Bone Marrow Transplantation, (1997) 19, 791–794

Outcome of allogeneic bone marrow transplantation with lymphocyte-depleted marrow grafts in adult patients with myelodysplastic syndromes

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Summary:

Thirty-five patients with myelodysplastic syndromes (MDS) were treated with BMT between 1986 and 1994. Their median age was 41 years (range 23–60). Thirteen patients had transfusion-dependent refractory anaemia (RA). Twenty-two patients suffered from more advanced stages of MDS, 15 being in complete remission (CR) after chemotherapy. In 31 recipients, pretransplant conditioning consisted of cyclophosphamide and TBI with or without the addition of idarubucin; four patients were conditioned with other schedules. Donors were genotypically HLA-identical and MLC-negative siblings in 32, and others in three cases. All patients received a graft depleted of 98% of T lymphocytes using counterflow centrifugation. Fourteen patients are alive and in continuous remission with a median follow-up of 20 months (range 15–113) after BMT. Seven patients relapsed between 3 and 18 months after BMT and subsequently died. Fourteen transplantation-related deaths occurred. Outcome in patients under and over 40 years old was comparable. The probability of disease-free survival (DFS) at 2 years after BMT was 39% (95% confidence interval (CI), 22–56%). Considering patients with HLA-identical and MLC-negative sibling donors transplanted for RA ($n = 11$) or more advanced stages of MDS in CR ($n = 14$), the probabilities of DFS were 73% (95% CI, 47–99%) and 42% (95% CI, 15–69%), respectively. This indicates that BMT with lymphocyte-depleted grafts can cure a substantial number of relatively old patients with MDS, especially when grafts from HLA-identical and MLC-negative siblings are used and patients are suffering from RA.

Keywords: bone marrow transplantation; myelodysplastic syndromes

Myelodysplastic syndromes (MDS) encompass a group of clonal haematopoietic disorders. They are characterized by refractory cytopenia and dysplastic changes in blood and bone marrow, and show a tendency to progress to AML. MDS are mostly seen in the elderly. While the overall incidence is about 2–4 per 100 000 per year, this is 20–30 per 100 000 per year in the population over 70 years.[1] The clinical course of MDS varies from an indolent form to a rapidly fatal disease. Patients die from infection or bleeding, complications of transfusion, or acute leukaemia. Conventional treatment is not curative.[2] In cases with excess of blasts or following progression to AML, intensive chemotherapy may result in CR in 50–60% of patients, but the median remission duration is usually less than 12 months, while a median survival following chemotherapy of 7–15 months has been recorded.[3,4] An increasing incidence of MDS is being observed in relatively young patients surviving after chemotherapy, immunotherapy and/or radiotherapy for other diseases. These treatment-related MDS have an even worse clinical course.[4,5]

Allogeneic BMT offers a potentially curative treatment for younger MDS patients. In a recent review, the probability of 5-year disease-free survival (DFS) following BMT in a group of 93 patients was 40%, while the actual DFS varied from 35 to 63% in six smaller studies with shorter follow-up.[6] Median age in these patient groups ranged from 23 to 36 years, and a younger age was found to be a favourable prognostic factor. We report a retrospective study of our results of BMT in a group of 35 adults with MDS. This patient group is relatively old as compared to the previously published series.[6]

Patients and methods

Between April 1986 and December 1994, 35 patients with MDS were treated with allogeneic BMT. Patient characteristics and transplantation data are summarized in Table 1. The median age was 41 years (range 23–60). Thirteen patients had refractory anaemia (RA) and were transfusion-dependent, seven patients had RA with excess of blasts (RAEB), 11 patients had RAEB in transformation (RAEB-t), and one patient suffered from chronic myelomonocytic leukaemia (CMMoL), as defined by the French–American–British (FAB) classification.[7] Three patients had secondary AML (sAML) which had evolved from MDS. Five out of the total group of 35 patients had developed MDS after previous radiotherapy (for malignant melanoma, $n = 1$) or immunosuppressive treatment for rheumatoid arthritis ($n = 2$), paroxysmal nocturnal haemoglobinuria ($n = 1$), and severe aplastic anaemia ($n = 1$). In the others, the MDS was

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Received 20 April 1996; accepted 30 November 1996

Table 1 Patient and transplantation characteristics

	Total	*≤40 years*	*>40 years*
No patients	35	17	18
Median age, years (range)	41 (23–60)	30	50
Sex, male/female	21/14	9/8	12/6
Stage of disease at transplantation			
RA, not pretreated	13	8	5
RAEB, not pretreated	3	1	2
RAEB in CR	4	2	2
RAEB-t in CR	9	4	5
RAEB-t in PR	2	0	2
CMMoL in CR	1	0	1
sAML in CR	1	1	0
sAML in PR	2	1	1
Disease aetiology			
Idiopathic	30	15	15
Previous radio- or immunosuppressive therapy	5	2	3
Median duration of disease before BMT, mo (range)	9 (4–69)	12	6
Marrow donors			
Median age, years (range)	40 (19–65)	33	47
Genotypically HLA-identical and MLC-neg sibling	32	14	18
Two-locus mismatched family member	1	1	0
Matched unrelated donor	2	2	0
Pretransplant conditioning regimen			
Cyclophosphamide (2 × 60 mg/kg i.v.), TBI (2 × 4, 5 Gy)	2	2	0
Cyclophosphamide (2 × 60 mg/kg i.v.), TBI (2 × 6 Gy)	7	3	4
Cyclophosphamide (2 × 60 mg/kg i.v.), idarubicin (42 mg/m^2 i.v.), TBI (2 × 4, 5 Gy)	22	9	13
Other	4	3	1

without apparent cause. The median duration of MDS before BMT was 9 months (range, 4–69). Prior to BMT, 19 patients received remission-induction and consolidation chemotherapy with schedules as used for the treatment of AML. This resulted in CR in 15 patients (four RAEB, nine RAEB-t, one CMMoL, and one sAML), and PR in four patients (two RAEB-t and two sAML). None of the 13 patients transplanted for RA were pretreated.

Donors were genotypically HLA-identical and MLC-negative siblings in 32 cases. One patient received a graft from a two-locus mismatched family member, and two from HLA-identical unrelated donors. Conditioning regimens consisted of cyclophosphamide (2 × 60 mg/kg i.v.) and TBI (2 × 4, 5–6 Gy) with or without the addition of idarubicin (42 mg/m^2 i.v.) in 31 patients, and other schedules in four patients. All patients received grafts depleted of approximately 98% of T lymphocytes using counterflow centrifugation elutriation, as described before.[8] Immunoprophylaxis post-transplant consisted of cyclosporin A. All patients were cared for in single rooms with filtered air under positive pressure, and all received oral selective gut decontamination, acyclovir for herpes virus prophylaxis, and cotrimoxazole for *Pneumocystis carinii* prophylaxis.

Acute GVHD was graded 1 to 4 according to the criteria described by Glucksberg *et al*.[9] Chronic GVHD was classified as limited or extensive, as described by Shulman *et al*.[10] Patients were considered evaluable for acute and chronic GVHD if they survived more than 14 days and more than 100 days after BMT, respectively.

Statistical analyses were performed using the Kaplan–Meier product-limit method. Actuarial curves were calculated for relapse and for DFS. 95% confidence intervals (CI) were calculated as: relapse or DFS estimate at 24 months after transplantation ±2 × s.e. Differences between subgroups were evaluated by the log rank test. P values <0.05 were considered significant.

Results

Fourteen out of 35 patients are alive in continuous CR with a median follow-up after BMT of 20 months (range 15–113). Relapse of disease was observed in seven patients including one patient transplanted for RA, two for RAEB in CR, one for RAEB-t in PR, one for CMMoL in CR, and two transplanted for sAML in PR. These relapses occurred between 3 and 18 months after BMT (median 6 months). Twenty-one patients have died. Eighteen of them died within 6 months (median 2 months) after BMT. Principal causes of death were relapse ($n = 4$), and transplantation-related causes encompassing graft failure ($n = 2$, including the patient with the two-locus mismatched family donor), infectious complications ($n = 9$, including the two patients with matched unrelated donors), acute GVHD ($n = 2$), and heart failure ($n = 1$). Three patients died beyond 6 months. All three had undergone retransplantation for relapse. One died of a cerebrovascular accident at 36 months after first BMT, and 10 days after retransplantation which was performed 24 months after relapse of RA. The other two patients were free of disease for 53 and 81 months, respectively, after retransplantation for relapsed RAEB. They ultimately relapsed again and died. Remarkably, both late relapses after second BMT presented primarily as an extramedullary myeloblastic infiltration in soft tissues (stomach and pleural cavity), followed by overt AML at a later stage. Figures 1 and 2 represent probabilities of relapse and DFS,

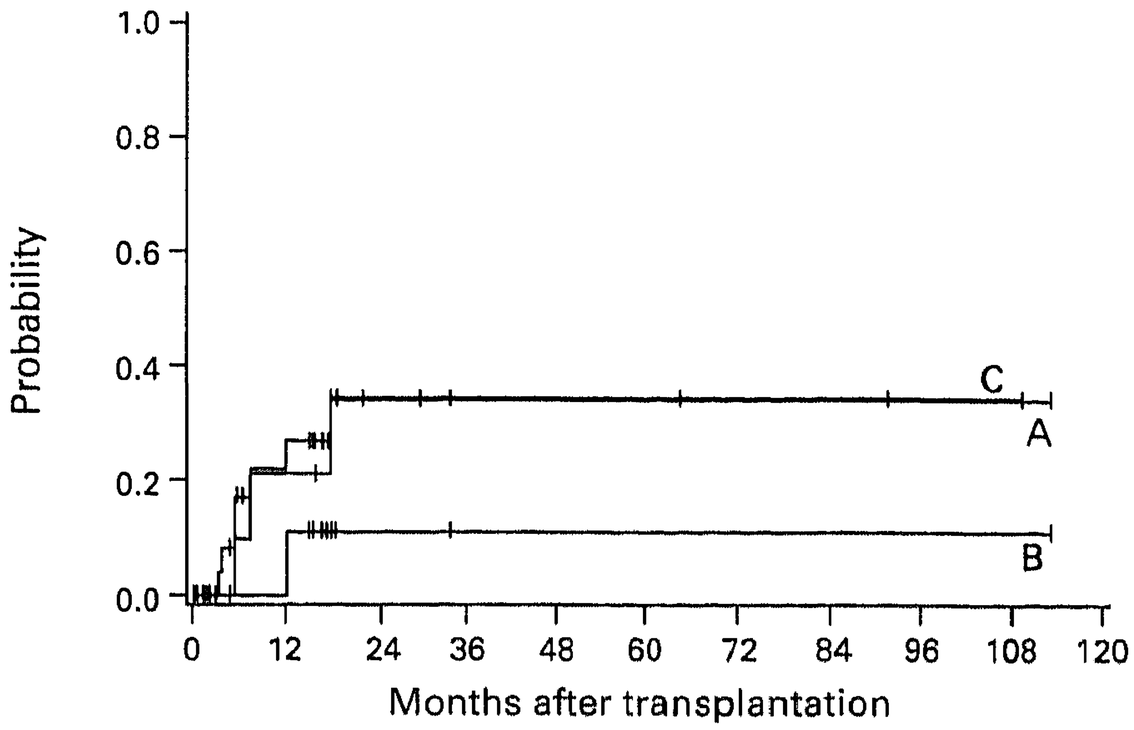

Figure 1 Probability of relapse of disease following BMT for patients with MDS. A, total group ($n = 35$); B, subgroup of patients with RA transplanted with marrow from HLA-identical and MLC-negative siblings ($n = 11$); C, subgroup of patients with RAEB, RAEB-t, CMMoL, or sAML, transplanted in CR with marrow from HLA-identical and MLC-negative siblings ($n = 14$). Log rank P, B *vs* C = 0.3. Bars represent relapse-free patients.

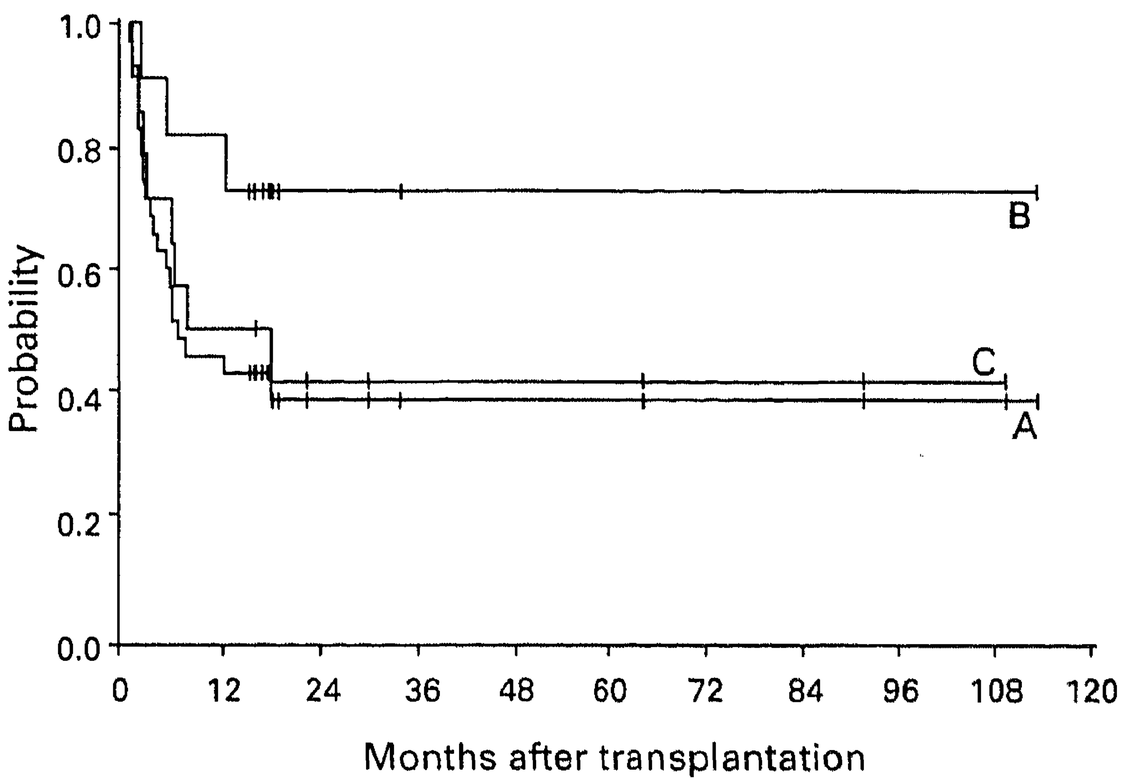

Figure 2 Probability of DFS following BMT for patients with MDS. A, total group ($n = 35$); B, subgroup of patients with RA transplanted with marrow from HLA-identical and MLC-negative siblings ($n = 11$); C, subgroup of patients with RAEB, RAEB-t, CMMoL, or sAML, transplanted in CR with marrow from HLA-identical and MLC-negative siblings ($n = 14$). Log rank P, B *vs* C = 0.2. Bars represent patients alive in continuous CR.

respectively, after BMT. Besides the total group (group A, $n = 35$), two more homogeneous subgroups were analyzed, encompassing patients with RA with HLA-identical and MLC-negative sibling donors (group B, $n = 11$), and patients with RAEB, RAEB-t, CMMoL or sAML, transplanted in CR with HLA-identical and MLC-negative sibling donors (group C, $n = 14$). The probability of relapse (Figure 1) at 2 years after BMT for the total group (A) is 34% (95% CI, 12–56%), and for the subgroups B and C 11% (95% CI, 0–32%) and 34% (95% CI, 2–66%), respectively. Figure 2 represents continuous DFS following (first) BMT. The median DFS for the total group is 6 months. Probabilities of DFS at 2 years after BMT are 39% (95% CI, 22–56%) for group A, 73% (95% CI, 47–99%) for group B, and 42% (95% CI, 15–69%) for group C. Although there was a tendency towards better outcome in patients with RA (group B), the differences between groups A, B and C were not statistically significant.

According to age two separate groups were analyzed, encompassing patients ⩽40 years and patients >40 years. With regard to disease and transplantation characteristics, these two groups were largely comparable (Table 1). On the one hand, the younger group included all three patients without genotypically HLA-identical sibling. On the other hand the older group included less patients with RA (five *vs* eight, Table 1). The probability of DFS for patients ⩽40 years ($n = 17$) was 33% (95% CI, 9–57%), and for patients >40 years ($n = 18$) 44% (95% CI, 21–67%), which was not significantly different (data not shown).

Thirty-one patients were evaluable for acute GVHD. Four of them (actual rate 13%) developed grade 2–4 acute GVHD. In two patients (6%), GVHD was the principal cause of death. Limited chronic GVHD occurred in four (17%), and severe chronic GVHD in three (13%) out of 23 evaluable patients.

Discussion

For patients with MDS and AML evolving from MDS, allogeneic BMT offers the only curative treatment option. Use of BMT, however, is limited to a minority of relatively young patients, especially those with HLA-identical sibling donors. Outcome of BMT in MDS and sAML has been described by several authors, mostly in retrospective analyses of heterogeneous patient groups.[6,11–17] The multiformity of MDS in itself, and the variety of preparative regimens used, obscure comparison and interpretation of reported results. Nevertheless, the actuarial DFS found here for MDS patients following BMT of 39% fits within the range of overall actuarial DFS of 35–56%, as described by others.[6,14–17] Our patient group, with a median age of 41 years, and 26% of the patients being 50–60 years of age, is one of the oldest BMT groups of MDS patients reported to date. Only Anderson *et al*[18] published a series with the same median age. Although a significantly better outcome has been described in younger patients (<30–35 years),[6,15,19] the 18 patients over 40 years old in our study did not fare worse than the 17 patients who were 40 years old or younger.

Besides a higher median age, use of T cell-depleted marrow grafts effected by counterflow centrifugation elutriation is specific for our MDS study group as compared to those published by others. T lymphocyte depletion of the marrow graft is performed in order to reduce the incidence and severity of GVHD. GVHD is a serious problem following allogeneic BMT, often resulting in death. In the previously reported MDS patient groups, the incidence of fatal GVHD was 20–35% in the studies without T cell-depletion[11,15,17,19] and 9–13% in groups, with about 30% of the patients receiving T cell-depleted marrow.[12,13] In comparison to this, the percentage of patients who died of GVHD in the present study is low (two out of 35, 6%). Lymphocyte depletion implies an increased risk of graft failure and disease relapse. In two of our 35 patients (6%), graft failure resulting in death occurred. The overall relapse rate of 20%,

however, is identical to previously reported series.[6,17,18] That the overall relapse rate is not higher could be explained by the intensive pretreatment our patients received, with remission-induction chemotherapy in cases with excess of blasts, and intensive conditioning with two cytotoxic agents besides TBI in most patients.

Since the present MDS population is quite heterogeneous, we distinguished two more homogeneous patient groups. The first subgroup consisted of 11 patients with RA, with HLA-identical and MLC-negative sibling donors. With their probability of relapse of 11% and probability of DFS of 73%, they appear to constitute a favourable subgroup, as was found by others before.[6,12,17,19]

The second subgroup encompassed 14 patients with more advanced MDS (RAEB, RAEB-t, CMMoL or sAML), transplanted in first CR after previous chemotherapy with marrow from HLA-identical and MLC-negative siblings. With a probability of DFS of 42%, their results were clearly better than for the seven patients not in CR before BMT (four in PR and three non-pretreated), and who all died (three of relapse, one of GVHD, one of graft failure and two of infectious complications). These groups are rather small, but improved outcome of MDS patients being in CR before BMT as compared to failures to chemotherapy has been described before.[12,14] Otherwise, in other series, comparable[6,12,13] or even better[14] results were obtained while no attempt was made to get MDS patients with excess of blasts into CR before BMT.

The experience with BMT in MDS patients with marrow from donors other than genotypically matched siblings is limited. In the present study the three patients in this category all died due to treatment-related causes. Both worse[16] and comparable[6,18] results as compared to procedures with genotypically HLA-matched sibling donors have been described before.

Our results indicate that BMT with T lymphocyte-depleted grafts from HLA-identical and MLC-negative siblings can cure patients with MDS up to 60 years old. A good probability of DFS was seen especially in patients with RA. Future studies will give us more information on favourable subgroups of MDS patients for BMT, on the criteria to be used for pretreatment with chemotherapy, and on the timing of BMT within the course of MDS.

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