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ORIGINAL REPORT

Impact of Disease Risk on Efficacy of Matched Related Bone Marrow Transplantation for Pediatric Acute Myeloid Leukemia: The Children's Oncology Group

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ABSTRACT

Purpose
There is considerable variation in the use of HLA-matched related bone marrow transplantation (BMT) for the treatment of pediatric patients with newly diagnosed acute myeloid leukemia (AML). Some oncologists have argued that BMT should be offered to most patients in first complete remission (CR). Others have maintained that transplantation in first remission should be reserved for patients with high-risk disease. We performed this study to determine how disease risk influences the efficacy of BMT.

Methods
We combined data from four cooperative group clinical trials: Pediatric Oncology Group 8821, Children's Cancer Group (CCG) 2891, CCG 2961, and Medical Research Council 10. Using cytogenetics and the percentage of marrow blasts after the first course of chemotherapy, patients were stratified into favorable, intermediate, and poor-risk disease groups. Patients who could not be risk classified were analyzed separately. Outcomes for patients assigned to BMT and for patients assigned to chemotherapy alone were compared.

Results
The data set included 1,373 pediatric patients with AML in first CR. In the intermediate-risk group, the estimated disease-free survival at 8 years for patients who did not undergo transplantation was 39% ± 5% (2 SE), whereas it was 58% ± 7% for BMT patients. The estimated overall survival for patients who did not undergo transplantation was 51% ± 5%, whereas it was 62% ± 7% for BMT patients. Both differences were significant ($P < .01$). There were no significant differences for survival in the other two risk groups or in the non–risk-stratified patients.

Conclusion
Our study indicates that HLA-matched related BMT is an effective treatment for pediatric patients with intermediate-risk AML in first CR.

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INTRODUCTION

The merits of using HLA-matched sibling bone marrow transplantation (BMT) as consolidation therapy for pediatric patients with acute myeloid leukemia (AML) in first complete remission (CR) have been contested vigorously. The superior survival achieved with BMT in several studies[1-10] has been mentioned in support of a broader use of transplantation,[11] whereas the recent improvements in chemotherapy[1-10] and the risks inherent in BMT have been cited in support of restricting the use of transplantation.[12] Proponents for a more selective use of BMT have suggested that transplantation should be reserved for patients at higher risk of relapse.[12] Although circumstantial evidence exists to support this recommendation, the impact of prognosis on the relative efficacy of BMT has not yet been rigorously assessed, largely because none of the cooperative group trials to date have been large enough to allow for such an analysis.

To create a sufficiently large data set to address this issue, we combined data on 1,373 patients drawn from four cooperative group phase III trials: Pediatric Oncology Group (POG) 8821, Children's Cancer Group (CCG) 2891, CCG 2961, and Medical Research Council (MRC) 10.[7-10] These studies were selected because all of them used BMT in first CR as a general strategy for children who had a matched, related donor, thus providing data for all risk groups.

METHODS

Patients with Down syndrome, t(15;17), secondary AML, or remission failures (as defined by each study) were excluded from the analysis. Patients were categorized as having had chemotherapy alone or matched related BMT on the basis of treatment assignment rather than treatment received. Data were originally aggregated from five studies (POG 8821, POG 9421, CCG-2891, CCG-2961, and MRC 10); the data from POG 9421, however, were not included in the final analysis, because intent-to-treat data were unavailable. Differences in study design were taken into account in classifying patients into chemotherapy-alone and matched related BMT groups. In the POG 8821 and CCG 2891 studies, after completing induction therapy, patients with a matched related donor were assigned to proceed to an allogeneic BMT, whereas patients lacking a donor were randomly assigned to proceed to consolidation chemotherapy or autologous transplantation. A similar design was used in CCG 2961, except that autologous transplantation was not used and, therefore, all patients lacking a related donor were assigned to proceed to consolidation chemotherapy. For these three studies, patients were classified as being in matched related BMT or chemotherapy-alone groups according to their assignments. The patients assigned to autologous transplantation in POG 8821 and CCG 2891 were excluded from our analysis, because the goal of our study was to compare allogeneic BMT with chemotherapy alone. In the MRC 10 trial, after completing the prescribed induction therapy, patients with a matched related donor were assigned to undergo an allogeneic BMT after completing two courses of consolidation chemotherapy. Patients without an available donor also went on to receive two courses of consolidation therapy, but were randomly assigned (before the second course) to an autologous BMT or to no further treatment after consolidation therapy. To prevent consolidation deaths and relapses from creating a bias against the chemotherapy alone group, all MRC 10 patients without a donor, including those who were ultimately assigned to autologous transplantation, were designated as chemotherapy alone for our analysis; to eliminate the impact of transplantation (patients undergoing autologous transplantation in the MRC 10 trial had significantly better event-free survival than patients receiving chemotherapy alone) on outcome the autologous BMT patients were censored at the time of transplantation.

The patients from the four trials were stratified into favorable-, intermediate-, and poor-risk disease groups. For the CCG and POG studies, patients with inv(16) and t(8;21) were considered to have favorable-risk disease; patients with monosomy 7, monosomy 5, deletions of 5q, or more than 15% blasts after the first course of chemotherapy were considered to have high-risk disease. All other patients were deemed to have intermediate-risk disease. The MRC study used similar criteria, but additionally classified patients with abnormalities of 3q and patients with five or more cytogenetic abnormalities as having high-risk disease. Patients who could not be classified because they lacked cytogenetic testing results were analyzed separately.

Postremission relapse, treatment-related mortality, disease-free survival, and overall survival are defined from the end of induction (two courses). Overall survival is defined as time to death from any cause. Disease-free survival is defined as time to relapse or death from any cause. Children lost to follow-up were censored at their date of last known contact or at a cutoff 6 months before the data set creation date for each study. Survival rates and corresponding Greenwood SEs were estimated at 8 years using the Kaplan-Meier method. Because the trials varied in many respects, including the transplantation and nontransplantation treatment approaches used, we also generated a Cox proportional hazard regression model in which we stratified by study to adjust for between-study differences. No other covariates were incorporated. Hazard ratios (HRs) comparing the chemotherapy-only patients with the matched related donor patients were calculated using the latter as the reference group. *P* values were generated for the hazard ratios.

RESULTS

Data Set

The data set aggregated from the four studies included 893 patients assigned to chemotherapy alone and 480 patients assigned to allogeneic BMT. There were 157, 411, and 38 patients in the chemotherapy-only group in the favorable-, intermediate-, and poor-risk disease groups, respectively (Table 1). There were 96, 204, and nine patients assigned to BMT in these risk groups, respectively. There were 171 and 287 patients who could not be risk classified in the BMT and chemotherapy-alone groups, respectively.

Non–Risk-Stratified Analysis

Overall survival was superior for the BMT group. At 8 years, the estimates for BMT and chemotherapy groups were 63% ± 5% (2 SE) and 57% ± 4% (HR = 0.77; $P = .007$). Similarly, disease-free survival was better in the BMT group: 56% ± 5% (2 SE) and 46% ± 4% (HR = 0.70; $P < .001$). The incidence of relapse was much lower in patients assigned to BMT: 28% ± 4% versus 47% ± 4% (HR = 0.51; $P < .001$). This gain, however, was partially offset by a higher rate of treatment-related mortality: BMT, 16% ± 3%; chemotherapy alone, 7% ± 2% (HR = 1.97; $P < .001$; Table 2).

Risk-Stratified Analysis

When patients were risk stratified, the analysis showed that transplantation in first CR enhances overall survival in patients with intermediate-risk disease, but not in patients with favorable-risk disease or poor-risk disease or in patients whose disease could not be risk classified (Table 3 and Fig 1). In the intermediate-risk group, the

Table 1. Patients by Study, Risk Group, and Treatment

Study and Risk Group	Treatment			
	BMT		Chemotherapy	
	No. of Patients	%	No. of Patients	%
MRC AML 10				
Total	76		164	
Favorable	14	18.4	31	18.9
Intermediate	45	59.2	94	57.3
Poor	2	2.6	19	11.6
Nonclassifiable	15	19.7	20	12.2
POG 8821				
Total	70		95	
Favorable	19	27.1	29	30.5
Intermediate	30	42.9	42	44.2
Poor	0	0	3	3.2
Nonclassifiable	21	30	21	22.1
CCG 2891				
Total	169		167	
Favorable	30	17.8	13	7.8
Intermediate	54	32	67	40.1
Poor	4	2.4	8	4.8
Nonclassifiable	81	47.9	79	47.3
CCG 2961				
Total	165		467	
Favorable	33	20.0	84	18.0
Intermediate	75	45.5	208	44.5
Poor	3	1.8	8	1.7
Nonclassifiable	54	32.7	167	35.8

Abbreviations: BMT, bone marrow transplantation; MRC, Medical Research Council; AML, acute myeloid leukemia; POG, Pediatric Oncology Group; CCG, Children's Cancer Group.

Table 2. Non–Risk-Stratified Outcomes Comparing Matched Sibling BMT and Chemotherapy Alone

Outcome	Therapy				Hazard Ratio	95% CI*	*P*
	BMT		Chemotherapy				
	8-Year Estimate (%)	2 SE (%)	8-Year Estimate (%)	2 SE (%)			
Relapse	28	4	47	4	0.51	0.42 to 0.63	< .001
Treatment-related mortality	16	3	7	2	1.97	1.39 to 2.80	< .001
Disease-free survival	56	5	46	4	0.70	0.59 to 0.83	< .001
Overall survival	63	5	57	4	0.77	0.64 to 0.93	.007

Abbreviation: BMT, bone marrow transplantation.
*Chemotherapy alone is the reference group.

estimated overall survival at 8 years for the patients assigned to chemotherapy alone was 51% ± 5%, whereas it was 62% ± 7% for the patients assigned to BMT (HR = 0.69; $P = .006$).

As shown in Table 3 and Figure 2, the benefit from BMT in the intermediate-risk group was driven by a large reduction in the incidence of relapse. The incidence was 26% ± 6% and 54% ± 5% in the BMT and chemotherapy-only patients, respectively (HR = 0.42; $P < .001$). By contrast, in the favorable-risk disease group, BMT was associated with a modest and statistically nonsignificant reduction in the risk for relapse (BMT, 21% ± 9%; chemotherapy only, 30% ± 8%; HR = 0.59; $P = .06$) that was obviated by the higher incidence of treatment-related mortality with transplantation.

An analysis was also conducted incorporating the as-treated data from the POG 9421 trial. This analysis included more than 1,800 patients and yielded similar results (data not shown), showing an improvement in survival that was restricted to the intermediate-risk disease group.

DISCUSSION

In this study, we sought to better define the role of HLA-matched, related BMT in the treatment of pediatric AML. By combining individual patient data from four cooperative group trials, we were able to create a data set of children and adolescents with AML in first CR that, for the first time, was large enough to perform a risk-based assessment of the efficacy of BMT. Our findings demonstrate that the antileukemic effect of BMT is strongly influenced by prognosis. In patients with intermediate-risk disease, BMT greatly reduces the risk for relapse and, thereby, improves survival; in patients with favorable-risk disease, its effect on relapse is less

Table 3. Risk-Stratified Outcomes Comparing Matched Sibling BMT and Chemotherapy Alone

Outcome	Therapy				Hazard Ratio	95% CI†	*P*
	BMT		Chemotherapy				
	Estimate* (%)	2 SE	Estimate* (%)	2 SE			
Favorable-risk disease							
Relapse	21	9	30	8	0.59	0.34 to 1.03	.06
Treatment-related mortality	16	8	9	5	1.99	0.93 to 4.26	.08
Disease-free survival	63	10	61	8	0.89	0.57 to 1.37	.58
Overall survival	73	9	71	8	0.95	0.57 to 1.59	.85
Intermediate-risk disease							
Relapse	26	6	54	5	0.42	0.31 to 0.57	< .001
Treatment-related mortality	16	5	7	3	1.83	1.09 to 3.05	.022
Disease-free survival	58	7	39	5	0.59	0.46 to 0.76	< .001
Overall survival	62	7	51	5	0.69	0.52 to 0.90	.006
Poor-risk disease							
Relapse	67	31	56	18	1.25	0.41 to 3.80	.69
Treatment-related mortality	0	0	9	10	Estimates do not converge		
Disease-free survival	33	31	35	17	1.13	0.38 to 3.38	.82
Overall survival	33	31	35	17	0.87	0.30 to 2.51	.80
Nonclassifiable							
Relapse	32	7	44	6	0.61	0.43 to 0.85	.004
Treatment-related mortality	16	6	6	3	2.38	1.21 to 4.66	.012
Disease-free survival	52	8	50	3	0.80	0.60 to 1.07	.14
Overall survival	60	8	61	6	0.89	0.64 to 1.24	.49

Abbreviation: BMT, bone marrow transplantation.
*Eight-year estimates (± 2 SE) are shown, except for BMT patients with poor-risk disease; for this group, estimates are for 4 years because of limited follow-up.
†Chemotherapy alone is the reference group.

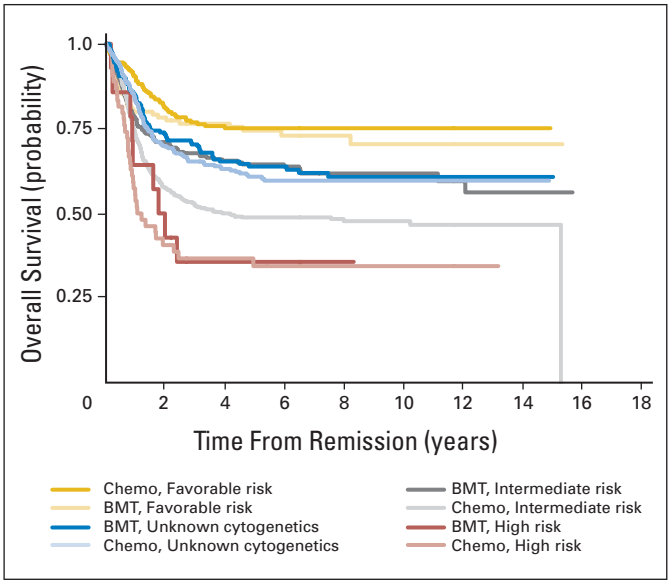

Fig 1. Estimated overall survival stratified by risk group and postremission treatment. Chemo, chemotherapy; BMT, bone marrow transplantation.

dramatic and largely negated by the greater risk for treatment-related mortality associated with BMT.

The small number of patients with poor-risk disease available for this analysis precludes any definitive conclusions from being drawn regarding the effect of BMT in this group of patients, but our results do suggest that even with transplantation, these patients fair badly.

Approximately one third of the patients in our analysis could not be risk stratified because of lack of cytogenetic results. In cooperative group trials, there are various reasons for this; in many cases, cytogenetic results are obtained but rejected on central review because of poor quality, and in other cases, results are never obtained. Our findings suggest that, in general, BMT is not indicated for these patients.

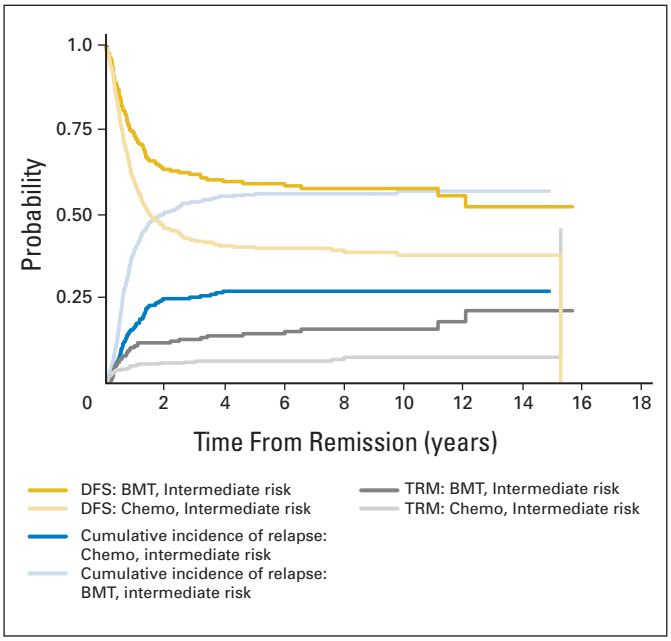

Fig 2. Estimated disease-free survival (DFS), treatment-related mortality (TRM), and relapse for intermediate-risk patients. BMT, bone marrow transplantation; Chemo, chemotherapy.

A limitation of our study is that the data were drawn predominantly from Children's Oncology Group studies. Consideration was given to including data from the MRC 12 trial as well as the MRC 10 trial to broaden the database. The decision not to, however, was made because transplantation was used sparingly in the MRC 12 trial. Given the lack of data from cooperative groups in Europe, Asia, and elsewhere, caution should be used in attempting to generalize the results of our study. The possibility that our findings may not be universally applicable is raised by the results of the Berlin-Frankfurt-Muenster (BFM) 98 and the MRC 12 trials; both studies demonstrated survival rates in intermediate-risk patients treated with chemotherapy alone that rival the rate we observed in patients receiving BMT (a straightforward comparison with the BFM experience is difficult, however, because it uses a dichotomous, rather than tripartite, prognostic system).[3,4] It is unclear whether the discordance in the results of these trials and the results of our analysis is solely a matter of treatment efficacy, because there are important demographic differences in the populations served by the Children's Oncology Group, MRC, and BFM, and age, race, and ethnicity have all been shown to influence survival in pediatric AML.[10,13]

The role of BMT in the treatment of children and adolescents with AML in first CR will need to be reassessed as the field evolves. As risk stratification schemes are refined through the identification of new prognostic markers, such as internal tandem duplication of the *FLT3* gene,[14] the population of patients who will benefit from BMT will need to be redefined. Also, future advances in chemotherapy will likely reduce the need for BMT, unless advances in transplantation occur at a similar pace.

The results of our study should not be given the same credence as those of a large, randomized, controlled study. Even though we used individual patient data, meta-analyses, in general, have limitations. There is one important question left unanswered by our study: What is the optimal timing of BMT for patients who have intermediate-risk disease? Although our analysis showed that for children with AML in first CR, HLA-matched, related BMT is more effective than continued chemotherapy, the possibility remains that the efficacy of BMT could be maximized by reserving it for the treatment of relapsed disease. Such a strategy might be advantageous, because it avoids unnecessarily exposing those patients who can be cured with chemotherapy alone to the risks of BMT. All four studies included in our analysis used biologic randomization; that is, they have assigned all patients with an HLA-matched, related donor to transplantation and all patients without such a donor to receive additional chemotherapy. Among the potential biases engendered by this method of assignment, the most obvious one is that patients receiving chemotherapy alone are left with inferior donor options for the treatment of relapseddisease. A patient with a matched related sibling is likely to proceed to BMT promptly after a second remission has been achieved; many patients without a matched related donor, on the other hand, will face delays as attempts are made to secure a well-matched, alternative donor—some will succumb to infection and some to relapse during this time. In some cases, no viable donor will be identified. The results of the studies that have used biologic assignment, then, may speak to the disadvantages of not having a readily available donor available, rather than to the importance of performing BMT in first CR.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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