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Transplant 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 transplant (HSCT) 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 were transplanted in first remission (CR1) while 35 (45%) were transplanted in ≥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 (LFS), overall survival (OS), relapse, and treatment related mortality (TRM) for the entire cohort were 51%, 56%, 27% and 22% respectively. Multivariate analysis confirmed that mortality risks were higher for patients transplanted in CR2 (HR 2.16, p=0.05), with chromosome number ≤43 (HR 2.15, p=0.05) and for those transplanted in the first decade of the study period (HR 2.60, p=0.01). Similarly, treatment failure risks were higher with chromosome number ≤43 (HR 2.28, p=0.04) and the earlier transplant period (HR 2.51, p=0.01). Although survival is better with advances in donor selection and supportive care, disease-related risk factors significantly influence transplantation outcomes.

Keywords

Hypodiploid ALL; HSCT

Introduction

Chemotherapy regimens have improved significantly over the last 50 years, and now more than 80% of children with 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 (CCG) analyzed a total of 4,986 children treated between 1988 and 1995 on CCG studies. Among these, 1,880 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 non-hypodiploid patients (58% vs 76% respectively P<0.0001). Six-year EFS estimates for patients with 45 chromosomes were 65%, 33 to 44 chromosomes 40%, and 24 to 28 chromosomes 25% respectively (log rank, P <0.002). 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 event free survival (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 of 30% vs. 52%, p=0.01, OS 37% vs 69%, p=0.017). 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 (MRC) 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 and twenty one patients had 42–45 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 42–44 chromosome group. In contrast, patients with 25–39 chromosomes had 29% survival at 3 years (p=0.002,) and all but one 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 post-transplant.

Patients and Methods

Patients

The Center for International Blood and Marrow Transplant Research is a voluntary working group of more than 450 transplant centers worldwide. Participating centers are required to report all consecutive transplants 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 end point was leukemia-free survival, defined as being alive and 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 ≥ 0.5×10^9/L for 3 consecutive measurements; and platelet recovery defined as platelets ≥ 20×10^9/L without transfusion for 7 days. Diagnoses of grades 2–4 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 overall survival were calculated using the Kaplan-Meier estimator (14). Cox regression multivariate models were built for LFS, OS, TRM and relapse (15). Due to the relatively modest sample size only variables known to influence relapse, TRM, leukemia-free and overall survival were tested: number of chromosomes (43 or less vs. 44 or 45); disease status (CR2/3 vs. CR1); with t(9;22) (yes vs. no); year of transplant (2000–2010 vs. 1990–1999). A p-value of 0.05 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 Transplant Characteristics

Patients and disease characteristics of the 78 patients aged ≤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, 3–18). Fifty percent of patients had 43 or fewer chromosomes, 15% had 44 chromosomes and 35%, 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 transplanted in CR2, 19 of 26 (66%) had a short duration CR1 (CR1 ≤36 months). The median follow-up of surviving patients is 80 (14–240) months.

Transplant 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 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 half of unrelated donor transplants 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 (TBI)-containing regimens. Similarly, most (86%) received a calcineurin inhibitor containing GVHD prophylaxis.

Outcomes

The results of univariate analysis for the entire population are shown in Table 3. The 5-year leukemia-free survival, overall survival, relapse, and TRM were 51%, 56%, 27% and 22% respectively. Results of multivariate analysis for leukemia-free survival, overall survival,

relapse and TRM are presented in Table 4. Hypodiploid (chromosome number 43 or less) was associated with higher mortality and treatment failure. Other factors associated with higher mortality included transplantation in second or third CR and transplant period 1990 – 1999. The probability of 5-year overall survival adjusted for disease status and transplant period for patients with chromosome number 43 or less was 38% (95% CI 24–52) and for those with chromosome number 44 or 45, 71% (95% CI 56–82), p=0.001 (Figure 1). Treatment failure (inverse of leukemia-free survival) was higher for transplant period 1990 – 1999. The effect of disease status on treatment failure did not reach the level of significance set for this analysis. The probability of 5-year leukemia-free survival adjusted for disease status and transplant period for patients with chromosome number 43 or less was 37% (95% CI 23–51) and for those with chromosome number 44 or 45, 64% (95% CI 48–76), p=0.01 (Figure 2). None of the variables tested attained the level of significance set for this analyses for TRM and relapse. At the last follow-up (median 80 months; range, 14–240 months), 35 (45%) patients had died. Seventeen (22%) died of recurrent disease, the predominant cause of treatment failure. Other causes of death include GVHD (n=5), infection (n=7), organ failure (n=4) and other causes (n=2). Two patients developed EBV associated lymphoma at 1.5 months and 10 years after transplantation. The patient who developed EBV associated lymphoma at 1.5 months died from an infection at 3 months after transplantation and the other patient is alive, 16 years after transplantation. There were 3 reported second malignant neoplasms: 1 patient with tumor of the parotid gland, 1 with brain tumor and 1 with cancer of the thyroid gland at 5.5 years, 7.5 years and 3.3 years respectively after transplantation. Two of these patients are alive and the patient with brain tumor died a year after diagnosis.

DISCUSSION

The remarkable progress achieved in the treatment of childhood ALL is the result of a series of large-scale clinical studies conducted by cooperative clinical trials groups. In addition, biologic investigations have improved risk group identification (17) and allowed administration of risk-adapted therapy. These advances combined with a better understanding of disease mechanisms and the ability to better target chemotherapy have occurred in parallel with important changes in transplantation techniques, donor availability, donor-recipient HLA match and other supportive care measures. Together, these events have led to changes in indications for, transplantation for childhood ALL as well as associated outcomes. Perhaps the best example of this is the use of the tyrosine kinase inhibitor imatinib in childhood ALL that has led to current data suggesting that transplant is routinely not needed for Philadelphia positive ALL in CR1 (18).

Our goal in the current study was to identify factors that predict for better overall and leukemia-free survival in children with hypodiploid ALL undergoing allogeneic HSCT. Data describing outcomes after transplantation for these patients are sparse. A previous Children’s Oncology group (COG) study described 9 patients who underwent HSCT during the study period of 10 years (9). Patients underwent transplantation in first remission, and 5 had an adverse event after transplantation. The current report with its larger population identified three prognostic factors; 43 or fewer chromosomes, second or subsequent CR and transplantation prior to 2000 as predictive for lower overall survival and 43 or fewer chromosomes and transplantation prior to 2000 predictive for lower leukemia-free survival.

Although the risks of leukemia recurrence were higher for patients with 43 or fewer chromosomes, second or subsequent CR and transplantation prior to 2000, this did not reach the level of significance set for the current analysis. The lack of a statistically significant association between these factors and leukemia recurrence is likely due to the modest sample size.

A limitation of the current analysis is that we report transplantation outcomes and therefore applicable only to those patients who attained remission and proceeded to transplantation. The series on hypodiploid ALL from the COG include patients treated on their chemotherapy trials and thereby capturing events beginning from time of diagnosis. Therefore it is not possible to compare the survival and leukemia-free survival rates from the current analysis to the COG studies. To be able to assess whether transplantation is indeed superior to intensive chemotherapy, would require a carefully planned clinical trial that randomly allocates those beyond CR1 with 43 or fewer chromosomes to HSCT or continuing chemotherapy. Such a trial will only be feasible with the cooperation of several international pediatric consortia such as the COG and others. In two recent COG reviews which included patients with hypodiploid ALL enrolled on their trials, minimal residual (MRD) ≥ 0.01% at the end of induction was associated with inferior outcome. We are unable to evaluate the effect of MRD status at end of induction therapy or pre-transplant, as this was not systematically tested for in our cohort (19, 20).

A recent publication by Holmfeldt et al. reported novel genomic properties of childhood hypodiploid ALL (21). Marked enrichment for Ras-pathway, RB1 and TP53 alterations were seen in patients with hypodiploid ALL. A high frequency of TP53 alterations in both pediatric and adult low-hypodiploid ALL (91.2% and 90.9%, respectively) were seen, suggesting that mutation of TP53 is a significant event in the pathogenesis of low-hypodiploid ALL. Furthermore, almost half of the TP53 mutations identified in pediatric low-hypodiploid ALL were present as heterozygous mutations in remission bone marrow or peripheral blood and in purified normal T-cell populations, and most of these are known Li-Fraumeni syndrome-associated mutations (22). The frequency of secondary malignancy in our cohort was significant and raises concern that possible excess of malignancy will be seen on longitudinal follow-up. Future studies should look directly for TP53 mutations, and longer follow-up will better define the risk of subsequent cancers.

Although the current analyses has several limitations, including its modest sample size, transplantation period that spanned over two decades and our inability to determine why some transplantations occurred in first CR and others in second or subsequent CR; the analyses confirms a worse outcome for patients with chromosome number 43 or less compared to chromosome number 44 or 45 and transplantation. This information is relevant for physicians, patients and their families, and for future clinical trial planning to determine a role for allogeneic transplant in the era of risk adapted therapy for ALL.

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Highlights

- Treatment failure and mortality after HSCT are higher with ≤43 chromosomes
- Higher mortality in CR2 compared to CR1, independent of chromosome number

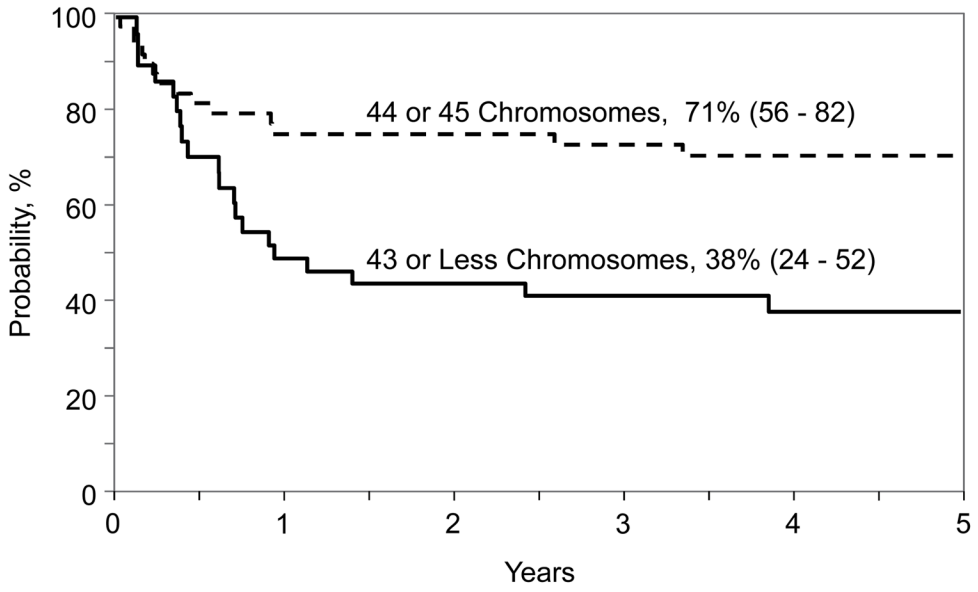

Figure 1.

The 5-year probability of overall survival by chromosome number and adjusted for disease status at transplantation and transplantation period

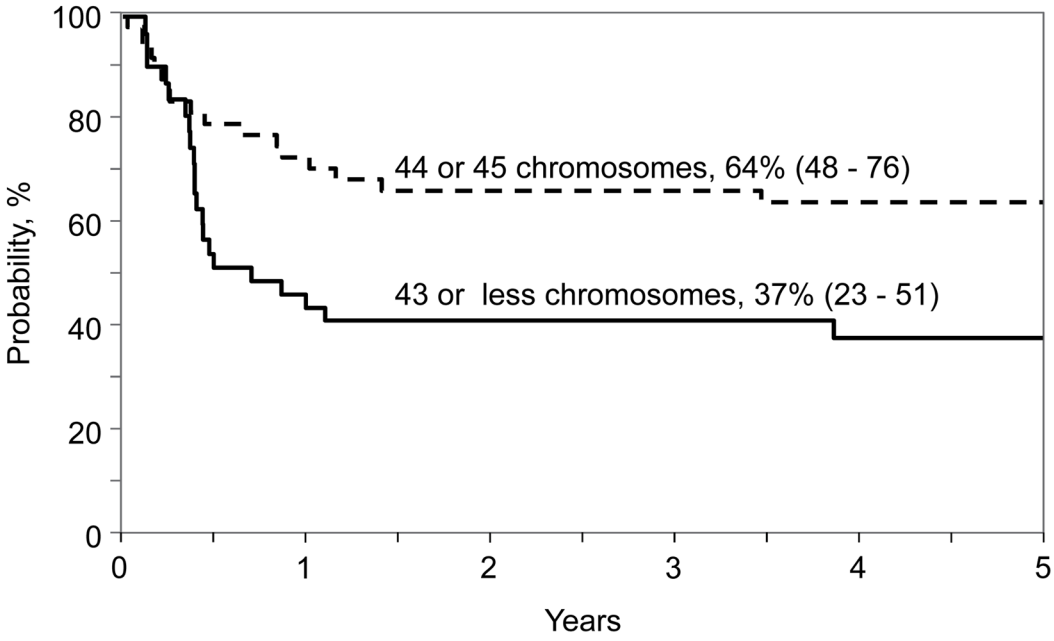

Figure 2.

The 5-year probability of leukemia-free survival by chromosome number and adjusted for disease status at transplantation and transplantation period

Table 1

Patient and Disease Characteristics

Characteristics	Number (%)
Number of patients	78
Number of centers	52
Age at transplant (years)	
≤5	11 (14)
6–10	30 (38)
11–15	22 (28)
16–18	15 (19)
Sex	
Male	47 (60)
Female	31 (40)
National Cancer Institute risk group	
Good risk	27 (35)
Poor risk	44 (56)
Unknown	7 (9)
Additional cytogenetic abnormalities*	
t(9;22) abnormality	9 (12)
t(4,11)	1 (1)
Monosomy 7	25 (32)
Monosomy 5/del 5q-	10 (13)
Other monosomies	11(14)
Trisomy 8/14	12 (15)
Lansky performance score prior to transplant	
<90	9 (12)
90 – 100	66 (85)
Unknown	3 (4)
Number of chromosomes	
≤ 43 chromosomes	39 (50)
44 chromosomes	12 (15)
45 chromosomes	27 (35)
Disease status at transplant	
First complete remission	43 (55)
Second complete remission	29 (38)
Third complete remission	6 (7)
Recipient cytomegalovirus serostatus	
Negative	43 (55)
Positive	35 (44)

*Not mutually exclusive. Most patients had more than one cytogenetic abnormality.

Table 2

Transplant Characteristics

Characteristics	Number (%)
Donor and Graft Source	
Related	
HLA-matched sibling	23 (29)
Other relative	6 (8)
Unrelated	
Matched unrelated donor	18 (23)
Mismatched unrelated donor	16 (21)
Matched cord blood	5 (6)
Mismatched cord blood	10 (13)
Conditioning regimen	
Total body irradiation + cyclophosphamide	66 (85)
Total body irradiation + other agents	8 (10)
Busulfan + cyclophosphamide	4 (5)
Anti-thymocyte globulin or alemtuzumab	
No	50 (64)
Yes	27 (35)
Not reported	1 (1)
GVHD prophylaxis	
Ex vivo T-cell depletion	10 (13)
Tacrolimus-containing	14 (18)
Cyclosporine- containing	53 (68)
Not reported	1 (1)
Year of transplant	
1990–1999	40 (51)
2000–2010	38 (49)

Table 3

Unadjusted probabilities of outcomes after transplantation for the entire cohort

	Probability (95% confidence interval)
Day-28 neutrophil recovery	79% (70–87)
Day-100 platelet recovery	78% (67–87)
Day-100 grade 2–4 Acute graft vs. host disease	56% (45–67)
5-year chronic graft vs. host disease	31% (22–42)
5-year relapse	27% (18–38)
5-year transplant-related mortality	22% (14–32)
5-year leukemia-free survival	51% (40–62)
5-year overall survival	56% (44–67)

Table 4

Results of multivariate analysis

	Hazard ratio (95% confidence interval)	p-value
Treatment Related Mortality		
Disease status		
First complete remission	1.00	
Second/third complete remission	1.84 (0.60 – 5.60)	0.28
Number of chromosomes		
44 or 45	1.00	
43 or less	1.81 (0.59 – 5.57)	0.30
Year of transplant		
2000 – 2010	1.00	
1990 – 1999	2.68 (0.93 – 7.75)	0.06
Relapse		
Disease status		
First complete remission	1.00	
Second/third complete remission	2.23 (0.76 – 6.56)	0.14
Number of chromosomes		
44 or 45	1.00	
43 or less	2.82 (0.92 – 8.61)	0.07
Year of transplant		
2000 – 2010	1.00	
1990 – 1999	2.46 (0.98 – 1.08)	0.06
Treatment Failure		
Disease status		
First complete remission	1.00	
Second/third complete remission	2.02 (0.93 – 4.36)	0.07
Number of chromosomes		
44 or 45	1.00	
43 or less	2.28 (1.04 – 5.01)	0.04
Year of transplant		
2000 – 2010	1.00	
1990 – 1999	2.51 (1.27 – 5.00)	0.01
Overall Mortality		
Disease status		
First complete remission	1.00	
Second/third complete remission	2.28 (1.02 – 5.10)	0.04
Number of chromosomes		
44 or 45	1.00	
43 or less	2.69 (1.17 – 6.15)	0.02

	Hazard ratio (95% confidence interval)	p-value
Year of transplant		
2000 – 2010	1.00	
1990 – 1999	2.60 (1.27 – 5.31)	0.01