

# Hematopoietic Stem Cell Transplantation for Advanced Myelodysplastic Syndrome After Conditioning With Busulfan and Fractionated Total Body Irradiation Is Associated With Low Relapse Rate but Considerable Nonrelapse Mortality

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## ABSTRACT

The objectives of this study were to develop transplantation regimens for patients with advanced myelodysplastic syndrome (MDS) that would be associated with low transplantation-related mortality and improved relapse-free survival. Sixty patients with advanced MDS or acute myeloid leukemia evolving from MDS (sAML), 12 to 62 years old (median, 40 years), were conditioned with busulfan (7 mg/kg) and TBI (6 × 200 cGy) (BU/TBI) and received transplants from related (n = 20) or unrelated donors (n = 40). By French-American-British (FAB) criteria, 21 patients had refractory anemia with excess blasts (RAEB), 16 had RAEB in transformation (RAEB-T), 15 had sAML, and 8 had chronic myelomonocytic leukemia (CMML). By International Prognostic Scoring System (IPSS) criteria, 1 patient had low, 10 had intermediate-1, 13 had intermediate-2, and 31 had high-risk MDS (5 patients had proliferative CMML). All evaluable patients achieved sustained engraftment. The cumulative incidence (CI) of acute GVHD grades II to IV was 83% with unrelated donors and 85% with related donors. The CI of relapse was 25% at 3 years. The incidence of nonrelapse mortality (NRM) at 100 days was 38%. The Kaplan-Meier estimate of survival was 26% at 3 years. Major causes of death were relapse, organ failure, GVHD, and infection. In multivariate analysis, improved relapse-free survival was associated with good cytogenetic risk ( $P = .002$ ) and shorter disease duration ( $P = .004$ ). NRM was increased with longer disease duration ( $P = .0002$ ), positive cytomegalovirus serology ( $P = .02$ ), and male sex ( $P = .02$ ). Relapse was associated with poor cytogenetic risk ( $P = .0004$ ). Thus, BU/TBI conditioning as used in this trial was associated with relapse rates comparable to those observed with a previously used more intensive regimen combining BU/TBI with cyclophosphamide. However, despite the omission of cyclophosphamide, transplantation-related morbidity and mortality were considerable, particularly with transplants from unrelated donors. Future trials should explore the efficacy and tolerability of reduced-intensity conditioning regimens.

## KEY WORDS

Advanced MDS • Conditioning regimen • Relapse • Nonrelapse mortality

**Table 1.** Patient and Disease Characteristics\*

Characteristic	Conditioning Regimen		
	BU/TBI (Present Study)	BU/CY/TBI [11]	CY/TBI [11]
No. of patients	60	31	44
Age, range (median), y	12-62 (40)	16-54 (41)	1-55 (36)
M/F, no. of patients	37/23	18/13	25/19
Etiology, no. of patients			
De novo	48	28	37
Secondary	12	3	7
Disease duration, range (median), mo	2-61 (12)	2-83 (5)	2-144 (8.5)
FAB stage, no. of patients			
RAEB	21	15	30
RAEB-T	16	8	14
CMML	8	8	0
sAML	15	0	0
Cytogenetic risk (IPSS), no. of patients			
Good	24	15	14
Intermediate	11	6	9
Poor	25	10	19
Not available	0	0	2
IPSS group, no. of patients			
Low	1	0	ND†
Intermediate-1	10	9	ND
Intermediate-2	13	9	ND
High	31	6	ND
Not scored‡	5	7	ND
CMV serology, no. of patients			
Positive	31	26	28
Negative	29	5	16
GVHD prophylaxis, no. of patients			
MTX/CSP	53	15	44
MTX/FK506	7	2	0
CSP/MP	0	10	0
CSP	0	4	0
Donor			
HLA-identical sibling	17	22	33
Alternative donor§	43	9	11

\*ND indicates not determined; MP, methylprednisolone.

†Not determined; not all parameters complete.

‡Proliferative CMML.

§HLA-nonidentical related or unrelated donor.

## INTRODUCTION

Patients with advanced myelodysplastic syndrome (MDS) have a poor prognosis due to complications related to peripheral blood cytopenias and the high probability of transformation into secondary acute myeloid leukemia (sAML). Using the criteria of the French-American-British (FAB) classification, median survival times for patients with refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML) [1] have been reported to be 9, 6, and 22 months, respectively. The International Prognostic Scoring System (IPSS), which considers cytogenetic abnormalities and the number of peripheral blood cytopenias in addition to the proportion of marrow blasts, appears to add prognostic accuracy in predicting survival and evolution to AML for patients with "de novo" MDS [2-6].

Hematopoietic stem cell transplantation (HSCT) is currently the only curative therapy for MDS [7]. However, in patients receiving transplants for advanced MDS, relapse rates of 30% to 50% and nonrelapse mortality (NRM) rates of 35% to 50% have resulted in event-free survivals of 15% to 30% [8]. High-risk IPSS scores, in particular the number of blasts (in marrow and blood), and unfavorable cytogenetic abnormalities are major determinants of high relapse rates [3-6,9-15]. Older patient age, longer disease duration, and male sex also have predictive value for higher NRM [9,10,12-15].

Trials at the Fred Hutchinson Cancer Research Center [10] showed that patients with advanced MDS conditioned with cyclophosphamide (CY) and total body irradiation (TBI) had a relapse incidence of 39% and a probability of survival of 30% at 3 years. The addition of busulfan (BU; 7 mg/kg) to a CY/TBI regimen led to a lower relapse rate (19%); however, with such a regimen, the incidence of NRM was 57% and relapse-free survival (RFS) was only 23% [11]. CY does not have anti-stem cell activity but may contribute to nonhematologic toxicity. Therefore, in an attempt to improve RFS, the present trial used a combination of BU (7 mg/kg) and TBI (6 × 200 cGy) without the inclusion of CY. To put results into perspective, outcomes in the present trial were compared to those observed after CY/TBI or BU/CY/TBI conditioning as reported previously [11].

## MATERIALS AND METHODS

### Patients

From January 1994 through October 1999, 60 patients with advanced MDS or MDS transformed into AML (sAML) were enrolled in this study. Patient characteristics are summarized in Table 1. At the time of diagnosis, 13 of these patients had RA; 28 patients had RAEB; 9 patients had RAEB-T; and 10 patients had CMML. Forty-eight of the 60 patients had de novo MDS, and 12 patients had disease considered secondary to previous therapy for acute lymphoblastic leukemia (n = 3), aplastic anemia (n = 2), Hodgkin's disease (n = 1), multiple myeloma (n = 1), breast cancer (n = 1), kidney transplantation (n = 1), systemic lupus erythematosus (n = 1), bare lymphocyte syndrome (n = 1), or pesticide exposure (n = 1). All patients with secondary MDS were in complete remission from the original disease. Five patients had not received therapy for MDS before transplantation; all remaining patients had been treated with transfusion support, vitamins, growth factors, or other modalities. Two patients had undergone splenectomy. At the time of HSCT, 21 patients had RAEB; 16 patients had RAEB-T; 15 patients had sAML; and 8 patients had CMML. Eighteen patients (3 with RAEB, 4 with RAEB-T, 8 with sAML, and 3 with CMML) received induction chemotherapy on protocols that included cytosine arabinoside and an anthracycline or topotecan, and 8 of these patients (2 with RAEB, 1 with RAEB-T, 4 with sAML, and 1 with CMML) achieved complete hematologic remissions (CR) and were in CR at the time of HSCT. Ten patients had no or only partial responses. The interval from diagnosis of MDS to HSCT for all patients was 2 to 61 months (median, 12 months; 6.6 months for related and 14.7 months for unrelated transplantation).

**Cytogenetic Characteristics.** At the time of diagnosis of MDS, cytogenetic data were available in 54 patients. By IPSS criteria [2], 20 patients were categorized as good risk (normal karyotype in 19 patients; 5q- in 1 patient), 19 patients as poor risk (chromosome 7 abnormalities in 10 patients; complex abnormalities in 9 patients), and 15 patients as intermediate risk (trisomy 8 in 3 patients; miscellaneous abnormalities in 12 patients). At the time of HSCT, cytogenetic analysis was performed in all patients: 24 of them were good risk (normal karyotype in 23 patients; 5q- in 1 patient), 25 patients were poor risk (chromosome 7 abnormalities in 16 patients; complex abnormalities in 9 patients), and 11 patients were intermediate risk (trisomy 8 in 3 patients, single miscellaneous in 5 patients, and double abnormalities in 3 patients).

**IPSS Scores.** Although the IPSS was developed for patients with de novo MDS [2], in the present analysis, we applied the IPSS criteria to all patients except those with proliferative CMML. At HSCT, 1 patient qualified as low risk, 10 patients as intermediate-1, 13 patients as intermediate-2, and 31 patients as high risk. Five patients had proliferative CMML.

### Conditioning Regimen

BU (0.44 mg/kg) was given orally every 6 hours for 16 doses on days -7 to -4 for a total of 7 mg/kg. Because plasma BU concentrations at steady state (BU C<sub>ss</sub>) can vary widely among patients [16], sequential plasma samples for pharmacokinetic monitoring were obtained. BU C<sub>ss</sub> levels ranged from 247 to 627 ng/mL (median, 450 ng/mL) [17]. TBI was delivered at an exposure rate of 6 to 7 cGy/min in fractions of 200 cGy twice daily on days -3 to -1 for a total dose of 1200 cGy.

### Source of Hematopoietic Stem Cells

Twenty patients received HSCT from related donors (17 were HLA genotypically identical and 3 were HLA-A, -B, -DR phenotypically matched), and 40 patients received transplants from unrelated donors (38 were HLA-A, -B, -C serologically matched and DRB1 matched; 1 donor was serologically mismatched for HLA-C, and 1 for HLA-A). The source of hematopoietic stem cells was marrow in 58 patients and peripheral blood in 2 patients (both related transplants); all transplants were T-cell replete. Median mononuclear cell dose was  $3.35 \times 10^8$ /kg for marrow recipients and 13.6 and  $5.9 \times 10^6$  CD34<sup>+</sup> cells/kg, respectively, for the 2 recipients of peripheral blood.

### Graft-Versus-Host Disease Prophylaxis

Graft-versus-host disease (GVHD) prophylaxis consisted of a short course of methotrexate (MTX) and cyclosporine (CSP) in 53 patients and tacrolimus (FK 506) and MTX in 7 patients, as described previously [18,19]. Acute and chronic GVHD were diagnosed and graded as described [20,21]. Acute GVHD was treated with prednisone, monoclonal antibodies, or rapamycin [22,23]. Chronic GVHD was treated with prednisone alone or combined with CSP.

### Engraftment and Rejection

The day of engraftment was defined as the first of 3 consecutive days on which neutrophil counts exceeded

$0.5 \times 10^9$ /L [24]. Evidence of graft rejection was sought in patients who survived at least 28 days and who failed to reach  $0.5 \times 10^9$  neutrophils/L and in patients who showed a decline after initial recovery. In patients with morphologic or cytogenetic evidence of recurrence of MDS, relapse rather than rejection was considered the cause of graft failure as long as donor T-lymphocytes persisted (see below). When patient and donor were of different sexes, in situ hybridization with X- and Y-chromosome probes [25] was performed on bone marrow and peripheral blood mononuclear cells (PBMC) stimulated with phytohemagglutinin to determine donor versus host origin. When patient and donor were of the same sex, DNA from bone marrow and PBMC was amplified for several variable number tandem repeat (VNTR) loci. The amplified fragments were examined to identify informative host and donor markers [26].

### Relapse

All patients were scheduled to have marrow samples examined morphologically and by cytogenetic and flow cytometric analyses at a minimum on day 28, at 3 months after transplantation, and then annually or as clinically indicated. Relapse was defined as the detection of metaphases in the marrow that showed the same clonal marker(s) identified before transplantation or as the reemergence of myeloblasts or aberrant precursors as defined with the use of flow cytometry [27].

### Infection

Blood samples were examined weekly for evidence of cytomegalovirus (CMV) either by culture or by the presence of CMV antigenemia. Interstitial pneumonia (IP) was diagnosed by culture, histologic or histochemical analysis of bronchoalveolar lavage fluid, open lung biopsy, or autopsy. Various strategies to prevent infections were employed during this study, including the prophylactic use of systemic antibiotics, fluconazole, acyclovir, and ganciclovir. All CMV-seronegative patients received either CMV-negative or filtered blood products. Acyclovir was given for prophylaxis throughout the study period to all patients who were seropositive for herpes simplex virus. Ganciclovir was given to all CMV-seropositive recipients at engraftment or at the first documentation of antigenemia [28].

### Causes of Death

Relapse was considered the primary cause of death for all deaths after relapse. Deaths in the absence of relapse were categorized as NRM. Infections were categorized according to whether or not they were associated with GVHD and with organ failure. Multiorgan failure was considered the cause of death if decompensation occurred in at least 2 organ systems (eg, liver and kidneys or liver and lungs) not associated with GVHD or infection.

### Historical Controls

In an attempt to put results of the present trial into perspective, we also included data on 2 previously reported trials: 31 patients who received transplants from 1990 through 1993 after conditioning with BU/CY/TBI and 44 patients who received transplants from 1982 through 1990 after conditioning with CY/TBI [11] (Table 1).

**Table 2.** Causes of Death Among Patients Conditioned With BU/TBI\*

Cause of Death	No. of Deaths (Before Day 28)
Relapse	14
Organ failure ± infection ± GVHD	19 (5)
GVHD ± infection	4
Infection	4 (2)
Infection + PTLD	1
CNS hemorrhage	2 (1)

\*PTLD indicates posttransplantation lymphoproliferative disorder; CNS, central nervous system.

### Statistical Analysis

RFS probabilities were estimated using the Kaplan-Meier method [29]. The incidences of relapse and NRM were expressed as cumulative incidence (CI) [30]. Cox regression was used to analyze risk factors related to the hazard rates for these outcomes. In these analyses, relapse and NRM were considered as competing events. The time to these outcomes was censored at the time of a competing event. Multivariate models were constructed by a forward selection procedure. At each step, the most significant factor at a level of at least 0.05 was added. Multivariate *P* values refer to the significance of the factor after adjusting for other factors in the final multivariate model. All *P* values are 2-sided and are based on likelihood ratio statistics from the Cox regression model. Results were analyzed as of June 1, 2001.

In addition, we compared the present data with those reported previously for CY/TBI and BU/CY/TBI conditioned patients [11].

## RESULTS

### Engraftment

Eight patients died on days 11 through 27 (see Table 2) and were considered unevaluable for engraftment. The remaining 52 patients achieved granulocyte counts  $>0.5 \times 10^9/L$  at 11 to 33 days (median, 19 days) and platelet counts  $>20 \times 10^9/L$  at 10 to 47 days (median, 23 days); there were no significant differences between related and unrelated transplant recipients. All surviving patients had complete donor engraftment as determined by chimerism analysis at 3 months and 1 year after transplantation.

### Graft-Versus-Host Disease

Acute GVHD grades II to IV occurred in 50 evaluable patients (grade II in 20 patients [10 related/10 unrelated], grade III in 19 patients [5/14], and grade IV in 11 patients [9/2]). The incidences of grades II to IV acute GVHD were 85% and 83% for related and unrelated donors, respectively. Twenty (8 related/12 unrelated) among 29 (11 related/18 unrelated) patients at risk developed extensive chronic GVHD for a CI of 70%.

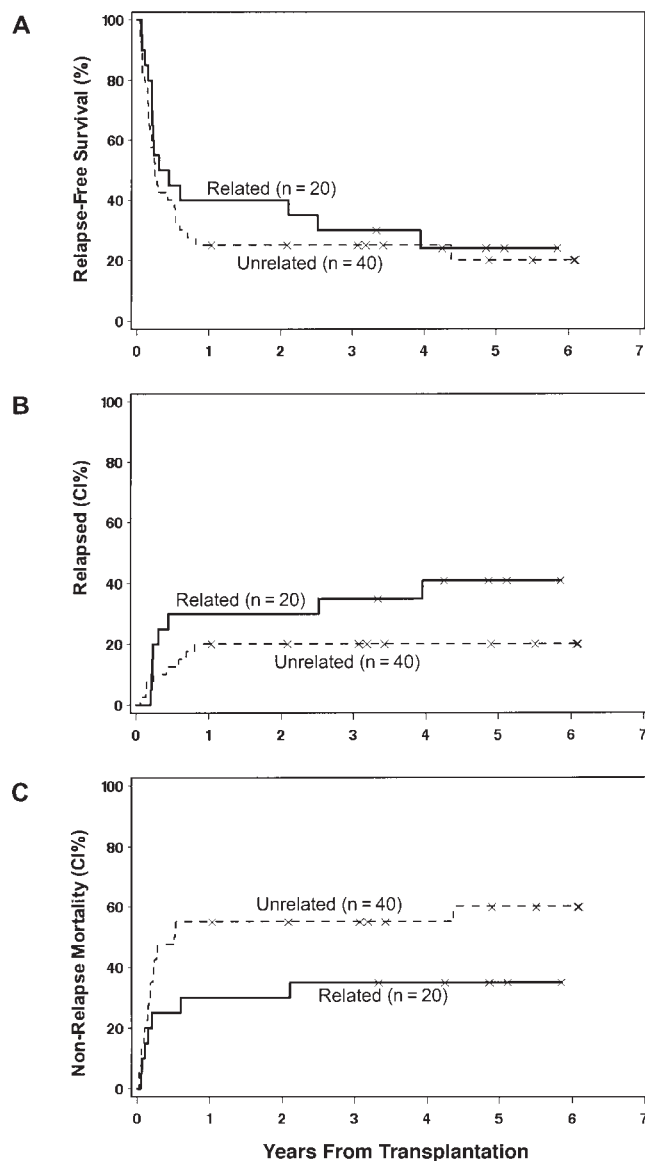
### Survival

With a follow-up of 20 to 89 months (median, 54 months), 16 patients are alive, and 15 of them are in CR, with Karnofsky performance scores of 90 to 100 in 11 patients and 50 to 80 in the remaining 5 patients. The 3-year RFS was 26% for the entire cohort, and 31% when

sAML cases were excluded. Three-year RFS was 13% for patients with sAML. RFS was 31% for patients with de novo MDS and 8% for patients with secondary MDS ( $P = .11$ ). There was no significant difference in RFS between patients receiving transplants from related donors (30%) and those receiving transplants from unrelated donors (25%) (Figure 1A). One of the 2 patients receiving transplants from HLA-mismatched unrelated donors is surviving.

### Relapse

Sixteen patients, 13 of whom had high-risk IPSS scores, relapsed 0.5 to 49 months (median, 3.7 months) posttransplantation; all but 2 relapses occurred within 9 months. The incidence of relapse at 3 years was 25% for the entire group



**Figure 1.** Outcome in patients with advanced MDS who received transplants from related or unrelated donors. All patients were conditioned with BU and TBI. X indicates censored patients. A, Relapse-free survival ( $P = NS$ ). B, Incidence of relapse ( $P = NS$ ). C, Non-relapse mortality ( $P = NS$ ).

**Table 3.** Probability of RFS, Relapse, and NRM Among BU/TBI Conditioned Patients: Univariate Analysis\*

Risk Factor	Endpoint, % at 3 y		
	RFS	Relapse	NRM
<b>All patients</b>	<b>26</b>	<b>25</b>	<b>49</b>
<b>Patient sex</b>			
<b>Female</b>	<b>35</b>	<b>39</b>	<b>26</b>
<b>Male</b>	<b>21</b>	<b>17</b>	<b>63</b>
<b>P</b>	<b>.36</b>	<b>.25</b>	<b>.04</b>
<b>Disease duration</b>			
<b>&lt;12 months</b>	<b>32</b>	<b>29</b>	<b>39</b>
<b>&gt;12 months</b>	<b>7</b>	<b>14</b>	<b>79</b>
<b>P</b>	<b>.007</b>	<b>.95</b>	<b>.001</b>
<b>Cytogenetic pattern</b>			
<b>Good/intermediate</b>	<b>33</b>	<b>15</b>	<b>51</b>
<b>Poor</b>	<b>14</b>	<b>43</b>	<b>43</b>
<b>P</b>	<b>.02</b>	<b>.0004</b>	<b>.72</b>
<b>IPSS risk</b>			
<b>Low/intermediate-1</b>	<b>46</b>	<b>9</b>	<b>46</b>
<b>Intermediate-2</b>	<b>31</b>	<b>8</b>	<b>62</b>
<b>High</b>	<b>16</b>	<b>39</b>	<b>45</b>
<b>Not available</b>	<b>40</b>	<b>20</b>	<b>40</b>
<b>P</b>	<b>.04</b>	<b>.003</b>	<b>.65</b>
<b>FAB classification</b>			
<b>RAEB</b>	<b>37</b>	<b>10</b>	<b>53</b>
<b>RAEB-T</b>	<b>25</b>	<b>25</b>	<b>50</b>
<b>sAML</b>	<b>13</b>	<b>47</b>	<b>40</b>
<b>CMML</b>	<b>25</b>	<b>25</b>	<b>50</b>
<b>P</b>	<b>.22</b>	<b>.02</b>	<b>.92</b>

\*Not significant for any of the 3 endpoints were patient age, disease etiology, donor relationship (related versus unrelated), and steady-state plasma BU levels.

(35% for related and 20% for unrelated transplants) (Figure 1B). The relapse incidence was 47% for patients with sAML and 18% for other patients. One patient who relapsed at 9 months received a donor lymphocyte infusion ( $2.75 \times 10^7$  CD3<sup>+</sup> cells/kg) and achieved another CR. Fourteen patients died with disease progression, and 1 patient is alive with recurrent disease.

Among the 8 patients who achieved pretransplantation CR with induction chemotherapy, 2 patients are surviving in CR (1 following donor lymphocyte infusion; see above) and 1 patient is alive in relapse. Five patients have died, 1 from relapse and 4 from NRM. Among the 10 patients who did

not respond to chemotherapy, 1 patient is alive in CR, and 9 patients have died, 3 from relapse and 6 from NRM.

**Nonrelapse Mortality**

Thirty patients died from transplantation-related complications, for a NRM of 49% (35% for related and 55% for unrelated transplants; *P* = NS; Figure 1C). The NRM incidence was 40% for patients with sAML and 51% for other patients (*P* = NS). Twenty-two patients died before day 100, including 8 patients who died before day 28. The causes of death are listed in Table 2. The most frequent cause was single or multiorgan failure, alone or associated with infection, GVHD, or both. The most frequent etiology of infection was fungal (*n* = 10), specifically, aspergillus species in 9 patients and mucor in 1 patient.

**Univariate Analysis**

Results are summarized in Table 3. Patients with poor-risk cytogenetics had a lower RFS (14%) and a higher relapse rate (43%) than did good- and intermediate-risk patients (RFS, 33%; *P* = .02; relapse rate, 15%; *P* = .0004). Other significant variables for lower relapse rates were the diagnosis of RAEB (*P* = .02) and low/intermediate-1 IPSS scores at transplantation (*P* = .003). Conversely, the diagnosis of sAML was predictive of a higher relapse rate (*P* = .02). FAB category or IPSS score at the time of diagnosis of MDS had no significant impact on outcome. Disease duration >12 months was also predictive for lower RFS (17%; *P* = .007) and was associated with higher NRM (79%; *P* = .001). Outcomes tended to be better with lower BU Css levels, but differences were not significant for any of the endpoints studied. Although patients with de novo MDS tended to fare better than patients with secondary MDS, differences did not reach statistical significance for any of the endpoints studied (RFS, 31% versus 8%, *P* = .14; relapse, 23% versus 33%, *P* = .24; NRM, 46% versus 58%, *P* = .33). Patient age and transplantation from unrelated compared to related donors had no significant impact on outcome.

**Multivariate Analysis**

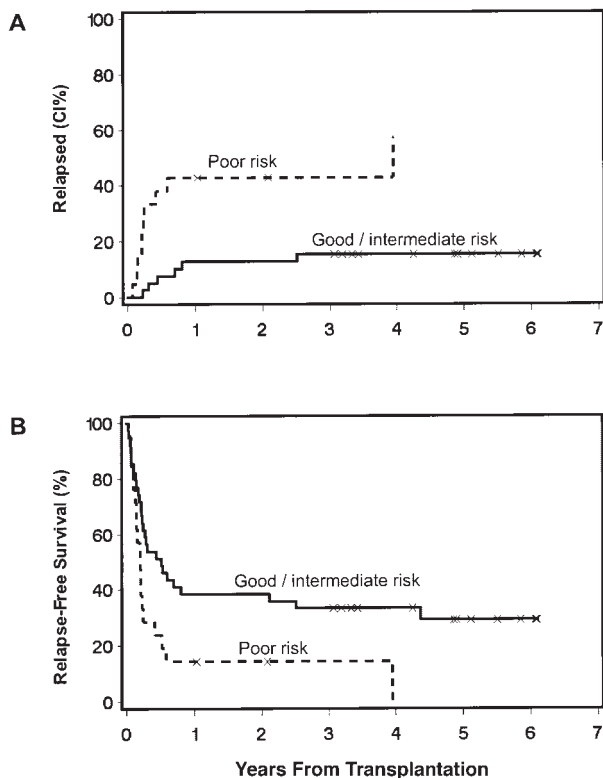
Results are as summarized in Table 4. Cytogenetic risk category was the only factor associated with relapse (*P* = .0004), which also affected RFS (*P* = .004) (Figure 2). Disease duration >12 months was significantly associated with higher NRM (*P* = .0002) and reduced RFS (*P* = .002). In

**Table 4.** Risk Factors for RFS, Relapse, and NRM in Patients Conditioned With BU/TBI: Multivariate Analysis\*

Risk Factor	Endpoint, RR (CI)		
	RFS	Relapse	NRM
<b>Cytogenetic risk (favorable: good/intermediate)</b>	<b>2.6 (1.4, 4.9)</b> <i>P</i> = .004	<b>6.6 (2.3, 18.6)</b> <i>P</i> = .0004	—†
<b>Disease duration (favorable: &lt;12 months)</b>	<b>3.1 (1.6, 5.9)</b> <i>P</i> = .002	—	<b>4.9 (2.3, 10.7)</b> <i>P</i> = .0002
<b>Patient CMV status (favorable: negative)</b>	—	—	<b>2.4 (1.1, 5.2)</b> <i>P</i> = .02
<b>Patient sex (favorable: female)</b>	—	—	<b>2.6 (1.1, 6.0)</b> <i>P</i> = .02

\*RR indicates relative risk; CI, confidence interval.

†Not significant.



**Figure 2.** Impact of pretransplantation clonal cytogenetic findings on posttransplantation outcome in patients with advanced MDS conditioned with BU and TBI. Shown are results among patients with poor risk compared to those with good or intermediate risk karyotypes. X indicates censored patients. A, Relapse ( $P = .0004$ ). B, Relapse-free survival ( $P = .004$ ).

addition, male patient sex ( $P = .02$ ) and positive CMV serology of the patient ( $P = .02$ ) were associated with higher NRM. Patient age, etiology of MDS, donor (related versus unrelated), and Bu Css levels did not have predictive value for the endpoints studied.

**Comparison to Historical Controls**

Outcome data among BU/TBI conditioned patients (present trial), BU/CY/TBI conditioned patients, and CY/TBI conditioned patients as reported previously [11] are summarized in Table 5. We refrained from carrying out formal statistical analyses of results obtained with these 3 regimens for several reasons: patients underwent transplantations over an interval of more than 17 years; over this interval, many aspects of patient management have changed considerably; some disease parameters required, for example, for IPSS scoring, were not available for earlier patients. An informal comparison of results suggests that 1 of the objectives of the present study, achieving a low frequency of relapse, was met. Use of BU/TBI and omission of CY did not result in an increased incidence of relapse. Further, for patients receiving transplants from HLA-matched related donors, NRM was lower and RFS tended to be higher than the outcomes observed with BU/CY/TBI. For unrelated transplant recipients, on the other hand, NRM remained high, and RFS was not improved in comparison to

BU/CY/TBI conditioned patients. In comparison to results with a CY/TBI regimen, relapses tended to be less frequent, the incidence of NRM somewhat higher, and the probability of RFS comparable with the present BU/TBI regimen.

The incidence of acute GVHD in BU/CY/TBI and CY/TBI conditioned patients was in the range of 65% to 71% compared to about 84% in the current trial. However, these figures are difficult to compare, because more than 70% of patients in previous trials received transplants from HLA-identical sibling donors compared to only 28% in the current trial. The number of those transplants ( $n = 17$ ) was too small to allow for detailed statistical analysis.

**DISCUSSION**

Patients with advanced MDS (by FAB criteria) and with high-risk scores (by IPSS) generally have short life expectancies [2]. The major causes of death are complications related to peripheral blood cytopenias and progression to AML. About half of the patients with advanced MDS respond to chemotherapy as used for patients with de novo AML [31,32]; however, remissions are usually of limited duration, and few, if any, patients appear to be cured.

The most promising currently available therapy for MDS is HSCT [3,5,9,10,12-15,33]. Most of the published information comprises results with allogeneic transplantations [3,5,8-15,33], although recent data suggest that a proportion of patients who achieve a complete remission with induction chemotherapy can be consolidated successfully with autologous HSCT [34]. However, posttransplantation relapse, nonrelapse (treatment-related) mortality, and for allogeneic transplants, donor availability have hampered progress with this approach [7,11,13,14]. Trials at our center revealed a high rate of relapse with a conditioning regimen that combined CY and TBI and a reduced incidence of relapse but high NRM with a combination of BU, CY, and TBI [10,11]. Results of the current study show that a combination of BU plus TBI was effective in securing engraftment from related as well as unrelated donors. No graft failure was observed, and the tempo of hemopoietic recovery was similar to that observed with a CY/TBI regimen [10]. Among related transplant recipients, NRM was reduced in comparison to BU/CY/TBI conditioned patients, and the

**Table 5.** Comparison of Outcomes (%) at 3 Years Among BU/TBI, BU/CY/TBI, and CY/TBI Conditioned Patients With RAEB, RAEB-T, or CMML

Endpoint	Conditioning Regimen		
	BU/TBI* (Present Trial)	BU/CY/TBI [11]	CY/TBI [11]
<b>All patients, n</b>	45	31	44
<b>RFS, %</b>	31	23	30
<b>Relapse, %</b>	18	19	39
<b>NRM, %</b>	51	57	32
<b>Among HLA-identical siblings, n</b>	16	22	33
<b>RFS, %</b>	31	15	27
<b>Relapse, %</b>	31	27	46
<b>NRM, %</b>	38	58	27

\*Excluding secondary AML.

relapse rate was not increased, particularly when patients with sAML, who were enrolled in the present but not in the previous studies, were excluded. As a result, RFS was improved above that achieved with a BU/CY/TBI regimen. Among unrelated recipients, the relapse rate was low [3], but NRM was high after BU/TBI conditioning [11,15], and as a result, RFS (25%) was not improved above that achieved in previous trials. Overall, these results are comparable to those reported by several American and European groups using various conditioning regimens [3,8,12,33,34]. The data are also consistent with the notion that CY does not have a major role as an antileukemic agent in these regimens but adds to nonhemopoietic toxicity.

The incidence of GVHD in the present BU/TBI trial was high and, particularly among related recipients, albeit in a small number of patients, was above previously reported figures. The reasons are not immediately apparent. Conditioning with BU/TBI represents high-intensity therapy, and a correlation of GVHD and conditioning intensity has been recognized [35]. However, the previously used regimen had employed 3 agents, BU, CY, and TBI, and at least among patients who received MTX plus CSP for GVHD prophylaxis, GVHD incidence was not in excess of that expected [6]. One presumably important difference between the present (BU/TBI) study and the 2 patient cohorts studied previously (BU/CY/TBI and CY/TBI) was a longer interval from diagnosis to transplantation (12 months versus 5 and 8.5 months, respectively). Prolonged disease duration is generally also correlated with prolonged transfusion support and increased colonization by infectious organisms and is associated with organ (eg, liver) damage. These alterations in turn may enhance the clinical manifestations of GVHD and conceivably even lead to a misdiagnosis of GVHD. As discussed elsewhere [36,37], patients with MDS often show severe dysregulation of cytokines such as interleukin-1, tumor necrosis factor  $\alpha$ , and Fas ligand. These molecules are also involved in the manifestations of GVHD [38]. It is conceivable that signaling mediated via those molecules is modulated by the type of conditioning regimen used and amplified in patients with MDS. BU steady-state plasma levels were not significantly associated with GVHD or any of the endpoints studied [39]. Finally, assessment of GVHD to some extent is subjective, and several studies have shown considerable interobserver variations that may contribute to fluctuations in the reported incidence of GVHD [40,41].

Relapses of MDS occurred to a large extent in patients with poor cytogenetic risk and high IPSS scores. This outcome is in agreement with a previously reported retrospective analysis of results in 251 patients with MDS from our group [4]. Similar data have been reported by Nevill et al. [3]. Other investigators did not find a significant impact of IPSS score, presumably because most patients included in those studies qualified as high risk by IPSS criteria [34]. The observed lower relapse rate among recipients of unrelated transplants in the present trial was reminiscent of results in patients who received transplants for other malignant hematologic disorders and is thought to be related to a greater allogeneic effect of unrelated donor cells [42-44]. Such a pattern suggests a role for immunotherapy with allogeneic cells in patients with MDS. In fact, 1 patient in the present BU/TBI trial who relapsed after transplantation was given a donor lymphocyte

infusion and achieved a complete and lasting CR. Conceivably, therefore, immunologic effects of donor cells can be exploited therapeutically in patients with MDS [44].

The impact of pretransplantation chemotherapy on long-term outcome in patients with MDS is not well defined. Whereas some authors found lower relapse rates and superior RFS among patients who underwent transplantations in chemotherapy-induced remission [3,9], others observed no reduction in relapse rates and, in fact, comparable or inferior outcome due to increased NRM [12,34]. In the present trial, outcome in patients who received pretransplantation therapy was poor—only 3 of 18 such patients are surviving in continuous remission—but the small numbers do not allow for firm conclusions.

The effect of CMV seropositivity on transplantation outcome has been discussed extensively in the literature [12,45]. The availability of potent antiviral agents and the prospective monitoring for CMV antigenemia, allowing for initiation of preemptive therapy, have significantly reduced the incidence of CMV disease and CMV-related mortality [46,47]. In agreement with those data, data from the present trial indicate that CMV disease was not a major cause of death, and it is not clear why CMV seropositivity of patients was a significant risk factor for NRM. Conceivably, tissue damage associated with reactivation of the virus was a contributing factor to organ failure. Also, recent data suggest interactions between CMV and invasive aspergillus infections (K. Marr, MD, unpublished data, December 2001), a complication that accounted for several deaths in the present study.

Inferior posttransplantation outcome due to higher NRM in male compared to female patients has also been reported by others [9]. Although the reasons are not clear, they may be related to hormonal effects, social habits (eg, tobacco, alcohol consumption), or environmental (eg, occupational) exposures.

To what extent the pathophysiologic mechanisms involved in MDS may contribute to transplantation-associated NRM remains speculative. It is of note, nevertheless, that many patients with MDS express high levels of proinflammatory cytokines and apoptosis-inducing signals, all of which are also involved in the pathophysiology of GVHD and tissue destruction [37,38,48,49]. Additional studies are needed.

In conclusion, a BU/TBI regimen was effective in securing engraftment of hemopoietic stem cells from related and unrelated donors. The incidence of posttransplantation relapse tended to be lower than observed historically in patients conditioned with CY/TBI and comparable to that in patients prepared with the triple-agent regimen BU/CY/TBI. The relapse incidence was particularly low in patients without high-risk cytogenetics. Overall, however, improvements over previously reported results were marginal, particularly in unrelated transplant recipients, and we do not recommend the use of the BU/TBI regimen described here in patients with MDS. Future trials should investigate the efficacy of reduced-intensity conditioning regimens.

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