Published in final edited form as:

Eur J Cancer. 2011 June ; 47(9): 1373–1379. doi:10.1016/j.ejca.2011.03.022.

The Low Incidence of Secondary Acute Myelogenous Leukemia in Children and Adolescents Treated with Dexrazoxane for Acute Lymphoblastic Leukemia: A Report from the Dana-Farber Cancer Institute ALL Consortium

Lynda M. Vrooman, MD, Donna S. Neuberg, ScD, Kristen E. Stevenson, MS, Barbara L. Asselin, MD, Uma H. Athale, MD, Luis Clavell, MD, Peter D. Cole, MD, Kara M. Kelly, MD, Eric C. Larsen, MD, Caroline Laverdière, MD, Bruno Michon, MD, Marshall Schorin, MD, Cindy L. Schwartz, MD, Harvey J. Cohen, MD, PhD, Steven E. Lipshultz, MD, Lewis B. Silverman, MD, and Stephen E. Sallan, MD

Dana-Farber Cancer Institute, Boston, MA (LMV, DSN, KES, LBS, SES); Children's Hospital Boston, Boston, MA (LMV, LBS, SES); University of Rochester Medical Center, Rochester, NY (BLA); McMaster University, Hamilton, Ontario, Canada (UHA); San Jorge Children's Hospital, San Juan, Puerto Rico (LC); Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY (PDC); Columbia University Medical Center, Morgan Stanley Children's Hospital of New York-Presbyterian, New York (KMK); Maine Children's Cancer Program, Portland, ME (ECL); Hospital Sainte Justine, University of Montreal, Montreal, Quebec, Canada (CL); Centre Hospitalier Universitaire de Quebec, Quebec City, QC, Canada (BM); Inova Fairfax Hospital for Children, Falls Church, Virginia (MS), Hasbro Children's Hospital, Warren Alpert Medical School of Brown University, Providence, RI (CLS), Stanford University School of Medicine, Palo Alto, CA (HJC), and the University of Miami Leonard M. Miller School of Medicine, Miami, FL (SEL)

Summary

Background—Dexrazoxane reduces the risk of anthracycline-related cardiotoxicity. In a study of children with Hodgkin lymphoma, the addition of dexrazoxane may have been associated with a higher risk for developing second malignant neoplasms (SMNs) including acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). We determined the incidence of SMNs in children and adolescents with acute lymphoblastic leukemia (ALL) who were treated with dexrazoxane.

Methods—Between 1996 and 2010, the Dana-Farber Cancer Institute ALL Consortium conducted three consecutive multicenter trials for children with newly diagnosed ALL. In the first

© 2011 Elsevier Ltd. All rights reserved.

Corresponding author: Lynda M. Vrooman, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, lynda_vrooman@dfci.harvard.edu, Phone: 617-632-2659, Fax: 617-632-2473.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributions:

LMV, LBS, SEL, DSN, KES, BLA, and SES were responsible for the design of this analysis. UHA, CL, PDC, LC, KMK, ECL, BM, MS, CLS, SES, and LBS all helped in designing the study protocols, contributed patients to the studies, and helped in analyzing the data and writing the manuscript; HJC helped in designing the study protocols, in analyzing the data, and in writing the manuscript; LMV, DSN, KES, and SEL all contributed to analyzing the data and writing the manuscript.

Conflicts-of-interest disclosure: The authors declare no competing financial interests.

(1996–2000), high risk patients were randomly assigned to receive doxorubicin (30 mg/m²/dose, cumulative dose 300mg/m²) preceded by dexrazoxane (300 mg/m²/dose, 10 doses), or the same dose of doxorubicin without dexrazoxane, during induction and intensification phases. In subsequent trials (2000–2005 and 2005–2010), all high risk and very high risk patients received doxorubicin preceded by dexrazoxane. Cases of SMNs were collected prospectively and were pooled for analysis. The frequency and 5-year cumulative incidence (CI) of SMNs were determined for patients who had received dexrazoxane.

Findings—Among 553 patients treated with dexrazoxane (1996–2000, N=101; 2000–2005, N=196; and 2005–2010, N=256), the number of SMNs observed by protocol was 0 (median follow-up 9.6 years), 0 (median follow-up 5.2 years), and 1 (median follow-up 2.1 years). The only SMN was a case of AML, which developed in a patient with MLL-rearranged ALL 2.14 years after initial diagnosis. The overall 5-year CI of SMNs for all 553 patients was $0.24 \pm 0.24\%$.

Interpretation—In a large population of children with high risk ALL who received dexrazoxane as a cardioprotectant drug, the occurrence of secondary AML was a rare event.

Introduction

Childhood acute lymphoblastic leukemia (ALL) is curable in more than 80% of patients.^{1–5} Treatment protocols utilize more intensive regimens for patients with “high risk” disease characteristics previously associated with inferior outcomes. Anthracyclines, including doxorubicin and daunorubicin, are commonly utilized for the treatment of high risk ALL patients.^{1,6,7} Anthracycline-associated cardiomyopathy is a well-characterized toxicity resulting from this class of drugs.^{8–10} One strategy aimed at minimizing heart damage includes the use of dexrazoxane, an agent that reduces both the acute and long-term cardiac toxicity associated with doxorubicin.^{11–14} We have previously reported that, in high risk ALL patients, dexrazoxane was cardioprotective without adversely impacting event-free survival.^{11,14}

In 2007, a report from the Pediatric Oncology Group described an increased risk of second malignant neoplasms (SMNs) in children treated with dexrazoxane for Hodgkin lymphoma.¹⁵ In the context of a randomized comparison, Tebbi and colleagues reported a 4-year cumulative incidence of SMNs of $3.43\% \pm 1.2\%$ in patients receiving dexrazoxane, and $0.85\% \pm 0.6\%$ in those receiving doxorubicin without cardioprotectant ($P=0.06$). The 4-year cumulative incidence of acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) was reported to be $2.55\% \pm 1.0\%$ for those receiving dexrazoxane, and $0.85\% \pm 0.6\%$ for those not receiving dexrazoxane ($P=0.160$). We previously reported the absence of SMNs in children with high risk ALL randomized to receive dexrazoxane in our prospective trial, Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocol 95-01, that randomized treatment with or without dexrazoxane (1996–2000).¹⁶ In the setting of continued uncertainty about the risk of SMNs, particularly AML/MDS, with dexrazoxane, we have updated the analysis of SMNs in dexrazoxane-treated patients on Protocol 95-01, and have pooled data from patients treated with dexrazoxane on two subsequent DFCI ALL Consortium protocols conducted between 2000 and 2010. We report here our experience with over 500 children treated for high risk ALL with multi-agent chemotherapy that included both doxorubicin and dexrazoxane.

Methods

Patients

Between January 1996 and February 2010, the DFCI ALL Consortium conducted three consecutive multicenter treatment protocols for children and adolescents with newly diagnosed ALL (excluding mature B-cell ALL): Protocol 95-01 (1996–2000, N=491),

Protocol 00-01 (2000–2004, N=492), and Protocol 05-01 (2005–2010, N=551). Patients were enrolled from the following DFCI ALL Consortium institutions: DFCI/Children's Hospital Boston, MA (1996–2010); Albert Einstein College of Medicine, Bronx, NY (2005–2010); Columbia University Medical Center, Morgan Stanley Children's Hospital of New York-Presbyterian, NY, NY (2000–2010); Hasbro Children's Hospital, Warren Alpert Medical School of Brown University, Providence, RI (2005–2010); Hospital Sainte Justine, Montreal, Canada (1996–2010); Le Centre Hospitalier de L'Université Laval, Quebec, Canada (1996–2010); Maine Medical Center/Maine Children's Cancer Program, Portland, ME (1996–2005); McMaster Children's Hospital, Ontario, Canada (1996–2010); Mount Sinai Medical Center, NY, NY (1996–2000); Ochsner Clinic, New Orleans, LA (1996–2000); Tulane Hospital for Children, New Orleans, LA (2000–2005); San Jorge Children's Hospital, San Juan, Puerto Rico (1996–2010); and the University of Rochester Medical Center, Rochester, NY (1996–2010). The institutional review board of each participating institution approved the protocols. Informed consent was obtained from parents or guardians for each patient prior to study enrollment and the initiation of therapy.

Patients on each of the three protocols were stratified into risk groups according to NCI age and leukocyte count criteria, on the basis of presenting characteristics. Standard risk patients met all of the following criteria: age 1–9.99 years, white blood cell (WBC) count less than 50,000/ μ L, B-precursor phenotype, no evidence of CNS leukemia (defined as CNS-1 or CNS-2 on Protocols 00-01 and 05-01, and CNS-1 on Protocol 95-01), and absence of a mediastinal mass (Protocol 95-01 and 00-01). All other patients were designated as high risk, including all patients with T-cell phenotype. Patients with Philadelphia chromosome-positive (Ph+) ALL were initially treated as high risk, but underwent allogeneic hematopoietic stem cell transplantation after achieving complete remission (CR). On Protocol 05-01, Ph+ patients received imatinib prior to stem cell transplantation. On Protocol 00-01, patients with MLL-rearranged ALL received one additional intensification cycle (including high-dose methotrexate and high-dose cytarabine.) On Protocol 05-01, a third risk group, very high risk, was established. Patients were assigned to the very high risk arm in the setting of MLL gene rearrangement, hypodiploidy, or high minimal residual disease at the end of the 4-week induction phase.¹⁷

Therapy

We analyzed data from children and adolescents with high risk and very high risk ALL who received dexrazoxane as a cardioprotectant. Standard risk patients received a cumulative dose of doxorubicin of only 60mg/m², never received dexrazoxane, and are not included in this analysis. Details of the treatment regimens have been previously published.^{6,18,19} Therapy on the high risk arm of Protocols 95-01 and 00-01 consisted of the following four phases: 1) a 4-week induction phase with vincristine, prednisone, doxorubicin, methotrexate, and L-asparaginase; 2) a CNS-intensification phase, including intrathecal chemotherapy, cranial radiation (18 Gy on Protocol 95-01, 12 Gy on 00-01) as well as doxorubicin, vincristine and 6-mercaptopurine; 3) a 30-week intensification phase with weekly asparaginase and every 3 week cycles with vincristine, 5-day pulses of steroid, 14-day courses of 6-mercaptopurine, and doxorubicin 30 mg/m²/dose; and 4) a continuation phase consisting of cycles once every 3 weeks of vincristine, steroid, 6-mercaptopurine, and methotrexate.

Protocol 05-01 was composed similarly, with the following differences: the addition of a 3-day methylprednisolone prophase prior to remission induction, some high risk patients were treated without cranial radiation, and the intensification phase was divided into two phases (consolidation I and II) separated by the CNS intensification phase. The consolidation I phase included high-dose methotrexate, doxorubicin, vincristine, 6-mercaptopurine, and intrathecal methotrexate; very high risk patients received a more-intensified consolidation I

phase with the addition of two cycles including cyclophosphamide, low-dose and high-dose cytarabine, 6-mercaptopurine, dexamethasone, L-asparaginase, and etoposide (100 mg/m²/day for 3 doses). The consolidation II phase included 30 consecutive weeks of L-asparaginase and every 3 week cycles with vincristine, steroid, 6-mercaptopurine, and doxorubicin as above. Prednisone was utilized as the post-induction steroid in Protocol 95-01, Protocol 00-01 included a randomized comparison of prednisone and dexamethasone, and dexamethasone was utilized in Protocol 05-01. Therapy for each patient was continued until 24 months of continuous complete remission.

On all three protocols, each doxorubicin dose was administered at 30 mg/m² to a total cumulative dose of 300 mg/m² in high risk and very high risk patients. On Protocol 95-01, children with high risk ALL were randomly assigned to receive doxorubicin preceded by dexrazoxane (300 mg/m²/dose, 10 doses) or the same dose of doxorubicin without dexrazoxane. On Protocols 00-01 and 05-01, all high risk and very high risk patients received doxorubicin preceded by dexrazoxane. Dexrazoxane was administered by rapid intravenous infusion immediately prior to each dose of doxorubicin during the induction and intensification phases.

Reporting of Second Malignant Neoplasms

Cases of SMNs were collected prospectively through required reporting by participating institutions. Institutions were required to report annually on relapse, incidence of SMN, and survival status for each patient. Following relapse, annual survival data was required. For deceased patients, cause of death was collected, and SMN was provided as possible cause of death. A SMN was defined as any malignancy occurring after the primary diagnosis of ALL, and was intended to include skin cancers, meningioma, AML/MDS, or any other malignancy.

Statistical Methods

We determined the frequency and estimated the 5-year cumulative incidence of AML/MDS and of all SMNs for high risk and very high risk patients who had received dexrazoxane with doxorubicin on Protocols 95-10, 00-01, and 05-01. Included in this pooled analysis were all high risk and very high risk patients who achieved CR; those with induction failure or who died during induction were excluded from the analysis. Relapse and death in remission were identified as competing risks. SMNs after relapse were not included in this analysis because of the possibility of incomplete ascertainment of SMN following relapse and the potential impact of relapse therapy on the development of SMN. We note that this did not exclude any known SMNs. Data after stem cell transplantation was included. The rate of SMNs, along with the standard error of that rate, was estimated using the method of cumulative incidence, as implemented in the *cmprsk* package in R.^{20,21} Patients who were last known to be alive without relapse and without SMN were censored in the cumulative incidence analysis. Although SMNs were collected prospectively on each protocol, this combined analysis of SMNs was not pre-specified.

Protocols 95-01 and 00-01 ended when full accrual was met, and Protocol 05-01 continues to actively accrue patients. Patients registered on Protocol 05-01 through February 2010 were included in the analysis.

Protocol 95-01 is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) with identifier NCT00165087, Protocol 00-01 with identifier NCT00165178, and Protocol 05-10 with identifier NCT00400946.

Role of the funding source—The funding source had no involvement in the study design, data collection, analysis or interpretation, or writing of the manuscript. The

corresponding author had full access to all data and the final responsibility to submit the manuscript for publication.

Results

Patient characteristics

Between January 1996 and February 2010, 590 patients from the three protocols were classified as high risk or very high risk, and were to receive dexrazoxane as a component of protocol therapy. This included 105 high risk patients from Protocol 95-01 who were randomly assigned to receive dexrazoxane, all 210 high risk patients from Protocol 00-01, and 275 high risk or very high risk patients on Protocol 05-01. Excluded from this analysis were 26 patients who did not achieve a CR with induction therapy (3 patients on 95-01, 13 on 00-01, and 10 on 05-01), and 11 patients who died during induction therapy (1 on 95-01, 1 on 00-01, and 9 on 05-01) (Figure 1). Therefore, the analysis included 553 high risk and very high risk patients; 101 from Protocol 95-01, 196 from Protocol 00-01, and 256 from Protocol 05-01 (190 high risk and 66 very high risk.) Patient presenting clinical characteristics are displayed in Table 1. The 5-year incidence of relapse or death in remission for these 553 patients was $17.8 \pm 2.0\%$.

Frequency and Cumulative Incidence of Second Malignant Neoplasms and AML/MDS

The number of SMNs observed by protocol was 0 on Protocol 95-01 (median follow-up 9.6 years, range 1.3 to 13.6 years), 0 on Protocol 00-01 (median follow-up 5.2 years, range 0.2 to 8.5 years), and 1 on 05-01 (median follow-up 2.1 years, range 0.2 to 5.1 years). The SMN was a case of AML that occurred in a patient with MLL-rearranged ALL treated on the very high risk arm of Protocol 05-01. Cytogenetic analyses of bone marrow aspirate samples were notable for a karyotype with a t(1;11) translocation at the initial ALL diagnosis and a t(11;19) translocation at the subsequent diagnosis of AML, suggesting that this was a case of secondary leukemia and not due to phenotypic shift of the original leukemic clone. The SMN was diagnosed 2.14 years after enrollment on Protocol 05-01. With 3.8 years median follow-up (range 0.2 to 13.6 years), the overall 5-year estimated cumulative incidence of SMNs for all 553 patients was $0.24 \pm 0.24\%$ (95% confidence interval 0.02–1.29%).

Discussion

Dexrazoxane is a cardioprotective agent that has been shown to prevent the cardiotoxicity associated with anthracycline exposure.^{11–13} We have reported that dexrazoxane provided long-term cardioprotection without compromising oncologic efficacy in children treated for high-risk acute lymphoblastic leukemia.^{11,14} Here, we report that in a large population of children with high risk ALL who received dexrazoxane as a cardioprotectant drug, occurrence of a SMN was an extremely rare event, observed in only 1 out of 553 patients.

Our findings contrast with a previous report from the Pediatric Oncology Group assessing a population of children with Hodgkin lymphoma who also received dexrazoxane as a cardioprotectant in the context of a randomized trial.¹⁵ On that trial, among 239 patients treated with dexrazoxane, there were 8 SMNs (6 AML/MDS and 2 solid tumors) compared with 2 SMNs in those treated without dexrazoxane (one AML, one MDS). With a median follow-up of 4.8 years, the 4-year cumulative incidence rate for any second malignancy was $3.43\% \pm 1.2\%$ in the group receiving dexrazoxane, compared with $0.85\% \pm 0.6\%$ for those not receiving dexrazoxane ($P=0.06$). Of note, two of the SMNs occurred after relapse, so the increased risk of SMN observed in dexrazoxane-treated patients on that trial may have been, in part, due to the effects of salvage therapies. The difference in the incidence of SMN did not effect the event-free survival of the two groups (86% versus 88%). Possible explanations

for the discrepancies in findings between our pediatric ALL population and the Hodgkin lymphoma population include differences in the underlying malignancy, other concurrently administered therapies, as well as cumulative dexrazoxane dose and schedule. In addition, our analysis did not include SMN after relapse therapies.

Although SMNs are known to occur after treatment for either ALL or Hodgkin lymphoma, the overall incidence of SMNs has been recognized to be higher in long-term survivors of Hodgkin lymphoma.²² The cumulative incidence of SMNs in survivors of Hodgkin lymphoma in childhood has been reported to be as high as 7% to 18% at 15 years of follow-up,^{23–25} although lower rates are described with reduced alkylator exposure and lower radiation doses.^{15,26,27} In long-term follow-up reports from a series of clinical trials of over 4000 children treated for ALL, the cumulative incidence of SMNs ranged from less than 1% to 9.9%, with the highest rates in etoposide-containing regimens, reflecting cases of secondary AML.^{28,29} Most studies that did not include etoposide reported rates of SMNs from less than 1% to 2%.^{5,7,29–33} Our findings are consistent with these regimens, none of which contained dexrazoxane, reporting low SMN rates.

The use of etoposide in the study reported by Tebbi and colleagues is an important difference in treatment exposures when considering their SMN results and those reported here. Etoposide is a topoisomerase II inhibitor associated with the development of SMNs, particularly acute myeloid leukemias and myelodysplasia.^{34,35} Dexrazoxane is a bisdioxopiperazine that acts as a topoisomerase II inhibitor,³⁶ and doxorubicin is considered a weak topoisomerase II inhibitor.³⁷ Our data demonstrate the absence of any SMNs in 487 high risk children with ALL who achieved a CR, treated with dexrazoxane, but not etoposide. Since 2005, treatment on our protocol for very high risk patients has included 3 doses of etoposide (cumulative dose 300mg/m²). It is interesting to note that the single SMN in this analysis occurred in a very high risk patient. Continued follow-up of the very high risk cohort will be required to determine whether the inclusion of etoposide (even at a relatively low cumulative dose not previously associated with an increased risk of secondary leukemias)³⁸ significantly impacts the incidence of secondary AML. While it is also possible that the SMN noted in our cohort may not be treatment-related, but rather a relapse with lineage shift in a patient with MLL rearrangement at initial diagnosis, the karyotype findings suggest that this was not a case of clonal evolution.³⁹

The Pediatric Oncology Group conducted a randomized trial of dexrazoxane in 363 patients with T-ALL (POG 9404).⁴⁰ The backbone of therapy for POG 9404 was based on DFCI ALL Consortium Protocol 87-01, which was similar to the high risk/very high risk treatment of the patients described here, except that the cumulative anthracycline dose on Protocol 87-01 was higher (360 mg/m²).⁴¹ On POG 9404, the use of dexrazoxane did not adversely impact event-free survival. SMNs occurred in $2.8 \pm 1.2\%$ of all patients, with a trend toward increased SMN in dexrazoxane-treated patients (cumulative incidence $4.2 \pm 2.2\%$ in those treated with dexrazoxane compared with $1.3 \pm 0.9\%$ in those treated without dexrazoxane), although the result did not reach statistical significance ($P=0.15$). Our finding presented here, assessing a larger cohort of patients treated with a nearly identical regimen, did not suggest an elevated risk of SMN when dexrazoxane was included in this therapeutic backbone.

Included in our report are 101 patients from Protocol 95-01 who were randomized to receive dexrazoxane with doxorubicin rather than doxorubicin alone. We previously reported that there were no SMNs among those receiving dexrazoxane and a total of three SMNs in high risk patients receiving doxorubicin alone, one of which occurred in the first 5 years following diagnosis.^{16,42} Now, with a median follow-up of 9.6 years, there have been no additional second malignancies in the dexrazoxane-treated group.

Limitations of the Study

There are limitations to this analysis. Excluded from this analysis were those with induction failure, as our information with regard to further treatment or the development of SMNs following induction failure may be limited. No SMNs after induction failure were reported. In addition, the median follow-up on our most recent protocol was relatively short. Although our pooled analysis has a median follow-up of only 3.8 years, cases of MLL-rearranged AML and MDS (the most common type of SMN associated with topoisomerase II inhibitors, like dexrazoxane) typically manifest within 2–3 years from initial diagnosis.⁴³ Indeed, the overall median follow-up of our pooled cohort is comparable to the report from Tebbi and colleagues, in which the median time to AML/MDS was relatively early (26 months). Finally, this analysis was not pre-specified at the time of protocol creation. Nonetheless, this pooled analysis represents a large group of childhood ALL patients exposed to dexrazoxane as a cardioprotectant.

Conclusions

Our findings suggest that dexrazoxane was not associated with an elevated risk of AML/MDS in children and adolescents with high risk ALL. We recommend continued use of dexrazoxane as a cardioprotectant in doxorubicin-containing childhood ALL regimens. Given that anthracyclines are used in a variety of pediatric malignancies and, while efficacious, are associated with significant risk of cardiotoxicity, the continued investigation of dexrazoxane as a cardioprotectant in other neoplasms is warranted, with close surveillance of SMN incidence.

Acknowledgments

This work was supported in part by grant 5 P01CA068484 from the National Cancer Institute of the National Institutes of Health (Bethesda, MD) and the Michael Garil Fund.

References

1. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009; 360(26):2730–2741. [PubMed: 19553647]
2. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood*. 2008; 111(9):4477–4489. [PubMed: 18285545]
3. Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TO. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005; 129(6):734–745. [PubMed: 15952999]
4. Veerman AJ, Kamps WA, van den Berg H, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997–2004). *Lancet Oncol*. 2009; 10(10):957–966. [PubMed: 19747876]
5. Gaynon PS, Angiolillo AL, Carroll WL, et al. Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983–2002: a Children's Oncology Group Report. *Leukemia*. 2010; 24(2):285–297. [PubMed: 20016531]
6. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007; 109(3): 896–904. [PubMed: 17003366]
7. Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia*. 2010; 24(2):265–284. [PubMed: 20010625]

8. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer*. 1973; 32(2):302–314. [PubMed: 4353012]
9. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Bmj*. 2009; 339:b4606. [PubMed: 19996459]
10. Barry E, Alvarez JA, Scully RE, Miller TL, Lipshultz SE. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. *Expert Opin Pharmacother*. 2007; 8(8): 1039–1058. [PubMed: 17516870]
11. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. *Lancet Oncol*. 2010; 11(10):950–961. [PubMed: 20850381]
12. Swain SM, Whaley FS, Gerber MC, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. *J Clin Oncol*. 1997; 15(4):1318–1332. [PubMed: 9193323]
13. Lopez M, Vici P, Di Lauro K, et al. Randomized prospective clinical trial of high-dose epirubicin and dexrazoxane in patients with advanced breast cancer and soft tissue sarcomas. *J Clin Oncol*. 1998; 16(1):86–92. [PubMed: 9440727]
14. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med*. 2004; 351(2): 145–153. [PubMed: 15247354]
15. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol*. 2007; 25(5):493–500. [PubMed: 17290056]
16. Barry EV, Vrooman LM, Dahlberg SE, et al. Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *J Clin Oncol*. 2008; 26(7):1106–1111. [PubMed: 18309945]
17. Zhou J, Goldwasser MA, Li A, et al. Quantitative analysis of minimal residual disease predicts relapse in children with B-lineage acute lymphoblastic leukemia in DFCI ALL Consortium Protocol 95-01. *Blood*. 2007; 110(5):1607–1611. [PubMed: 17485550]
18. Vrooman LM, Supko JG, Neuberg DS, et al. Erwinia asparaginase after allergy to *E. coli* asparaginase in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2010; 54(2): 199–205. [PubMed: 19672973]
19. Silverman LB, Supko JG, Stevenson KE, et al. Intravenous PEG-asparaginase during remission induction in children and adolescents with newly diagnosed acute lymphoblastic leukemia. *Blood*. 2010; 115(7):1351–1353. [PubMed: 20007809]
20. Gray R. A Class of K-sample tests for comparing the cumulative incidence of competing risks. *Annals of Statistics*. 1988; 16:1141–1154.
21. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*. 1999; 94:496–509.
22. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst*. 2001; 93(8):618–629. [PubMed: 11309438]
23. Beaty O 3rd, Hudson MM, Greenwald C, et al. Subsequent malignancies in children and adolescents after treatment for Hodgkin's disease. *J Clin Oncol*. 1995; 13(3):603–609. [PubMed: 7884422]
24. Kushner BH, Zauber A, Tan CT. Second malignancies after childhood Hodgkin's disease. The Memorial Sloan-Kettering Cancer Center experience. *Cancer*. 1988; 62(7):1364–1370. [PubMed: 3046737]
25. Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med*. 1996; 334(12):745–751. [PubMed: 8592547]
26. Schellong G, Riepenhausen M, Creutzig U, et al. Low risk of secondary leukemias after chemotherapy without mechlorethamine in childhood Hodgkin's disease. German-Austrian Pediatric Hodgkin's Disease Group. *J Clin Oncol*. 1997; 15(6):2247–2253. [PubMed: 9196137]

27. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst.* 2003; 95(13): 971–980. [PubMed: 12837833]
28. Winick NJ, McKenna RW, Shuster JJ, et al. Secondary acute myeloid leukemia in children with acute lymphoblastic leukemia treated with etoposide. *J Clin Oncol.* 1993; 11(2):209–217. [PubMed: 8426196]
29. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia.* 2010; 24(2):371–382. [PubMed: 20010620]
30. Conter V, Arico M, Basso G, et al. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. *Leukemia.* 2010; 24(2):255–264. [PubMed: 20016536]
31. Kamps WA, van der Pal-de Bruin KM, Veerman AJ, Fiocco M, Bierings M, Pieters R. Long-term results of Dutch Childhood Oncology Group studies for children with acute lymphoblastic leukemia from 1984 to 2004. *Leukemia.* 2010; 24(2):309–319. [PubMed: 20016528]
32. Mitchell C, Richards S, Harrison CJ, Eden T. Long-term follow-up of the United Kingdom medical research council protocols for childhood acute lymphoblastic leukaemia, 1980–2001. *Leukemia.* 2010; 24(2):406–418. [PubMed: 20010621]
33. Tsurusawa M, Shimomura Y, Asami K, et al. Long-term results of the Japanese Childhood Cancer and Leukemia Study Group studies 811, 841, 874 and 911 on childhood acute lymphoblastic leukemia. *Leukemia.* 2010; 24(2):335–344. [PubMed: 20016539]
34. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med.* 1991; 325(24):1682–1687. [PubMed: 1944468]
35. Pedersen-Bjergaard J, Daugaard G, Hansen SW, Philip P, Larsen SO, Rorth M. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. *Lancet.* 1991; 338(8763):359–363. [PubMed: 1713639]
36. Classen S, Olland S, Berger JM. Structure of the topoisomerase II ATPase region and its mechanism of inhibition by the chemotherapeutic agent ICRF-187. *Proc Natl Acad Sci U S A.* 2003; 100(19):10629–10634. [PubMed: 12963818]
37. Foglesong PD, Reckord C, Swink S. Doxorubicin inhibits human DNA topoisomerase I. *Cancer Chemother Pharmacol.* 1992; 30(2):123–125. [PubMed: 1318169]
38. Smith MA, Rubinstein L, Anderson JR, et al. Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J Clin Oncol.* 1999; 17(2):569–577. [PubMed: 10080601]
39. Germano G, Pigazzi M, del Giudice L, et al. Two consecutive immunophenotypic switches in a child with MLL-rearranged acute lymphoblastic leukemia. *Haematologica.* 2006; 91(5 Suppl):ECR09. [PubMed: 16709517]
40. Salzer WL, Devidas M, Carroll WL, et al. Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984–2001: a report from the children's oncology group. *Leukemia.* 2010; 24(2):355–370. [PubMed: 20016527]
41. LeClerc JM, Billett AL, Gelber RD, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber ALL Consortium Protocol 87-01. *J Clin Oncol.* 2002; 20(1):237–246. [PubMed: 11773175]
42. Silverman LB, Stevenson KE, O'Brien JE, et al. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985–2000). *Leukemia.* 2010; 24(2):320–334. [PubMed: 20016537]
43. Hijiya N, Ness KK, Ribeiro RC, Hudson MM. Acute leukemia as a secondary malignancy in children and adolescents: current findings and issues. *Cancer.* 2009; 115(1):23–35. [PubMed: 19072983]

Figure 1. Selection process of 553 patients with high risk or very high risk acute lymphoblastic leukemia in an analysis of the incidence of second malignant neoplasms after treatment with dexrazoxane.

Table 1

Patient characteristics of children and adolescents treated for high risk or very high risk ALL who achieved CR and received dexrazoxane on Protocols 95-01, 00-01, or 05-01.

	N (%)	N (%)	N (%)	N (%)
Protocol	Overall	95-01	00-01	05-01
N	590	105	210	275
Induction Failure	26	3	13	10
Induction Death	11	1	1	9
N evaluable	553	101	196	256
Age (years), median (range)	10 (<1, 17)	7 (<1, 17)	10 (1, 17)	10 (1, 17)
Sex				
Female	226 (41)	39 (39)	85 (43)	102 (40)
Male	327 (59)	62 (61)	111 (57)	154 (60)
WBC, median (range)	33.1 (0.6, 875.0)	41.9 (1.9, 875.0)	36.4 (1.2, 655.0)	29.9 (0.6, 793.5)
Immunophenotype				
T-cell	131 (24)	24 (24)	42 (21)	65 (25)
B-cell	419 (75)	76 (75)	152 (78)	191 (75)
Unknown	3 (1)	1 (1)	2 (1)	0 (0)
CNS Status				
1	389 (70)	68 (67)	153 (78)	168 (66)
2	102 (18)	20 (20)	28 (14)	54 (21)
3	27 (5)	5 (5)	15 (8)	7 (3)
Traumatic Tap	32 (6)	6 (6)	0 (0)	26 (10)
Unknown	3 (1)	2 (2)	0 (0)	1 (<1)
Mediastinal Mass				
Yes	69 (12)	15 (15)	25 (13)	29 (11)
No	480 (87)	84 (83)	171 (87)	225 (88)
Not Evaluated	4 (1)	2 (2)	0 (0)	2 (1)