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The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: A report from the Dana-Farber Cancer Institute ALL Consortium

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ABSTRACT

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 leukaemia (AML) and myelodysplastic syndrome (MDS). We determined the incidence of SMNs in children and adolescents with acute lymphoblastic leukaemia (ALL) who were treated with dexrazoxane.

Methods: Between 1996 and 2010, the Dana-Faber Cancer Institute ALL Consortium conducted three consecutive multicentre trials for children with newly diagnosed ALL. In the first (1996–2000), high risk patients were randomly assigned to receive doxorubicin (30 mg/m^2/dose, cumulative dose 300 mg/m^2) preceded by dexrazoxane (300 mg/m^2/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

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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 ± 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.

1. Introduction

Childhood acute lymphoblastic leukaemia (ALL) is curable in more than 80% of patients.[1–5] Treatment protocols utilise more intensive regimens for patients with 'high risk' disease characteristics previously associated with inferior outcomes. Anthracyclines, including doxorubicin and daunorubicin, are commonly utilised for the treatment of high risk ALL patients.[1,6,7] Anthracycline-associated cardiomyopathy is a well-characterised toxicity resulting from this class of drugs.[8–10] One strategy aimed at minimising 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 (CI) of SMNs of 3.43 ± 1.2% in patients receiving dexrazoxane, and 0.85 ± 0.6% in those receiving doxorubicin without cardioprotectant ($P = 0.06$). The 4-year cumulative incidence of acute myelogenous leukaemia (AML) and myelodysplastic syndrome (MDS) was reported to be 2.55 ± 1.0% for those receiving dexrazoxane, and 0.85 ± 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.

2. Methods

2.1. Patients

Between January 1996 and February 2010, the DFCI ALL Consortium conducted three consecutive multicentre 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 enroled 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'Universite 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 enrolment and the initiation of therapy.

Patients on each of the three protocols were stratified into risk groups according to NCI age and leucocyte 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/μL, B-precursor phenotype, no evidence of central nervous system (CNS) leukaemia (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 haematopoietic 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]

2.2. Therapy

We analysed data from children and adolescents with high risk and very high risk ALL who received dexrazoxane as a