) used in the HD study have not been previously associated with an increased risk of secondary leukemia. However, others have reported such an association, even with relatively low doses, calling into question whether a safe dose of etoposide exists.[37] It is possible that the combined use of doxorubicin, dexrazoxane, and etoposide—all topoisomerase II inhibitors—led to a synergistic effect, as suggested by Tebbi et al, and contributed to the reported risk of SMN. However, dexrazoxane has been used for many years in combination with doxorubicin without reports of increased rates of SMNs. In addition, ionizing radiation was used in both our study and the study by Tebbi et al, although the radiation fields and radiation dose differed, which may have impacted the different rates on SMNs observed in the two studies.

It is interesting to note that both of the SMNs in our study were malignant melanomas. Both occurred outside of the radiation field and in patients who did not receive dexrazoxane. Melanoma is a relatively rare SMN reported in pediatric ALL patients. In a recent report from the St Jude Children's Research Hospital (Memphis, TN), only one melanoma was reported in more than 2,000 patients after a median follow-up of 18.7 years.[30] Similarly, in our own published experience of 1,600 patients treated for ALL on our protocols, no melanomas were observed as SMNs.[38] Given this, it is not clear if there is an association between ALL treatment and the development of melanoma, and longer follow-up will be needed to determine the incidence of melanoma in children with a history of ALL.

We note that our sample size is small and thus we have limited power to detect a difference in the incidence of SMNs between our two groups. We also acknowledge that our median follow-up was only 6.2 years, and that more SMNs may develop over time. However, median follow-up time in the study by Tebbi et al[20]was similar to ours (5.8 years). In addition, no SMNs have been observed to date in our successor ALL study, Protocol 00-01, in which all HR patients (N = 212) received dexrazoxane (data not shown). Given the important role of dexrazoxane as a cardioprotectant and the lack of association with SMN in other reports, we recommend continued use of dexrazoxane in doxorubicin-containing pediatric ALL regimens. In addition, we recommend that the use of dexrazoxane be considered in other cancers in which pediatric patients receive relatively high doses of anthracyclines, and that patients receiving this cardioprotective agent be closely monitored for the development of late-occurring cardiac morbidity and SMNs. Finally, continued research regarding the incidence and cause of SMNs in HD patients is warranted before any conclusions regarding the use of dexrazoxane in this patient population can be made.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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