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Transplantation Outcomes for Children with Hypodiploid Acute Lymphoblastic Leukemia

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ABSTRACT

Children with hypodiploid acute lymphoblastic leukemia (ALL) have inferior outcomes despite intensive risk-adapted chemotherapy regimens. We describe 78 children with hypodiploid ALL who underwent hematopoietic stem cell transplantation between 1990 and 2010. Thirty-nine (50%) patients had ≤ 43 chromosomes, 12 (15%) had 44 chromosomes, and 27 (35%) had 45 chromosomes. Forty-three (55%) patients underwent transplantation in first remission (CR1) and 35 (45%) underwent transplantation in $\geq$ second remission (CR2). Twenty-nine patients (37%) received a graft from a related donor and 49 (63%) from an unrelated donor. All patients received a myeloablative conditioning regimen. The 5-year probabilities of leukemia-free survival, overall survival, relapse, and treatment-related mortality for the entire cohort were 51%, 56%, 27%, and 22%, respectively. Multivariate analysis confirmed that mortality risks were higher for patients who underwent transplantation in CR2 (hazard ratio, 2.16; $P = .05$), with number of chromosomes ≤ 43 (hazard ratio, 2.15; $P = .05$), and for those who underwent transplantation in the first decade of the study period (hazard ratio, 2.60; $P = .01$). Similarly, treatment failure risks were higher with number of chromosomes ≤ 43 (hazard ratio, 2.28; $P = .04$) and the earlier transplantation period (hazard

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ratio, 2.51; $P = .01$). Although survival is better with advances in donor selection and supportive care, disease-related risk factors significantly influence transplantation outcomes.

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INTRODUCTION

Chemotherapy regimens have improved significantly over the last 50 years, and now more than 80% of children with acute lymphoblastic leukemia (ALL) are cured with chemotherapy [1–7]. Children with hypodiploid ALL, however, continue to have inferior outcomes despite risk-adapted intensive chemotherapy treatment. An early report from Children's Cancer Group analyzed a total of 4986 children treated between 1988 and 1995 on Children's Cancer Group studies. Among these, 1880 cases had centrally reviewed and accepted cytogenetic data and 110 cases (6%) were classified as hypodiploid. Six-year event-free survival (EFS) was worse in hypodiploid cases than nonhypodiploid patients (58% versus 76%, respectively, $P < .0001$). Six-year EFS estimates for patients with 45 chromosomes were 65%; 33 to 44 chromosomes, 40%; and 24 to 28 chromosomes, 25% (log rank, $P < .002$). Of note, only 23 patients had fewer than 45 chromosomes [8]. More recently, a case series of pediatric hypodiploid ALL patients with <45 chromosomes ($n = 139$) treated by 10 different national ALL study groups between 1986 and 1996 [9], reported an 8-year EFS of 38.5% and overall survival (OS) of 49.8%. Patients with fewer than 44 chromosomes fared significantly worse than those with 44 chromosomes (EFS, 30% versus 52%; $P = .01$; OS, 37% versus 69%; $P = .017$). Most of the patients received treatment on higher risk regimens and, notably, there were no induction failures, but relapses tended to occur early (within 2 years).

A similar report from the Medical Research Council included 226 children and adults treated with chemotherapy between 1990 and 2002 [10]. In that report, patients with ≤ 45 chromosomes were considered hypodiploid. One hundred twenty-one patients had 42 to 45 chromosomes and had acceptable survival with chemotherapy at 66%. The majority ($n = 114$) of these patients had 45 chromosomes, with only 7 children in the 42 to 44 chromosome group. In contrast, patients with 25 to 39 chromosomes had 29% survival at 3 years ($P = .002$) and all but 1 of 14 near haploid patients died.

The goals of the present study were to describe the outcome of children undergoing related or unrelated donor hematopoietic cell transplantation for hypodiploid ALL (defined as 45 or fewer chromosomes) and to identify disease-related prognostic factors that may affect overall and leukemia-free survival after transplantation.

PATIENTS AND METHODS

Patients

The Center for International Blood and Marrow Transplant Research is a voluntary working group of more than 450 transplantation centers worldwide. Participating centers are required to report all consecutive transplantations and compliance was ensured by on site audits. Patients are followed longitudinally until death or lost to follow-up. Patients or their guardians provided written informed consent. The institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Endpoints

The primary endpoint was *leukemia-free survival*, defined as being alive without leukemia recurrence. Death from any cause or relapse was considered an event (treatment failure). Other outcomes studied included

neutrophil recovery, defined as achieving an absolute neutrophil count $\geq 5 \times 10^9/L$ for 3 consecutive measurements, and *platelet recovery*, defined as platelets $\geq 20 \times 10^9/L$ without transfusion for 7 days. Diagnoses of grades 2 to 4 acute graft-versus-host disease (GVHD) and chronic GVHD were based on published criteria [11,12]. *Treatment-related mortality* (TRM) was defined as death not attributed to relapse, and relapse was defined as morphologic recurrence of leukemia. Surviving patients were censored at last follow-up and death from any cause was considered an event.

Statistical Methods

The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, TRM, and relapse were calculated with the use of the cumulative-incidence function method [13]. For TRM, relapse was the competing event and for relapse, TRM, the competing event. The probabilities of leukemia-free and OS were calculated using the Kaplan-Meier estimator [14]. Cox regression multivariate models were built for leukemia-free survival, OS, TRM, and relapse [15]. Due to the relatively modest sample size, only variables known to influence relapse, TRM, leukemia-free and OS were tested, including number of chromosomes (43 or fewer versus 44 or 45); disease status (complete remission [CR] 2 and 3 versus CR1); with $t(9;22)$ (yes versus no); year of transplantation (2000 to 2010 versus 1990 to 1999). A P value of .05 or less was considered statistically significant. All P values are 2 sided, and analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients, Disease, and Transplantation Characteristics

Patients and disease characteristics of the 78 patients ages ≤ 18 years with hypodiploid ALL who received a transplant from HLA-matched siblings, HLA-mismatched relatives, HLA-matched or HLA-mismatched unrelated donors between 1990 and 2010 are shown in Table 1. Twenty-nine of 78 patients received grafts from a related donor and 49 patients received their grafts from an unrelated donor. Median age at transplantation was 10 years (range, 3 to 18). Fifty percent of patients had 43 or fewer chromosomes, 15% had 44 chromosomes, and 35% had 45 chromosomes. Nine of 78 patients were reported to have a Philadelphia chromosome, but only 2 of these patients had 43 or fewer chromosomes. Fifty-five percent of transplantations occurred in CR1 and 38% in CR2. Among patients who underwent transplantation in CR2, 19 of 26 (66%) had a short duration CR1 (CR1 ≤ 36 months). The median follow-up of surviving patients is 80 (range, 14 to 240) months.

Transplantation characteristics are summarized in Table 2. Twenty-nine percent of patients received their graft from a matched sibling, 8% from other relatives, and 63% from unrelated donors. Donor-recipient pairs considered well matched were defined as having no known disparity at human leukocyte antigen (HLA) -A, -B, -C, and -DRB1; those considered mismatched were defined as having 1, 2, or more disparities [16]. Among recipients of matched sibling transplants, 1 received umbilical cord blood and the remaining received bone marrow ($n = 20$) or peripheral blood ($n = 1$). The corresponding distribution of graft type for unrelated donor transplantation was 15, 29, and 5, respectively. Over one half of unrelated donor transplantations were HLA mismatched. Mismatched related donors received bone marrow ($n = 5$) or peripheral blood ($n = 1$). All recipients received a myeloablative preparative regimen with 95% of patients receiving total body irradiation—containing

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