Allogeneic Bone Marrow Transplantation for 93 Patients With Myelodysplastic Syndrome

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We treated 93 patients with myelodysplastic syndrome using cyclophosphamide and either total body irradiation (n = 88) or busulfan (n = 5) followed by marrow transplantation. Sixty-five marrow donors were genotypically HLA-identical siblings and 28 were other family members or unrelated donors. Before transplantation all patients had either severe neutropenia or thrombocytopenia or had greater than 5% blasts in the marrow or peripheral blood. The probabilities of disease-free survival, relapse, and nonrelapse mortality at 4 years were 41%, 28%, and 43%, respectively. Multivariate analysis revealed that younger age and shorter disease duration were significantly associated with improved disease-free survival and decreased nonrelapse mortality. Relapse was seen only in patients with excess blasts at the time of transplantation (51% at 4 years). Patients younger than age 40 and without excess blasts had a 4-year disease-free survival of 62%. This study confirms that allogeneic marrow transplantation can cure some patients with myelodysplasia. Because of the favorable outcome in younger patients without excess blasts, we recommend that transplantation be considered early for patients younger than age 40, before disease progression or development of life-threatening cytopenias. For older patients and those with excess blasts, changes in the transplant procedure will be necessary to improve outcome.

THE MYELODYSPLASTIC syndrome (MDS) is a group of clonal hematopoietic disorders characterized by ineffective hematopoiesis and peripheral cytopenias. Although the natural history of MDS varies, traditional treatments are not curative and patients die a median of 15 months after diagnosis.[1-4]

Allogeneic marrow transplantation offers potentially curative treatment for MDS. In a review of the first 59 patients transplanted in Seattle we found an actuarial disease-free survival (DFS) of 45% 3 years posttransplantation.[5] In a multivariate analysis, youth and abnormal karyotype were associated with improved survival, while more advanced disease was associated with an increased relapse rate.[5] Since that report we treated an additional 34 patients, after whom the protocol using cyclophosphamide (CY) and total body irradiation (TBI) was closed to enrollment. This present analysis of the 93 patients, each followed for more than 1 year, provides an opportunity to characterize better the prognostic features and the long-term outcome for patients with myelodysplasia treated with marrow transplantation and to present general treatment guidelines.

PATIENTS AND METHODS

Between October 1981 and October 1990, 93 consecutive patients were treated for myelodysplasia on a single protocol using CY and TBI (n = 88) or, in those cases where TBI was contraindicated, CY and busulfan (n = 5) followed by allogeneic or syngeneic marrow transplantation. Patients with MDS that had evolved to acute myeloid leukemia (AML), as defined by any pretransplant marrow examination showing >30% blasts, are not included in this report.

Table 1 outlines the patients' clinical characteristics and the transplantation procedure. All patients were judged to have advanced MDS, based on having either granulocyte count less than 1,000/μL (median, 250; range, 0 to 45,000), platelet count less than 40,000/μL (median, 8,000; range, 2,000 to 732,000), or increased numbers of blasts in the marrow or peripheral blood (>5%). Each patient's diagnosis was based on a review of the clinical history, peripheral blood, bone marrow morphology, and cytogenetic analysis. In 11 patients the marrow was morphologically consistent with aplastic anemia, but there was a clonal cytogenetic abnormality. Two of these 11 patients initially had normal cytogenetics, but each developed monosomy 7 1 year after treatment with antithymocyte globulin, whereas the remaining 9 could be classified as primary hypocellular MDS. Four patients had severe myelofibrosis with dysplastic features, and two patients were unclassifiable, as described in our previous study.[5] Five patients had Fanconi's anemia with evidence of MDS (four with marrow dysplasia and one with trisomy 8).

Chromosomal analysis of bone marrow cells was performed by G-banding after 1.5 and 24 hours in culture without added mitogens. Among the 57 patients with clonal cytogenetic abnormalities, those most commonly observed were monosomy 7 (22 patients, including 5 with additional abnormalities), trisomy 8 (11 patients, including 3 with additional abnormalities), and deletion of all or part of chromosome 5 (3 patients). A variety of other cytogenetic abnormalities was seen in 1 or 2 each of the remaining 21 patients.

Human leukocyte antigen (HLA) typing, administration of the conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis and grading have been previously described.[7-14] Five patients were given busulfan instead of TBI because of concern for excessive radiation toxicity: three with prior mediastinal radiation for Hodgkin's disease, one who had Fanconi's anemia, and one young infant. GVHD prophylaxis varied depending on protocols active at time of transplantation. All patients were fully informed of the risks of the treatment and consent was obtained using forms approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

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Table 1. Clinical and Transplantation Characteristics of 93 Patients With Myelodysplasia

Characteristic	Data
No. studied	93
Median age, yr (range)	30 (1-60)
Sex	56 males
Median disease duration, mo (range)	10 (1-180)
Disease etiology (no. of patients)	
Idiopathic	78
Cytotoxic treatment for	
Hodgkin's disease	6
AML (16 yr earlier)	1
Polycythemia vera	1
Fanconi's anemia	5
Family history of MDS or aplastic anemia	2
Marrow morphology (no. of patients)	
Aplastic anemia (AA)	11
Refractory anemia, with or without ringed sideroblasts (RA)	29
Refractory anemia with excess blasts (RAEB)	31
RAEB in transformation (RAEBT)	14
Myelofibrosis (MF)	4
Chronic myelomonocytic leukemia (CMML)	2
Unclassified	2
Marrow cellularity* (no. of patients)	
Acellular	7
Markedly hypocellular	15
Mildly hypocellular	16
Normocellular	21
Hypercellular	34
Marrow fibrosis† (no. of patients)	
Grade 0	70
Grade 1	8
Grade 2	8
Grade 3	4
Grade 4	3
Cytogenetics (no. of patients)	
Normal	30
Abnormal	57
Not obtained	6
Patient cytomegalovirus antibody titer (no. of patients)	
Negative (<1:8)	42
Positive (≥1:8)	51
Marrow donor (no. of patients)	
Identical twin	3
Genotypically HLA-identical sibling	62
Phenotypically HLA-matched family member	2
1-3 HLA antigen mismatched family member	20
Unrelated donor	6
Preparative regimen‡ (no. of patients)	
Cyclophosphamide§ and 1,200 cGy TBI	77
Cyclophosphamide§ and other TBI schedules‖	11
Cyclophosphamide§ and busulfan¶	5
GVHD prophylaxis (no. of patients)	
None	3
Methotrexate	2
Methotrexate and cyclosporine	74
Methotrexate, cyclosporine, and glucocorticoids	14

* Relative to normal for patient's age.

† Bauermeister grading system.[6]

‡ Two patients with HLA-incompatible donors also received antithymocyte globulin to prevent graft rejection.

§ One hundred twenty milligrams per kilogram over 2 days (92 patients), 200 mg/kg (two patients).

‖ Ten Gray (one patient), 13.2-15.75 Gy (10 patients with mismatched or unrelated donors).

¶ Sixteen milligrams per kilogram over 4 days.

The methods of time to an event analysis with data censored before August 1, 1992 were used.[15] Relapse was identified by recurrence of a prior cytogenetic abnormality or by return of morphologic evidence of disease. Survival and other related curves were described by the product-limit (Kaplan-Meier) method. Multivariate modeling was performed using the stepwise step-up proportional hazards Cox regression model. The covariates age and disease duration were entered as continuous variables.

RESULTS

Forty of the 93 patients are alive and disease free between 434 and 3,714 days after transplantation. The 4-year Kaplan-Meier DFS estimate is 41% (Fig 1). Seventeen patients, all of whom had either refractory anemia with excess blasts or refractory anemia with excess blasts in transformation, relapsed between 14 and 783 days posttransplantation. All of these patients subsequently died. The actuarial probability of relapse at 4 years is 28% for the entire group (Fig 1) and 51% for patients with greater than 5% blasts. Thirty-six patients died of nonmalignant causes between 6 and 1,432 days after transplantation, resulting in an actuarial probability of 43% at 4 years. GVHD, infection, and interstitial pneumonitis accounted for 28 of these 36 deaths, in roughly equal proportions. The remaining eight patients died from either organ failure or hemorrhage.

Results of a multivariate analysis using the covariates age, sex, morphology, disease duration and cause, marrow cellularity and fibrosis, cytogenetics results, cytomegalovirus serology, donor histocompatibility, and grade II-IV acute GVHD (Table 2) confirm several of our earlier conclusions.[5] Younger age remained associated with improved overall survival and improved DFS (48% for age <40 and 17% for age ≥40 at 4 years), due to a significant decrease in non-relapse mortality (38% for age <40 and 68% for age ≥40 at 4 years). Disease morphology continued to be associated with relapse, as all patients who relapsed had excess blasts at the time of transplantation. A multivariate analysis limited to patients with excess blasts showed that older age was also significantly associated with an increased relapse rate. Based on these results the most favorable subset of patients are those younger than age 40 and without excess blasts: 20 of 32 remain alive for an actuarial DFS of 62% at 4 years (Fig 2).

Previously, we found that shorter disease duration was associated with fewer non-relapse deaths. Our current multivariate analysis showed, additionally, that shorter disease duration was associated with improved overall survival and DFS, after adjusting for age. The highest non-relapse mortality occurred in patients with a disease duration of 60 months or greater: 9 of 12 died without relapse. Six of these patients died from disseminated fungal infection, of whom 2 had documented opportunistic infections and 1 had prolonged neutropenia before transplantation. One patient who had documented iron overload secondary to transfusions before transplantation died of multiple causes including veno-occlusive disease of the liver. No remarkable features of the pretransplant history could be identified in the other five patients who suffered a non-relapse death.

In our original study we unexpectedly found that cytoge-

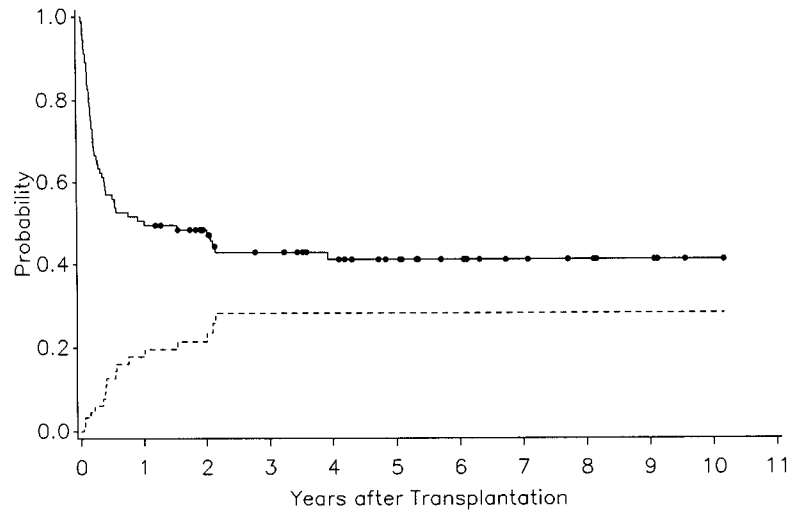

Fig 1. Probability of disease-free survival (——) and relapse (– – –) for all 93 patients transplanted for MDS. Points represent patients alive in continuous complete remission.

netic abnormalities were significantly associated with improved overall survival and DFS and with decreased non-relapse mortality. In our current study, however, we found that cytogenetic results were not significantly related to outcome.

Several results did not reach statistical significance, possibly because of small sample size, but may be of clinical interest. Patients without excess blasts had a 4-year actuarial DFS of 54% compared with 32% for patients with greater than 5% blasts (log rank $P = .07$). All 7 patients with grade 3 or 4 fibrosis died (one from relapse, two from graft failure, and four from other non-relapse causes). Among the 8 patients who had MDS secondary to previous cytotoxic therapy, only 2 remain alive and disease free (2 relapsed and 4 died from non-relapse causes). Similarly, 4 of 5 patients with MDS arising in a setting of Fanconi's anemia have died (all due to non-relapse causes). Finally, the outcome of the 28 patients with an unrelated or non–HLA-identical family donor was similar to the 65 with an HLA-identical sibling donor (4-year actuarial DFS 50% and 39%, respectively, log rank $P = .7$).

Table 2. Multivariate Proportional Hazards Regression Analysis

Endpoint Covariate	Univariate *P* Value	Entry Step	Multivariate *P* Value	Relative Risk (95% CI)*
Survival				
Age	.0001	1	.0001	1.68 (1.31, 2.16)
Disease duration	.1261	2	.0156	1.11 (1.02, 1.20)
Disease-free survival				
Age	.0001	1	.0001	1.64 (1.29, 2.10)
Disease duration	.1725	2	.0318	1.09 (1.01, 1.19)
Relapse				
Morphology†	.0001	†	†	†
Age‡	.0021	‡	.0208	1.68 (1.08, 2.61)
Non-relapse mortality				
Disease duration	.0028	1	.0007	1.15 (1.06, 1.25)
Age	.0095	2	.0034	1.59 (1.17, 2.17)

The multivariate analysis only includes patients with complete data; therefore, the patients without cytogenetics results, acute GVHD results, or classifiable morphology are excluded. The four patients with myelofibrosis are excluded because blast count could not be assessed. A total of eight patients are excluded.

* The relative risk, estimated from the proportional hazards regression analysis, is the increased risk of occurrence of adverse event per decade of age and per year of disease duration. The 95% confidence intervals (CI) are included.

† The morphology variable compares patients without excess blasts (ie, AA and RA) to those with excess blasts (ie, RAEB, RAEBT, and CMML). None of the 40 patients with AA or RA relapsed, whereas 17 of 47 patients with RAEB or RAEBT did relapse. The model does not converge when trying to estimate an infinite coefficient. Therefore, the multivariate *P* value and relative risk are not given.

‡ Age is statistically significant when analyzing only those patients with excess blasts.

DISCUSSION

In this study, 40 of 93 patients who underwent allogeneic marrow transplantation for MDS are alive without disease from 1 to 10 years after treatment. Of the patients who failed, all but seven did so within 1 year and none relapsed more than 2 years after transplantation. This updated analysis with more patients and longer follow-up, therefore, strongly supports the conclusion that marrow transplantation cures approximately 40% of eligible patients with MDS. Four other series in the literature,[16-19] although smaller in size and different in patient selection and treatment regimens, reported similar long-term DFS of 35% to 45% (Table 3).

Our current study confirmed two important previous observations.[5] Younger age predicted for improved overall and disease-free survival, in part because of less transplant-related mortality, and advanced disease morphology predicted for greater relapse. Among the 40 patients without excess blasts none have relapsed and those younger than age 40 (n = 32) have a 62% DFS at 4 years.

A new finding of this study was that after adjusting for age, shorter disease duration was associated with improved overall and disease-free survival, largely because of decreased non-relapse mortality. These findings of improved DFS in patients with younger age, less advanced disease, and shorter disease duration are similar to those observed in patients with chronic myelogenous leukemia (CML).[20,21]

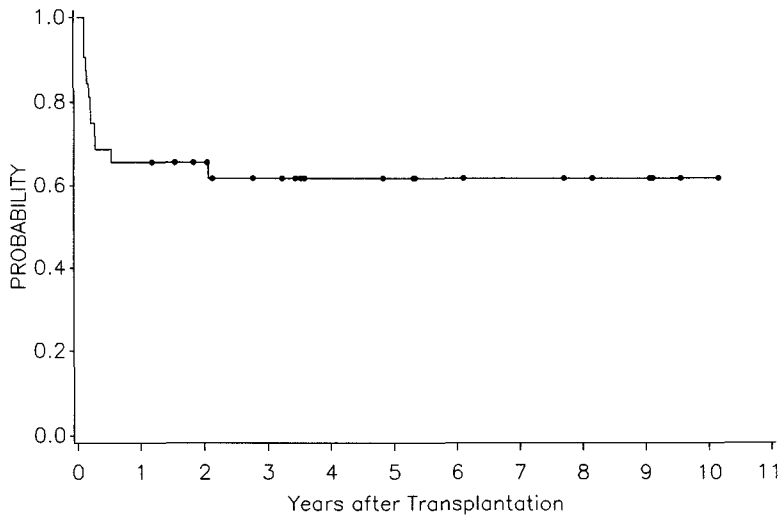

Fig 2. Probability of disease-free survival for 32 patients younger than age 40 and without excess blasts. Points represent patients alive in continuous complete remission.

Additionally, we have now found that among patients with excess blasts older age also predicted for greater relapse.

In our earlier analysis we observed the unexpected finding that cytogenetic abnormalities were significantly associated with improved survival and decreased non-relapse mortality, a finding inconsistent with our general understanding of MDS and the transplant procedure. This observation was likely artifactual since with a larger cohort of patients and longer follow-up, we found that cytogenetic abnormalities were no longer significantly associated with an improved outcome.

Previously, we recommended marrow transplantation for MDS only for patients with excess blasts or life-threatening cytopenias because patients with less advanced disease often survive several years with minimal treatment. However, by adhering to such criteria, some patients may die from cytopenic complications or develop acute leukemia before transplantation is attempted and others may develop complications that either prevent transplantation or decrease the likelihood of surviving the procedure. Because of the results of the multivariate analysis described above, we now propose that transplantation be considered earlier in the disease course for patients younger than age 40 with an HLA-matched family donor, before complications develop or the disease progresses. This recommendation is similar to the one generally accepted for patients with CML,[20] which has a disease course resembling MDS: it is often initially indolent, but is always fatal without marrow transplantation. For patients over age 40, however, transplantation should be approached more cautiously, potentially reserv-

Table 3. Published Reports of Bone Marrow Transplantation for MDS

Source	No. of Patients	Preparative Regimen	Morphology, No. of Patients	DFS	Relapse	NRM
Sutton et al[16]	86	Cy-TBI	RA, 20	33/86	20/86	33/86
		Bu-Cy	RAEB, 26	(38%)	(23%)	(38%)
			RAEBT, 18			
			sAML, 17			
			Other, 5			
DeWitte et al[17]	78	Chemotherapy	RA, 9	35/78	18/78	25/78
		+/− TBI	RAEB, 16	(45%)	(23%)	(32%)
			RAEBT, 20			
			sAML, 32			
			CMML, 1			
Longmore et al[18]	23	Cy-TBI	RA, 6	10/23	4/23	9/23
		Bu-Cy	RAEB, 6	(43%)	(17%)	(39%)
		Ar-Cy-TBI	RAEBT, 5			
		BCNU-VP-Cy	sAML, 6			
O'Donnell et al[19]	20	Cy-TBI	RAEB, 4	7/20	4/20	9/20
		Bu-Cy	RAEBT, 8	(35%)	(20%)	(45%)
		Ar-Cy-TBI	sAML, 1			
		VP-TBI	CMML, 2			
		Bu-VP-TBI	Other, 5			

Abbreviations: sAML, secondary AML; DFS, disease-free survival; NRM, non-relapse mortality; Cy, cytoxan; Bu, busulfan; Ar, cytosine arabinoside; VP, VP-16.

ing it for those with life-threatening cytopenias or excess blasts.

The timing of marrow transplantation for patients without an HLA-matched family donor is less clear. Although our results of 28 such patients are favorable, we did not have a sufficient sample size to analyze outcome for matched unrelated donors alone or for mismatched family donors by degree of HLA-disparity. Kernan et al[22] reported an 18% 2-year actuarial DFS for 32 patients with MDS receiving unrelated marrow through the National Marrow Donor Program. The reasons for this less favorable outcome are unclear, but did not appear related to age of the patients or their disease morphology. Continued study of mismatched family and unrelated donors is necessary to define their outcome more precisely.

Further progress in the use of allogeneic transplantation in MDS for patients without excess blasts and for those over age 40 centers on methods to reduce transplant-related mortality. For patients with excess blasts, both methods of reducing transplant-related mortality as well as preventing disease recurrence are needed.

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