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Comparable Survival for Pediatric Acute Myeloid Leukemia With Poor-Risk Cytogenetics Following Chemotherapy, Matched Related Donor, or Unrelated Donor Transplantation

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Abstract

Background—We sought to better define the role of hematopoietic cell transplantation (HCT) in first remission (CR1) for high-risk pediatric acute myeloid leukemia (AML).

Procedures—Outcomes were compared among patients aged less than 21 years with cytogenetically defined poor-risk AML treated with chemotherapy, matched related (MRD), or unrelated donor (URD) transplantation in CR1. Poor-risk cytogenetics was defined as monosomy 7/del7q, monosomy 5/del 5q, abnormalities of 3q, t(6;9)(p23;q34), or complex karyotype. Included are patients treated on Children's Oncology Group trials or reported to the Center for International Blood and Marrow Transplant Research from 1989 to 2006.

Results—Of the 233 patients, 123 received chemotherapy, 55 received MRD HCT, and 55 received URD HCT. The 5-year overall survival from the time of consolidation chemotherapy or transplant conditioning was similar: chemotherapy (43% ± 9%), MRD (46% ± 14%), or URD (50% ± 14%), $P = 0.99$. Similarly, multivariate analysis demonstrated no significant differences in survival [(reference group = chemotherapy); MRD HR 1.08, $P = 0.76$; URD HR 1.13, $P = 0.67$] despite lower relapse risk with URD HCT (HR = 0.43, $P = 0.01$).

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Conclusions—Our findings do not provide support for the preferential use of HCT over chemotherapy alone for children with cytogenetically defined poor-risk AML in CR1.

Keywords

acute myeloid leukemia; chemotherapy; hematopoietic cell transplantation; pediatrics

INTRODUCTION

The optimal role of allogeneic hematopoietic cell transplantation (HCT) for pediatric acute myeloid leukemia (AML) in first remission is unclear [1–3]. While HCT more effectively prevents relapse than chemotherapy alone [1,4], much of its benefit is offset by the risk of treatment related mortality (TRM) and late effects [5,6]. Many cooperative groups now limit its use to children at higher risk for relapse [7–9]. For instance, in its ongoing phase III trial, the North American Children’s Oncology Group (COG) assigns only children with high-risk disease, defined by cytogenetics, FLT3 mutation status and by minimal residual disease, to HCT with an HLA matched related (MRD), unrelated donor (URD) or other alternative donor [10].

The benefit of HCT to children with high-risk disease, however, remains uncertain. A cross-study analysis, published in 2008, comprised of COG and the Medical Research Council (MRC) phase III trials, comparing bone marrow transplant (BMT) and chemotherapy alone, failed to demonstrate a survival benefit to children with poor-risk AML treated with BMT [5]. However, this study was limited by relatively small number of poor-risk patients who received BMT.

Therefore, we sought to better understand the role of HCT for pediatric AML patients with high-risk disease in first complete remission (CR1). Using data from COG trials and data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), we compared clinical outcomes in pediatric patients with poor-risk cytogenetics treated in CR1 with chemotherapy, MRD, or URD HCT.

METHODS

Study Population and Treatments

This analysis includes patients (aged <21 years) who were treated with either HCT or chemotherapy alone for AML with poor-risk cytogenetics in CR1 between 1989 and 2006. Data for patients who received chemotherapy and MRD HCT were obtained from COG trials: CCG 2891, POG 9421, CCG 2961, and AAML03P1 which allocated subjects with a HLA matched family donor to HCT in CR1, regardless of disease risk. The cohorts from trials CCG 2891 and CCG 2,961 have been previously included in a comparison of outcomes by treatment with either chemotherapy or matched-related bone marrow transplant by cytogenetic risk group [5]. The details of treatment on these trials have been previously reported [11–14]. Patients in CR1 proceeded to HCT after the second cycle of induction chemotherapy except those enrolled on AAML03P1, who proceeded to HCT after three cycles of chemotherapy (two cycles of induction and one cycle of intensification) [13].

Data for additional HCT patients with poor-risk AML in CR1 were obtained from the CIBMTR. These patients received either a MRD or URD transplant during the same period as the COG trials. It is plausible that most patients who received URD HSCT were enrolled on the above-mentioned COG trials and received URD HSCT in the absence of a matched sibling. Transplants using any hematopoietic stem cell source were included. URD

transplants were categorized by the degree of HLA matching as either matched URD or mismatched URD [15].

Risk Group Definitions

Poor-risk cytogenetics was defined by presence of any of the following abnormalities in the absence of the favorable cytogenetic abnormalities t(8;21)(q22q22), inv(16)(p13;q22), and t(15;17)(q22;q21): monosomy 7, deletion of 7q (del(7q)), monosomy 5, deletions of 5q, abnormalities of 3q, t(6;9)(p23;q34), and complex karyotype: defined as five or more cytogenetic abnormalities [16–18]. The cytogenetic abnormality del(7q) was included because the data collection forms used by the CIBMTR during the study period grouped del(7q) and monosomy 7 together. Therefore, to maintain consistency del(7q) was included as a poor-risk abnormality for the COG cohort.

Statistical Methods

Descriptive characteristics of patient- and disease-related factors were prepared. Differences in proportions were analyzed using the χ^2 test or the Fisher's exact test. Differences in medians were analyzed using the Wilcoxon rank-sum test.

To account for the time to transplantation, overall survival (OS), treatment-related mortality (TRM), and the cumulative incidence of relapse are defined from the end of induction or intensification cycle one (AAML03P1) for the patients treated with either chemotherapy or HCT on the COG studies, or the time of HCT for patients registered through the CIBMTR, to an event. OS is defined as time to death from any cause. The Kaplan–Meier method was used to calculate estimates of OS separately for patients with poor-risk disease treated with either chemotherapy only, MRD HCT, or URD HCT [19]. The log rank test was used to compare OS outcomes [20]. The Cox proportional hazards model was used to estimate hazard ratios (HRs) for OS [20]. Methods of competing events were used to calculate estimates of TRM and relapse [21]. TRM is defined as time to death in CR where relapses were competing events. Relapse is defined as time to relapse where deaths without a relapse were competing events. Gray's test was used to compare the cumulative incidence or relapse and TRM. Competing risk regression models were used to estimate HRs for TRM and relapse risk in univariate and multivariate analyses [22]. The log-rank test was also used to compare clinical outcomes within treatment groups stratified by time period. Children lost to follow-up were censored at their date of last known contact. All patient outcome data were analyzed using an “as treated” analysis.

The incidence rates of acute and chronic graft versus host disease (GVHD) among the MRD and URD patients were calculated to describe the acute and chronic morbidities associated with MRD and URD for poor-risk patients [23].

Because del(7q) has been shown to confer an improved prognosis compared to monosomy 7 a sensitivity analysis was performed to compare outcomes of del(7q) and monosomy 7 patients among the COG patients for whom it could be distinguished which subjects had del(7q) and which had monosomy 7 [24].

Human Subjects

All COG studies were reviewed and approved by the institutional review boards (IRBs) of participating COG institutions and appropriate written informed consent/assent was obtained before treatment. Consent for reporting/research participation to the CIBMTR was obtained by transplant centers. Separate approvals were granted from the IRB of the Tufts Medical Center/Tufts University School of Medicine for the analysis of de-identified cytogenetic

data and from the IRBs of the Medical College of Wisconsin and the National Marrow Donor Program.

RESULTS

Patient, Disease, and Treatment Characteristics

A total of 233 patients were included in this study of which 123 were treated with chemotherapy, 55 with MRD HCT and the remaining 55, with URD HCT (Table I). Children in the chemotherapy group were more likely to be 2 years of age or younger, and to be of African-American race. There was a higher proportion of patients with a high white blood cell (WBC) count at diagnosis in the chemotherapy group. There was a similar distribution of monosomy 5 or del5q, abnormal 3q, and t(6;9) among the treatment groups. Children treated with chemotherapy were more likely to have a complex karyotype and less likely to have monosomy 7 or del(7q).

Of the URD transplants, 40% were HLA-matched and 60%, HLA-mismatched. Bone marrow was the predominant graft; peripheral blood stem cells were the graft for 6 transplants, and umbilical cord blood was the graft source for 10 transplants. Three of the cord blood units were 4/6 human leukocyte antigen matched and six of the cord blood units were 5/6 human leukocyte antigen matched. The average cell dose of the cord blood units was 3.6×10^7 total nucleated cells per kilogram. Characteristics of one cord blood unit were not reported.

Results of Univariate Analysis

The results of the univariate analysis are shown in Table II and Figure 1. Overall survival from the start of conditioning or consolidation chemotherapy was not significantly different for those treated with chemotherapy alone ($43 \pm 9\%$ at 5 years), MRD HCT ($46 \pm 14\%$), or URD HCT ($50 \pm 14\%$), ($P = 0.99$, Fig. 1). The pattern of treatment failure, however, differed by treatment group. Relapse rates were significantly lower and TRM rates were significantly higher with URD HCTs. The 5-year cumulative incidence of relapse was $61 \pm 9\%$, $51 \pm 13\%$, and $30 \pm 12\%$, after chemotherapy, MRD, and URD transplant respectively ($P = 0.001$). The corresponding 5-year TRM rates were $7 \pm 5\%$, $13 \pm 9\%$, and $23 \pm 11\%$ ($P = 0.005$). African-American race and a WBC count $> 50,000/\mu\text{l}$ at diagnosis were associated with significantly lower OS and higher relapse risk. Among the COG cohort for which patients with del(7q) ($n = 28$) and monosomy 7 ($n = 17$) could be identified, the OS ($50 \pm 19\%$ vs. $41 \pm 24\%$, $P = 0.54$) was not significantly different.

Results of Multivariate Analysis

The results of multivariate analysis are shown in Table III. Consistent with the results of univariate analysis, there were no differences in overall survival between the three treatment groups. The only factor significantly associated with overall survival was patient race; the effect of patient race was independent of treatment type. Overall mortality risks were higher in African Americans. Other factors such as age, WBC at diagnosis, and treatment period were not significantly associated with survival.

Unlike the results of univariate analysis, there were no statistically significant differences in TRM risks between the three treatment groups (Table III). In a competing risks regression model relapse risks were lower after URD transplantation (HR 0.43, $P = 0.01$) but not MRD transplantation (HR 0.82, $P = 0.42$) when compared to chemotherapy only.

Results by Time Period

Because of changes in clinical practice during the time period over which patients in this study were treated, OS, RR, and TRM results were stratified by time period within each treatment group and compared (Table IV). There was no significant difference in OS, RR, or TRM within the treatment groups by time period. There was a non-significant reduction in TRM and improvement in OS for those treated with URD over time.

Graft Versus Host Disease

As expected, rates of GVHD were higher among URD HCT recipients than MRD recipients. The rates of grade II–IV acute GVHD were 27% and 45% among the MRD and URD groups, respectively ($P = 0.06$). The rates of chronic GVHD were 17% and 39%, respectively, ($P = 0.01$). Nearly half of the URD HCT recipients with chronic GVHD had extensive disease.

Causes of Death

There were a total of 30 deaths attributed to TRM (chemotherapy, $n = 9$, MRD, $n = 7$, and URD $n = 14$). There were no predominant causes of death in any of the groups; causes included infection, interstitial pneumonitis, adult respiratory distress syndrome and GVHD and organ failure (HCT only).

DISCUSSION

This study demonstrates that for children with AML in CR1 with poor-risk cytogenetic abnormalities, treatment with HCT or chemotherapy alone on COG trials CCG 2891, POG 9421, CCG 2961, and AAML03P1 achieve comparable OS. Our observations confirm and extend the findings of others [5,25]. In an earlier report from the COG [5], nine recipients of MRD HCT were compared to 38 recipients of chemotherapy alone and significant differences in survival were not observed between the two poor-risk groups. In the recent report from the Berlin-Frankfurt-Munster group (AML-BFM98) [25], a subgroup analysis of 30 patients with poor-risk disease as defined by the COG study also did not observe significant survival differences among those with ($n = 11$) and without a matched sibling donor ($n = 19$). We defined poor-risk cytogenetics to be as consistent as possible with the COG's earlier study [5] but there are distinctions between the definitions used. We included del7q and t(6;9) as poor risk abnormalities and included only cytogenetics to define poor risk; we did not use the blast count at day-15 in our risk definition. Several trials led by the pediatric cooperative groups worldwide have utilized MRD HCT for children with poor-risk cytogenetic abnormalities [1,7,13,25], and others have assigned treatment with MRD, URD, or other alternative donor HCT for these high-risk patients in the absence of a clear advantage for HCT over chemotherapy [8–10,26,27]. The current analysis challenges the convention that HCT should be offered for AML patients in CR1 with poor-risk cytogenetics as the only adverse risk factor.

Given that consolidation chemotherapy, MRD HCT, and URD HCT, appear to offer children with poor-risk cytogenetics similar hope for survival, it is important to consider health related quality of life and cost. The recent report from the BFM study group highlights the burden of toxicity associated with the transplantation procedure as compared to chemotherapy alone and in the absence of a survival advantage after MRD or URD HSCT [25]. Further, transplant recipients are at risk for chronic GVHD the risk of which varies by donor source and degree of donor-recipient HLA-match. In severe cases, chronic GVHD can be associated with compromise of physical function, and altered health-related quality of life (HRQL) [28]. Chronic GVHD is also a risk factor for late mortality for those that survive at least 2 years after HCT [29]. There is insufficient evidence to draw conclusions regarding

the costs of treatment with chemotherapy compared to HCT with AML [30]. A pediatric specific cost-effectiveness analysis is needed.

Although there was no significant difference in survival, our findings highlight the protection against relapse that can be achieved through allogeneic HCT, specifically URD HCT. Recipients of URD HCT had nearly half the relapse risk than the children treated with chemotherapy. Unfortunately, the protection against relapse for URD HCT recipients was offset by higher risk of TRM. While one could debate about the relative merits of a graft-versus-leukemia effect from transplantation [31], TRM is high even with substantial improvements in supportive care in the current era [32,33] and higher TRM diminishes the anti-leukemia benefit.

There is no “standard” definition of poor-risk cytogenetics in pediatric AML [34]. We chose to define poor-risk cytogenetics according to the definitions used by the MRC and the COG at the times the studies were conducted so that the results would complement the results of previous studies comparing the treatment effect of BMT compared to chemotherapy by cytogenetic risk group [5,16,25]. We therefore included complex cytogenetics (5 cytogenetic abnormalities) in our definition of poor-risk although complex cytogenetics has been found to be associated with a poor prognosis by some pediatric study groups [18,34] but not others [17]. We additionally included t(6;9) in our definition of poor-risk as this translocation has been associated with inferior survival [17,18]. However, there are several other cytogenetic abnormalities that should be considered in future definitions of poor-risk. Specific MLL rearrangements have been identified as high-risk by the partner chromosome that translocates with 11q23 [35]. Other poor-risk abnormalities include abnormal 12p, t(7;12)(p36;q13) and t(5;11)(q35;p15.5) [17,18,34]. Due to the data collection forms used at the time to the transplants we were unable to identify these abnormalities in subjects drawn from the CIBMTR.

A limitation is that we were unable to distinguish between monosomy 7 and del(7q) abnormalities in all of the patients in our cohort. Although we explored the differences in survival among monosomy 7 and del(7q) patients for which we could differentiate the specific cytogenetic abnormality (the COG patients) in a sensitivity analysis, del(7q) has been demonstrated to be an intermediate risk abnormality and should be classified as such in future analyses [24].

There are several limitations when performing retrospective comparisons but we have performed a carefully controlled analysis. When comparing three different treatment options it is important to ensure comparable groups of patients. We adjusted for imbalances in patient characteristics in the three groups through the conduction of a multivariate survival analysis. In addition, the start time for analyses was the start of consolidation for the chemotherapy only group and for the HCT group, start of transplant conditioning. We remind the reader that the favorable survival reported here for this high risk group of pediatric AML patients should not be compared to reports of overall survival from the diagnosis AML. Another limitation is the assignment of HLA-match for the URD cohort. Newer techniques of HLA typing and the wide spread adoption of allele-level HLA typing in recent years has lowered TRM risks after URD HCT. During the course of this study, less stringent HLA-matching guidelines were employed.

Because of the changes in HLA-typing and other treatment practices over time that have likely contributed to improvements in survival for children with AML treated with both chemotherapy and HCT we considered the effect of time period of treatment in our analysis. We included time period as a variable in both the univariate and multivariate analyses but did not find a significant association of time period with OS, RR, or TRM in either analysis.

We further explored the effect of time period by comparing OS, RR, and TRM within each treatment group by time period. Although OS improved and TRM decreased in more recent years for those treated with URD HCT the improvement was not statistically significant. However, the comparisons of outcomes by time period within treatment group are limited by the small numbers of patients in each treatment group, particularly for those treated with MRD or URD HCT.

High-risk AML is no longer defined solely by cytogenetics, but is also defined by response to therapy, minimal residual disease status at the end of induction, and the presence of molecular mutations such as FLT3 mutations with high allelic ratios [34]. Our analysis included patients treated over a 15-year time period during which the COG trials' risk stratification evolved which prohibited us from testing for these relatively recent definitions of high risk AML. Minimal residual disease status and FLT3 mutation status was not collected at the time most of the patients in this analysis were treated. We caution the reader to remember that our findings apply only to those with poor risk cytogenetics, not all high-risk AML patients. The size of the current analysis is a strength. Previous analyses and reviews have been limited in their ability to compare treatments for these patients given that they comprise a small subset of patients on any one study [1,5,12,25]. To our knowledge this is the largest description of pediatric AML patients with poor-risk cytogenetics. As data accrues, the role of HCT in the presence of adverse risk factors such as response to induction therapy and the presence of molecular mutations should be examined. In the mean time, our observations do not support the routine use of HCT in CR1 for AML in children and adolescents with poor-risk cytogenetics and should only be offered in the setting of carefully controlled clinical trials designed to incorporate the relatively new adverse risk factors.

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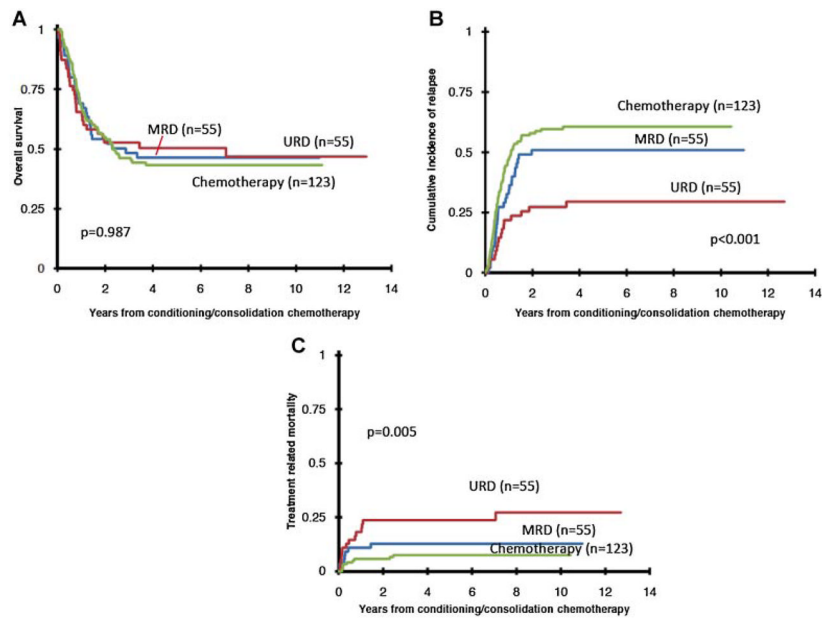


Fig. 1. Overall survival (A), relapse risk (B), and treatment related mortality (C) by treatment group.

TABLE I

Clinical Characteristics of the Study Population

Characteristic	Chemotherapy, N = 123			MRD, N = 55			URD, N = 55			P
	N	%	N	%	N	%	N	%		
Gender										
Male	58	47	25	45	31	56				
Female	65	53	30	55	24	44			0.44	
Age at diagnosis										
0–2 yo	58	47	13	24	9	16			<0.001	
3–11 yo	34	28	21	38	24	44			0.09	
12–21 yo	31	25	21	38	22	40			0.07	
Race ^d										
White	76	70	43	86	47	90			0.004	
African American	23	21	4	8	1	2			0.002	
Other	10	9	3	6	4	8			0.79	
Unknown	14		5		3					
Ethnicity										
Hispanic	14	12	3	6	1	2			0.07	
Not Hispanic	105	88	50	94	52	98				
WBC ($\times 10^3/\mu\text{l}$)										
<50,000	102	83	49	91	48	96			0.04	
50,000	21	17	5	9	2	4				
Weight category ^b										
Underweight	3	4	7	14	4	8			0.14	
Middleweight	55	74	38	76	41	80			0.73	
Overweight	16	22	5	10	6	12			0.15	
Unknown	49		5		4					
Monosomy 7 or del7q										
Negative	89	72	31	56	23	42			<0.001	
Positive	34	28	24	44	32	58				
Monosomy 5 or del5q										

Characteristic	Chemotherapy, N = 123		MRD, N = 55		URD, N = 55		P
	N	%	N	%	N	%	
Negative	111	90	50	91	47	85	0.57
Positive	12	10	5	9	8	15	
Abnormal 3q							
Negative	107	87	50	91	52	95	0.29
Positive	16	13	5	9	3	5	
t(6;9)							
Negative	106	86	43	78	51	93	0.09
Positive	17	14	12	22	4	7	
Complex cytogenetics							
Negative	54	44	39	71	47	85	
Positive	69	56	16	29	8	15	<0.001
Study							
CIBMTR	0	0	27	53	55	100	
POG 9421	36	29	5	9	0	0	
CCG 2891	23	19	8	15	0	0	
CCG 2961	30	24	11	20	0	0	
COG AAML03P1	34	28	4	7	0	0	
Stem cell source							
Bone marrow	N/A		53	96	41	75	
Peripheral blood			2	4	4	7	
Cord blood					10	18	
Time period							
1989–1997	46	37	34	62	22	40	0.008
1998–2006	77	63	21	38	33	60	

MRD, matched related donor; URD, unrelated donor; yo, years old.

^aPercentage distribution based on known values.

^bWeight category definitions: For Age 2 years old: underweight <5% bone mass index (BMI) percentile; middleweight 5–95% BMI percentile; overweight >95% BMI percentile; for age 1–2 years old: underweight <10% WT/LT percentile; middleweight 10–90% WT/LT percentile; overweight >90% WT/LT percentile; WT/LT, weight for length. Data for height/weight used at time of pre-conditioning or beginning of chemotherapy.

TABLE II
Univariate Analysis of Patient- and Treatment-Related Factors Associated With OS, TRM and RR

Treatment group	OS			TRM			RR			
	N	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Poor-risk: chemotherapy ^a	123	1		1	1		1	1		
Poor-risk: MRD	55	0.97	0.63–1.51	0.90	1.79	0.66–4.82	0.25	0.74	0.48–1.14	0.17
Poor-risk: URD	55	0.97	0.62–1.51	0.89	3.77	1.65–8.62	0.002	0.37	0.21–0.64	<0.001
Age at diagnosis										
3–11 yo ^d	79	1		1	1		1	1		
0–2 yo	80	0.86	0.55–1.34	0.49	0.37	0.12–1.18	0.09	1.11	0.71–1.71	0.65
12–21 yo	74	1.49	0.98–2.27	0.07	1.81	0.83–3.97	0.14	0.98	0.63–1.53	0.93
Race										
Not African American ^d	183	1		1	1		1	1		
African American	28	2.15	1.34–3.44	0.001	0.82	0.24–2.77	0.75	2.58	1.61–4.12	<0.001
Ethnicity										
Not Hispanic ^d	207	1		1	1		1	1		
Hispanic	18	0.72	0.35–1.48	0.38	0.40	0.06–2.83	0.36	0.81	0.40–1.64	0.55
WBC at diagnosis										
<50,000 ^d	199	1		1	1		1	1		
50,000	28	1.99	1.23–3.23	0.005	0.53	0.12–2.31	0.39	1.93	1.08–3.46	0.03
Weight category										
Not overweight ^d	148	1		1	1		1	1		
Overweight	27	1.07	0.62–1.87	0.80	1.52	0.56–4.12	0.41	0.83	0.45–1.53	0.55
Cytogenetics: monosomy 7 or del7q										
Negative ^d	143	1		1	1		1	1		
Positive	90	1.01	0.70–1.44	0.98	2.14	1.04–4.39	0.04	0.91	0.62–1.31	0.60
Cytogenetics: complexity 5										
Negative ^d	140	1		1	1		1	1		
Positive	93	0.88	0.61–1.27	0.50	0.44	0.19–1.01	0.05	0.98	0.68–1.42	0.92

Time period	OS			TRM			RR			
	N	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
1989–1997 ^a	102	1		1	1		1			
1998–2006	131	0.84	0.59–1.20	0.34	0.92	0.45–1.88	0.86	0.84	0.58–1.20	0.34

OS, overall survival; TRM, treatment-related mortality; RR, relapse risk; HR, hazard ratio; CI, confidence interval; MRD, matched related donor; URD, unrelated donor; yo, years old.

^aIdentifies reference group.

TABLE III

Multivariate Analysis of Clinical Outcomes

	OS			TRM			RR			
	N	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Treatment group										
Poor-risk: chemotherapy ^a	109	1		1			1			
Poor-risk: MRD	49	1.08	0.65–1.80	0.76	1.32	0.38–4.62	0.66	0.82	0.50–1.34	0.42
Poor-risk: URD	47	1.13	0.66–1.92	0.67	2.66	0.93–7.62	0.07	0.43	0.23–0.81	0.01
Race										
Not African American ^a	178	1		1			1			
African American	27	2.02	1.20–3.40	0.009	1.35	0.32–5.75	0.69	2.01	1.22–3.30	0.01
Age at diagnosis										
3–11 yo ^a	72	1		1			1			
0–2 yo	64	0.94	0.56–1.55	0.80	0.66	0.19–2.26	0.51	0.98	0.60–1.58	0.92
12–21 yo	69	1.45	0.92–2.29	0.11	2.01	0.85–4.73	0.11	0.94	0.58–1.54	0.82
WBC at diagnosis										
<50,000 ^a	179	1		1			1			
50,000	26	1.54	0.90–2.65	0.12	0.65	0.12–3.37	0.61	1.52	0.81–2.86	0.19
Time period										
1989–1997 ^a	89	1		1			1			
1998–2006	116	0.90	0.61–1.34	0.62	0.94	0.41–2.15	0.88	0.84	0.57–1.25	0.39

OS, overall survival; TRM, treatment-related mortality; RR, relapse risk; HR, hazard ratio; CI, confidence interval; MRD, matched related donor; URD, unrelated donor; yo, years old.

^aIdentifies reference group.

TABLE IV

Comparison of Clinical Outcomes Within Treatment Group by Time Period

Treatment group	N	Time period	OS ^a	P	Relapse ^b	P	TRM	P
Poor risk: chemotherapy	46	1989–1997	39 ± 14%	0.64	65 ± 14%	0.49	7 ± 7%	0.72
	77	1998–2006	46 ± 12%		58 ± 12%		8 ± 6%	
Poor risk: MRD	34	1989–1997	47 ± 17%	0.80	53 ± 17%	0.51	9 ± 10%	0.26
	21	1998–2006	46 ± 22%		48 ± 22%		19 ± 17%	
Poor risk: URD	22	1989–1997	36 ± 21%	0.11	32 ± 20%	0.67	36 ± 21%	0.17
	33	1998–2006	60 ± 17%		27 ± 16%		15 ± 13%	

OS, overall survival; RR, relapse risk; TRM, treatment-related mortality; MRD, matched related donor; URD, unrelated donor.

^a All outcomes are rates at 5 years.

^b Relapse refers to cumulative incidence of relapse.