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Long term follow-up of allogeneic stem cell transplantation in patients with myelodysplastic syndromes using busulfan, cytosine arabinoside, and cyclophosphamide

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Abstract

We report here the 10-year follow-up of 86 patients who underwent allogeneic stem cell transplantation (ASCT) for myelodysplastic syndrome (MDS). All patients received the busulfan, cytosine arabinoside, and cyclophosphamide (BAC) preparative regimen which consisted of busulfan 16 mg/kg, cytosine arabinoside 8 g/m² IV, and cyclophosphamide 120 mg/kg IV. Fifty-nine patients (69%) had de novo MDS; 26 (30%) had secondary MDS (treatment related), and one had a preceding aplastic anemia which progressed to MDS before transplant. Cytogenetics (80 patients) was classified as good (34%), intermediate (17%), or poor (42%). With a median follow-up for survivors of 124 months, the 10-year Kaplan-Meier estimates for overall survival (OS) was 43% (95% confidence interval [CI]: 31–53%). Cumulative nonrelapse mortality (NRM) and relapse was 43% (95% CI: 32–54%) and 19% (95% CI: 11–27%), respectively. No patient relapsed after 2 years. In patients with RAEB-T/AML, 10-year relapse-free survival (RFS), relapse, and NRM was 36%, 36%, and 27%, respectively. Younger age ($P = 0.05$), human leukocyte antigen (HLA) match ($P = 0.002$), good risk cytogenetics ($P = 0.008$), and having a related donor ($P = 0.03$) significantly improved overall and RFS in the multivariable analysis. The long-term follow-up of patients receiving the BAC regimen with ASCT in this study indicated durable relapse-free and OS with acceptable toxicity in this group of patients with high-risk features.

Introduction

Although several new therapies are currently available for the treatment of myelodysplastic syndrome (MDS) [1–3], allogeneic stem cell transplantation (ASCT) remains the only curative therapy for the majority of patients. Without therapy, the median survival ranges considerably based on several well-characterized risk factors associated with MDS. For patients with low-risk disease based on the International Prognostic Scoring System (IPSS) the median survival is 5.7 years. In contrast, patients with high-risk disease have a median survival of 0.4 years [4]. Efforts at improving the outcome using transplantation have often

targeted patients with high-risk disease. In two large registry studies evaluating the role of full intensity transplants for the treatment of MDS, the disease-free survival was 40% [5] at 3 years and 29% [6] at 2 years for MDS patients receiving related and unrelated bone marrow transplants, respectively. The nonrelapse mortality (NRM) ranged from 37 to 54%, with a relapse rate of 23 to 14%.

Recent efforts at reducing NRM have focused on the use of reduced intensity transplantation. In a large retrospective analysis, the use of reduced intensity regimens in patients with MDS resulted in lower NRM but a higher relapse rate without improvement in overall and disease-free survival [7]. Conversely, multiple studies using an increased intensity myeloablative preparative regimen were successful in reducing the relapse rate, but at the cost of an increase in NRM [8,9], therefore providing no improvement in survival.

Herein, we report the 10-year follow-up of a myeloablative preparative regimen using busulfan, cytosine arabinoside, and cyclophosphamide (BAC) in allogeneic and unrelated transplantation for patients with MDS. In a Phase I study, cytosine arabinoside at a dose of 1–1.5 gm/m²/48 hr was added to the BuCy2 regimen with acceptable toxicity and a high response rate [10]. We had shown that cytosine arabinoside could be escalated to a dose at 4 gm/m²/48 hr without undue toxicity [11]. On the basis of the above studies, we have used the BAC regimen with allogeneic transplant for the treatment of MDS aiming at reducing the relapse rate and improving overall survival (OS). Our series represents one of the longest follow-up of patients treated for MDS with allogeneic transplant from a single institution.

Materials and Methods

Patients

We reviewed all charts from October 1988 to March 2005 of patients with MDS who received a stem cell transplant using BAC as a preparative regimen at The Karmanos Cancer Institute. All available pathology slides were reviewed at the time of this retrospective analysis and were reclassified according to the WHO classification. Patients were classified as good, intermediate, or poor risk cytogenetics according to the IPSS categories [4]. The standard minimal acceptable organ function for eligibility for a myeloablative transplant was applied. The study was approved by the Institutional Review Board at Wayne State University.

Preparative regimen

The BAC regimen included busulfan (4 mg/kg po in divided doses daily on days 9 through 6; total dose 16 mg/kg), cytosine arabinoside (2000 mg/m² twice daily by 2-hr infusion on days 5 and 4; total dose 8000 mg/m²) and cyclophosphamide (60 mg/kg once daily by 2-hr infusion on days 3 and 2; total dose 120 mg/kg) (15). Phenytoin was given to prevent busulfan-induced seizures. As of December 2003, intravenous busulfan replaced the oral formulation and 10 patients received 0.8 mg/kg IV per dose $\times$ 16 doses of busulfan.

Donor bone marrow harvest or leukapheresis, recipient transplantation

Donors were matched at the antigen level at the A and B loci and the allele level at DR. Allogeneic marrow cells were harvested from related or unrelated donors for a targeted marrow dose of 4.0×10^8 MNC/kg. Peripheral blood stem cell (PBSC) donors received granulocyte colony-stimulating factor 5 lg/kg subcutaneous for 4 days followed by a leukapheresis on the fifth. The harvest target was 5.0×10^6 /CD 34+ cells/kg. Marrow or PBSC was infused on day 0.

Statistical methods

Descriptive statistics were calculated for the study population using proportions and exact confidence limits for categorical variables and the median range for continuous variables. The event of interest for the estimation of OS is death from any cause; the event of interest for estimation of relapse-free survival (RFS) is relapse or death from any cause.

Kaplan-Meier methods were used to estimate OS and RFS for the group as a whole and for subgroups defined by categories of the covariates. Before fitting a Cox proportional hazards model, we evaluated the association between covariates. Biologic considerations were the primary determinant for selecting predictors. If pairs of predictors that were highly associated, one was excluded from the model. Predictors with more than two categories were parameterized with indicator variables. Both graphic and analytic methods were used to assess whether the proportional hazards assumption was tenable. Cumulative incidence was used for calculation of acute and chronic graft vs. host disease (GVHD). Cumulative incidence of relapse- and nonrelapse-related mortality were calculated under the assumption that one was the competing risk for the other [12]. Cumulative incidence of acute and chronic GVHD was computed with relapse and death from any cause as competing risks.

Results

Patient characteristics

A retrospective review of charts from October 1988 to March 2005 identified 86 patients with MDS who received a stem cell transplant using BAC as a preparative regimen at The Karmanos Cancer Institute. Seventy nine of the 86 patients had their pathology slides reviewed at the time of this retrospective analysis and were reclassified according to the WHO.

The characteristics of the 86 patients with MDS are shown in Table I. Median follow-up time was 124 months for those still alive; only two patients were followed for <3 years. Fifty-seven patients received stem cells from a related donor; seven of these were a one antigen mismatch. Twenty nine patients received stem cells from an unrelated donor; four were one antigen mismatch.

GVHD

Cyclosporine (3 mg/kg/d) or tacrolimus (0.03 mg/kg/d) calculated according to patient's lean body weight were administered by continuous IV infusion starting on day 1. In the absence of GVHD, cyclosporine and tacrolimus doses were tapered by 20% per month beginning at day 56 post transplant and discontinued at the end of 6 months.

Seventy six patients received a cyclosporine-based regimen for GVHD prophylaxis; Forty-five methotrexate (15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11) and 29 received methylprednisolone (0.25 mg/kg IV bid) in addition to cyclosporine. Two patients received cyclosporine as a single agent. Nine patients received a tacrolimus containing regimen; five received mycophenolate (10 mg/kg) and four received solumedrol in addition to tacrolimus. One patient received steroids alone as immunosuppression.

Overall, 54 patients (58%) developed acute GVHD grade I–IV (95% confidence interval [CI]: 47–68%), and 30 (35%) patients had Grade II–IV (see Fig. 1). Thirty patients (22% 95% CI: 14–32%) developed chronic GVHD with nearly half occurring during the first 6 months after transplant (see Fig. 2).

OS, RFS, and relapse

With a median follow-up of 124 months for survivors, the 10-year OS and RFS were 43% (95% CI: 31–53%) (see Fig. 3) and 40% (95% CI: 29–51%) (see Fig. 4), respectively. The 1-year OS was 59% (95% CI: 48–69%) and the 100-day mortality was 29% (95% CI: 21–40%).

In the univariate analysis, the 10-year RFS was 47%, 53%, 40%, 31%, and 36% for RA/RARS, RCMD, RAEB1, RAEB2, and RAEB-T/AML, respectively. The RFS was 45% and 29% for primary and secondary MDS patients, respectively. Patients with poor and intermediate cytogenetics had a worse survival than patients with good cytogenetics. RFS was 62%, 42%, and 19% for patients <20 years, 20–55 years, >55 years old, respectively, because of increased both relapse and nonrelapse mortality.

Sixteen patients relapsed post transplant with a 2-year cumulative incidence of relapse of 19% (95% CI: 11–27%) (Fig. 5). There were no relapses beyond 24 months. Of the patients who relapsed eight had RAEB-T/AML, five had RAEB-2, one had RAEB-1, and two had RCMD. None of the patients with RA/RARS relapsed. Of the eight patients with RAEB-T/AML that relapsed, three received induction chemotherapy, and one patient was in CR at time of transplantation. Three of the 16 patients who relapsed are alive at the time of this analysis. One is disease free after second ASCT followed by donor lymphocyte infusion and the other two are alive with disease.

Thirty five patients died from nonrelapse causes. The causes of death are listed in Table II. Most patients died from either GVHD or infection. The cumulative incidence of NRM was 43% (95% CI: 32–54%; Table III).

A Cox proportional hazard model was used to evaluate the influence of pretransplant characteristics on OS and DFS. The characteristics used as covariates in the model included age at transplant (<20 years, 20–55 years, >55 years), related vs. unrelated donor, de novo or secondary MDS, HLA match vs. mismatch, and cytogenetics (good, intermediate, or poor). The results of the analysis are shown in Table IV. Antigen matching, younger age, and good risk cytogenetics were all associated with significant improvement in RFS and OS.

The risk of death for those with an antigen mismatch was 3.5 times greater than for those with identical match ($P = 0.002$). Patients with intermediate or poor cytogenetics had a 3-fold higher risk of dying as those with good cytogenetics ($P = 0.008$). There was no difference in risk of dying between those with intermediate and poor cytogenetics ($P = 0.71$).

Individuals receiving SCT from a related donor had half the risk of dying as those receiving an unrelated donor transplant, but the reduction did not reach statistical significance ($P = 0.06$) for OS; however, patients with a related transplant achieved a statistically significant improvement in RFS ($P = 0.03$) when compared with unrelated transplants.

There was no difference in OS ($P = 0.22$) and RFS ($P = 0.12$) between patients with denovo and secondary MDS.

Discussion

ASCT remains the only curative therapy for most patients with MDS. However, the toxicity remains substantial, with treatment-related mortality exceeding that of relapse. To improve survival with SCT, efforts to decrease both relapse and the regimen-related toxicity are necessary. In an attempt to reduce the incidence of relapse in patients with myeloid malignancies cytosine arabinoside was added to a busulfan/cyclophosphamide preparative

regimen, because it is one of the most active agents in the therapy of myeloid malignancies [13]. We had previously reported encouraging results with the BAC regimen in myeloid malignancies [11] with acceptable toxicity [14]. On the basis of those results we have adopted the BAC regimen as the standard regimen for patients with myeloid malignancies for the last 15 years at our institution.

In this report, using the BAC regimen, the RFS, relapse, and NRM at 10 years were 40%, 19%, and 43%, respectively. Deeg et al. using targeted busulfan/cyclophosphamide (t-BuCy) reported RFS of 57% at 3 years with a relapse rate of 14%. In their multivariable analysis, only etiology of MDS and either IPSS or FAB classification were significantly associated with RFS and relapse, respectively [15]. We further analyzed our data to identify variables associated with outcome. In this study, cytogenetics was significantly associated with both the OS and RFS in the multivariable analysis ($P = 0.008$). The 10-year RFS was 59% and 28% for the good and poor cytogenetic groups, respectively, and the relapse rate was 14% and 31% for the good and poor cytogenetic group, respectively. However, there was no difference between the intermediate and poor cytogenetic group. Others have reported similar findings [16].

In our study, age remained a strong predictor for outcome with a RFS of 19% for patients older than 55 years. The low RFS in this group of patient is secondary to the increased risk of relapse (38%) and the higher NRM (44%) using this aggressive regimen. The increased risk of relapse could be explained by the high-risk features of this group of patients as seven had poor cytogenetics, five had a high IPSS, and five had RAEB-T/AML. Older patients have had a worse prognosis historically. Several studies have found a decreased RFS for older patients because of increased NRM [17], increased risk of relapse [18], or both [19].

We added cytosine arabinoside to Bu/Cy in an attempt to reduce the risk of relapse without increasing NRM. We show a cumulative incidence of relapse of 19% and no relapses occurred after 2 years. We and others [15,17] have found a low risk of relapse in patients with RA/RARS with no relapses seen in the 15 patients with a follow-up of 10 years. In contrast, in the 22 patients with RAEB-T/AML, the cumulative incidence of relapse and NRM was 36% and 27%. Other investigators have attempted to improve the results of this poor prognostic group. In a phase II study, TBI was added to busulfan/cytosine in patients with high-risk MDS (RAEB/RAEB-T or CMML). The incidence of relapse decreased to 28% at the expense of a higher NRM of 68% with a DFS of 23% [8]. In a second study, the combination of Busulfan with TBI was evaluated in patients with RAEB, RAEB-T, and s-AML. The 3-year DFS was 26% with a NRM of 49% [20]. Investigators from MDACC [9] added thiopeta to busulfan/cyclophosphamide and reported the results in 62 high-risk AML/MDS patients. Of those, only 12 had MDS and three of those would be classified as AML with the new WHO classification. The 100-day mortality, relapse risk, and 3-year survival was 42%, 67%, and 17%, respectively for patients with MDS.

Conclusion

Stem cell transplant with the BAC regimen produces durable long-term cures with acceptable NRM. Age, cytogenetics, donor relation, and antigen mismatch remain the main determinants of RFS in our study. On the basis of these long-term results, we suggest that young patients with high-risk disease receive a more aggressive preparative regimen as BAC, whereas less aggressive regimens may be used in older and low-risk patients.

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Figure 1.
Cumulative incidence of acute GVHD.

Figure 2.
Cumulative incidence chronic GVHD.

Figure 3.
Overall survival.

Figure 4.
Relapse-free survival.

Figure 5.
Cumulative incidence of recurrence.

TABLE I

Patient and Donor Characteristics (N = 86)

Age at BMT in years (median, range)	43 (3–62)
Age groups	
>20 years	13 (15%)
20–55 years	57 (66%)
>55 years	16 (19%)
Disease duration months (median, range)	6 (1–65)
Male/female	50 (58%)/36 (42%)
MDS	
Secondary	27 (31%)
De novo	59 (69%)
IPSS risk (De-novo only)	80 (93%)
Low	4 (5%)
Intermediate-1	16 (19%)
Intermediate-2	8 (9%)
High	13 (15%)
WHO	
RA/RARS	15 (17%)
RCMD	17 (20%)
RAEB1	5 (6%)
RAEB2	22 (26%)
RAEB-T/AML	22 (26%)
CMMML	2 (2%)
MDS/MPD-U	3 (3%)
Cytogenetics (IPSS categories)	
Good	29 (34%)
Intermediate	15 (17%)
Poor	36 (42%)
Missing	6 (7%)
Induction therapy	
No	77 (90%)
Yes	9 (10%)
Blasts at time of transplant	
<20	67 (78%)
20	11 (13%)
Missing	8 (9%)
HLA-antigen match	
5/6	11 (13%)
6/6	75 (87%)
Transplant type	
BMT	62 (72%)

PBSC	24 (28%)
Patient/donor relation	
Related	
HLA-identical	50 (58%)
HLA-nonidentical	7 (8%)
Unrelated	
HLA-identical	25 (29%)
HLA-nonidentical	4 (5%)
GVHD prophylaxis	
Cyclosporon + methotrexate	45
Cyclosporin + methylprednisolone	29
Tacrolimus + cellcept	5
Tacrolimus + methotrexate	4
Cyclosporon or medrol only	3

BMT, bone marrow transplant; PBSC, peripheral blood stem cell transplant; GVHD, graft vs. host disease

TABLE II

Cause of Death

Cause of death	Number (% of all patients)
GVHD	14 (16)
Relapse	13 (15)
Infection	12 (13)
Pulmonary	4 (4)
Liver	2 (2)
Unknown	2 (2)
Cardiac	1 (1)
Total	48 (56)

TABLE III

Survival, Relapse-Free Survival, and Cumulative Incidence of Relapse and Nonrelapse Mortality

	10-year survival		Cumulative incidence	
	Overall	Relapse free	Relapse	NRM
Overall	43% (31%, 53%)	40% (29%, 51%)	0.19 (0.11, 0.27)	0.43 (0.32, 0.54)
Gender				
Male	41% (26%, 55%)	39% (25%, 53%)	0.18 (0.09, 0.30)	0.43 (0.28, 0.57)
Female	46% (28%, 61%)	41% (25%, 56%)	0.19 (0.09, 0.34)	0.44 (0.27, 0.60)
Age at BMT				
<20 years	62% (31%, 82%)	62% (31%, 82%)	0.15 (0.02, 0.39)	0.23 (0.06, 0.47)
20–55 years	46% (32%, 59%)	42% (28%, 55%)	0.14 (0.07, 0.24)	0.47 (0.33, 0.60)
>55 years	19% (5%, 40%)	19% (5%, 40%)	0.38 (0.15, 0.60)	0.44 (0.20, 0.66)
MDS				
Secondary	31% (15%, 49%)	29% (14%, 47%)	0.22 (0.09, 0.39)	0.54 (0.33, 0.72)
De novo	48% (33%, 61%)	45% (31%, 58%)	0.17 (0.09, 0.27)	0.38 (0.25, 0.51)
IPSS category				
Low	<i>_a</i>	<i>_a</i>	0.25 (0.01, 0.67)	0.50 (0.06, 0.84)
Intermediate-1	67% (37%, 85%)	67% (37%, 85%)	0.33 (0.12, 0.57)	0.38 (0.09, 0.67)
Intermediate-2	63% (23%, 86%)	63% (23%, 86%)	0.31 (0.09, 0.55)	0.54 (0.21, 0.78)
High	19% (1%, 52%)	15% (1%, 45%)	0.22 (0.09, 0.39)	0.54 (0.33, 0.72)
Class				
RA/RARS	47% (21%, 69%)	47% (21%, 69%)	0.00	0.53 (0.26, 0.74)
RCMD	59% (33%, 78%)	53% (28%, 73%)	0.12 (0.02, 0.31)	0.49 (0.19, 0.73)
RAEB1	40% (5%, 75%)	40% (5%, 75%)	0.20 (0.01, 0.58)	0.40 (0.05, 0.75)
RAEB2	31% (11%, 54%)	31% (11%, 54%)	0.23 (0.08, 0.41)	0.47 (0.22, 0.68)
RAEB-T/AML	43% (22%, 63%)	36% (17%, 56%)	0.36 (0.17, 0.56)	0.27 (0.11, 0.46)
Transplant type				
BMT	47% (34%, 59%)	47% (34%, 59%)	0.29 (0.13, 0.48)	0.49 (0.27, 0.68)
PBSCT	<i>_a</i>	<i>_a</i>	0.15 (0.07, 0.24)	0.41 (0.28, 0.53)
Donor				
Unrelated	36% (19%, 53%)	34% (17%, 51%)	0.17 (0.06, 0.33)	0.49 (0.30, 0.66)
Related	46% (32%, 60%)	44% (30%, 57%)	0.19 (0.10, 0.30)	0.40 (0.26, 0.53)
Cytogenetics				
Good	62% (39%, 78%)	59% (38%, 75%)	0.14 (0.04, 0.29)	0.33 (0.15, 0.52)
Intermediate	<i>_a</i>	<i>_a</i>	0.00	0.73 (0.44, 0.89)
Poor	29% (15%, 44%)	28% (14%, 43%)	0.31 (0.17, 0.46)	0.42 (0.26, 0.57)
Antigen match				
5/6	27% (7%, 54%)	27% (7%, 54%)	0.18 (0.03, 0.44)	0.68 (0.30, 0.88)
6/6	45% (32%, 56%)	42% (30%, 53%)	0.19 (0.11, 0.28)	0.40 (0.28, 0.51)
Blasts				
<20	41% (28%, 53%)	41% (28%, 53%)	0.16 (0.09, 0.26)	0.43 (0.30, 0.55)

	10-year survival		Cumulative incidence	
	Overall	Relapse free	Relapse	NRM
20	28% (5%, 58%)	9% (1%, 33%)	0.45 (0.17, 0.71)	0.45 (0.17, 0.71)

^aInsufficient data. BMT, bone marrow transplant; PBSCT, peripheral blood stem cell transplant; NRM, nonrelapse-related mortality.

TABLE IV

Multivariable Cox Proportional Hazards Models

	Overall survival			Relapse-free survival		
	HR	95% CI	Significance	HR	95% CI	Significance
Age at BMT			0.01			0.05
<20 years	1.0	–		1.0	–	
20–55 years	2.4 ^a	(0.8–7.3)		2.9 ^a	(1.0–8.8)	
>55 years	5.51	(1.6–18.3)		5.72	(1.7–19.1)	
Antigen match			0.002			0.004
6/6	1.0	–		1.0	–	
5/6	3.5	(1.6–7.8)		3.1	(1.4–6.9)	
Cytogenetics			0.008			0.008
Good	1.0	–		1.0	–	
Intermediate	3.3 ^c	(1.4–7.7)		2.8 ^d	(1.2–6.6)	
Poor	2.93	(1.4–5.9)		2.94	(1.4–5.9)	
Donor			0.06			0.03
Unrelated donor	1.0	–		1.0	–	
Related donor	0.5	(0.3–1.0)		0.5	(0.3–0.9)	
MDS			0.22			0.12
Secondary	1.0	–		1.0	–	
De novo	0.7	(0.4–1.2)		0.6	(0.4–1.1)	

^aThe difference in hazard ratios for death between those 20–55 years and those >55 years is significant at $P = 0.03$;

^bThe difference in hazard ratios for relapse or death between those 20–55 years and those >55 years is marginally significant, $P = 0.06$;

^cThe difference in hazard ratios for death between those with intermediate and those with poor cytogenetics is not statistically significant, $P = 0.71$;

^dThe difference in hazard ratios for relapse or death between those with intermediate and those with poor cytogenetics is not statistically significant, $P = 0.94$