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Allogeneic Bone Marrow Transplantation for Acute Leukaemia or Chronic Myeloid Leukaemia in the Fifth Decade of Life

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Abstract—*To determine the influence of advanced age on long-term survival after allogeneic bone marrow transplantation (BMT), the probability of survival and the frequency of transplantation-associated complications were analysed retrospectively in 20 patients with acute leukaemia (AL) or chronic myeloid leukaemia (CML), who were 40–49 years of age (median 44.5 years) at the time of transplant. The results of this patient group were compared to those of 32 patients aged 30–39 years (median 33.5 years) with AL or CML, who also underwent BMT during the same period of time. The overall actuarial survival of the two age groups was comparable with 44% and 41% at 5.9 and 5.6 years, respectively. Patients with standard risk criteria (i.e. HLA-genotypically identical sibling donor, 1st chronic phase of CML or 1st remission of AL) showed a higher probability of survival in both groups (62% at 5.9 years in older patients and 59% at 5.5 years in younger patients, respectively). In contrast, actuarial survival in patients who underwent BMT at an advanced stage of their disease or with marrow from a partially HLA-compatible donor was significantly inferior (P = 0.04).*

The cumulative incidence of acute and chronic graft-versus-host disease was low in older patients (27%), who received marrow from an HLA-identical sibling donor.

The most frequent cause of death was interstitial pneumonia, occurring in seven of the older patients (35%) and in seven of the younger patients (22%). This difference, however, was not statistically significant.

Our results indicate that allogeneic marrow transplantation in the fifth decade of life might be associated with a tolerable risk of transplantation-related complications. This treatment modality may therefore be regarded as first-line therapy for patients in 1st remission of AL or first chronic phase of CML, who show a normal performance status. The same applies to older patients in advanced stages of disease, since the results are comparable to those achieved in the younger patient group.

INTRODUCTION

Success of allogeneic BMT after high-dose chemo-radiotherapy, as a treatment modality for acute leukaemia (AL) or chronic myeloid leukaemia (CML), is strongly influenced by typical transplantation-related problems, such as acute or chronic graft-versus-host disease (GvHD) and infectious or toxic pulmonary complications. Retrospective analyses have suggested an increased age-dependent risk for these life-threatening complications, with poor survival rates in older patients as compared to children, adolescents or young adults [1–4]. Many centres have therefore restricted BMT to patients under 40 to 45 years of age, although it is still unclear whether excluding patients is justified over this arbitrarily chosen age limit. Haematologic

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malignancies are common in this age group. Thus, an age restriction deserves further study to determine whether BMT in patients over 40 years of age is associated with a tolerable risk of transplantation-related complications. This question is of special relevance for patients with CML, since BMT is presently the sole mode of treatment, which leads to long lasting cytogenetic and morphologic remissions, and offers the chance of cure [5]. As of September 1986, 20 patients with AL or CML, who had entered the fifth decade of life, received an allogeneic marrow graft at the West German Tumour Centre, Essen. This retrospective analysis presents the outcome in this patient group with special reference to type and frequency of major transplantation-related complications. The results were compared to 32 patients between 30 and 39 years of age, who underwent BMT for AL or CML during the same period of time.

PATIENTS AND METHODS

From May 1977 to September 1986 20, patients between 40 and 49 years of age (median 44.5 years) underwent BMT (group 1). The median interval between diagnosis and BMT was 18 months (1–80 months). Prior to BMT the Philadelphia-chromosome could be demonstrated as a specific cytogenetic marker in all patients with CML. The definition of CML in the accelerated phase corresponded to the cytogenetic, morphologic and clinical criteria as previously published [6].

Sixteen patients received marrow from HLA-genotypically identical and mixed lymphocyte culture (MLC) negative sibling donors. Four patients were grafted with marrow from partially HLA-compatible family members. Prerequisites were identity of all class-I and class-II antigens of one chromosome, a maximum of two antigen differences of the second chromosome and a non-reactive MLC. Three of these patients received marrow from their respective children and one from a grand-uncle. Median donor age was 42 years (11–70 years). Four recipient–donor pairs showed major incompatibility of the ABO-erythrocyte antigens. Details of the chemoradiotherapy prior to BMT have been previously described [7]. Prophylaxis of acute GvHD consisted of methotrexate alone or in conjunction with cyclosporine [8, 9].

All patients were nursed under strict protective isolation using laminar air-flow systems or barrier-nursing units. For total decontamination of the gastrointestinal tract non-absorbable antimycotics and antibiotics were given in conjunction with sterile food. These measures were started about 2 weeks before BMT and were maintained for a minimum of 50 days post BMT. Decontamination efficiency was monitored by regular gnotobiotic analysis of oral washings, skin swabs, faeces and urine. As *Pneumocystis carinii* prophylaxis, trimethoprim–sulfamethoxazole was given. All except the first five patients received cytomegalovirus (CMV) hyperimmunoglobulin every 3 weeks starting 1 week before BMT, and lasting until 12 weeks post BMT. In addition, blood product substitution was performed using preparations from CMV-antibody negative blood bank donors since July 1984.

Diagnosis and grading of acute GvHD were established on the basis of clinical criteria and skin biopsies [10]. Diagnosis of interstitial pneumonia (IP) was based on clinical and radiological findings. Since open lung biopsies were not performed, the cause of IP was usually not established *ante mortem*. Histological, bacteriological and virological examinations were carried out *post mortem* in all cases with IP to differentiate between infectious and non-infectious causes. Patient characteristics and outcome of BMT are summarized in Tables 1 and 2.

Results of patients from group 1 were compared with those of 32 consecutive patients between 30 and 39 years of age (median 33.5 years) (group 2) grafted during the same time interval with special reference to probability of survival, risk of GvHD and incidence of IP. To allow for comparison, the two groups were divided into patients with standard risk (AL in 1st remission, CML in 1st chronic phase) and patients with high risk (AL in relapse or 2nd or subsequent remission, CML in acceleration or acute transformation; marrow donors other than HLA-identical siblings) (Table 1).

Differences between numeric values for the two groups were analysed by a two-sided Wilcoxon rank-sum test. Categorical values were compared using the two-sided Fisher's exact test. The survival estimates and the cumulative incidence of GvHD were calculated by non-parametric estimation for incomplete observations [11]. A test of equality of the survival curves was performed using the log-rank test [12] or Mantel–Cox test [13].

RESULTS

Actuarial survival of all patients in the two groups is given in Fig. 1 (44% vs. 41% at 5.9 and 5.5 years, respectively, $P = 0.73$). Seven of 11 older patients (64%) fulfilling standard risk criteria are currently alive with a median observation time of 24 months, resulting in an actuarial survival probability of 62% between 12 and 71 months post BMT. This is comparable to the results of younger patients with standard risk criteria: 13 of 22 (59%) are alive with an actuarial probability of survival of 59% between 9 and 66 months post BMT ($P = 0.83$). In contrast, only two of nine of the older patients (22%) with high risk criteria are alive and disease-free at 10 and 32 months, which again is comparable to the actuarial probability of survival in younger patients with high risk criteria (15% at

Table 1. *Patient characteristics and survival data of the two age-groups*

	Group 1	Group 2	
Number of patients	20	32	
Age (years)*	44.5 (40–49)	33.5 (30–39)	$P = 0.0001$§
Sex (F/M)	10/10	19/13	
Diagnosis (number of patients)			
AML, 1st remission	3	10	
AML, 2nd remission	1	3	
AML, relapse	1	4	
ALL, 1st remission	1	1	
ALL, 2nd–4th remission	1	1	
CML, 1st chronic phase	9	11	
CML, accelerated phase or blast crisis	4	2	
Proportion of patients alive (%)			
Standard risk†	7/11 (64)	13/22 (59)	n.s.‖
High risk‡	2/9 (22)	2/10 (20)	n.s.‖
Duration of follow-up (months)*	24 (8–71)	27 (9–66)	n.s.§
Actuarial survival at 5 years post BMT (%)	44	41	n.s.¶

AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia.

*Median (range).

†Patients grafted in the 1st remission of acute leukaemia or the 1st chronic phase of CML with marrow from an HLA-genotypically identical sibling donor.

‡Patients grafted in advanced stages of their disease or with marrow from a donor, who differed from recipient for at least one HLA-antigen.

§By two-sided Wilcoxon rank-sum test.

‖By Fisher's exact test.

¶Survival estimates calculated by non-parametric estimation for incomplete observations, test of equality was calculated by the log-rank test.

42 months, $P = 0.30$) (Fig. 2). The survival rate of all standard risk patients is 60% (20/33) as opposed to 21% (4/19) for high risk patients ($P = 0.009$). Corresponding actuarial disease-free survival is 54% at 5.9 years and 13% at 3.5 years, respectively ($P = 0.04$).

The cumulative incidence of acute or chronic GvHD of patients in group 1 is 27% as compared to 63% in group 2. This difference, however, which might be attributable to the relatively low number of patients in group 1, is not statistically significant ($P = 0.08$) (Table 3). Seven of 20 patients (35%) in group 1 and seven of 32 patients (22%) in group 2 developed fatal IP ($P = 0.26$). In 13 of these 14 patients no infectious cause of IP could be identified (Tables 2 and 4). Recurrence of leukaemia was seen in 3 patients of group 1, of whom two had undergone BMT in advanced stages of their disease (Table 2). Leading causes of death in group 1 were IP in seven patients, recurrence of leukaemia, septic shock, aspiration pneumonia and cerebral bleeding in one patient each. Three of these patients had active GvHD at the time of death. Eight of the nine surviving patients are living in complete remission with normal activity. Three patients have mild chronic GvHD, which is well controlled in all cases. The major transplantation-associated complications of both groups (GvHD excluded) are summarized in Table 4.

DISCUSSION

Various factors influence the development of transplantation-related complications and thus determine the probability of survival after allogeneic BMT. Among others these include the primary disease and its pretreatment, the stage of disease, the patient's performance status, the time interval between diagnosis and BMT and the HLA relationship between recipient and donor. Concerning the age restriction, two recent studies have suggested that selected older patients up to 50 years of age may benefit from this treatment modality [14, 15].

Our preliminary experience in 20 patients between 40 and 49 years of age confirms and extends this suggestion, since survival probability in this group was comparable to that achieved in a group of patients aged 30–39 years. For patients grafted with marrow from an HLA-identical sibling donor in an early stage of their disease, actuarial survival in the two groups is 62% at 5.9 years and 59% at 5.5 years, respectively ($P = 0.83$). This contrasts significantly with the outcome of patients grafted in advanced stages of their disease or with marrow from donors other than HLA-identical sib-

Table 2. Outcome of allogeneic marrow transplantation in patients 40–49 years of age (group 1)

Unique patient number	Age (years)	Sex	Diagnosis*	Conditioning regimen†	GvHD prophy-laxis‡	Acute GvHD (grade)	Chronic GvHD	Outcome and day	Cause of death/late complications‖
5	41	F	AML relapse	1	MTX	0	n.e.**	D 58	Relapse
21	41	F	AML 1st remission	1	MTX	0	No	A 2169	—
30	41	F	AML 1st remission	1	MTX	0	No	A 1826	—
41	40	F	AML 1st remission	1	MTX	0	n.e.	D 23	IIP
61	43	F	CML accel. phase	1	MTX	0	n.e.	D 53	IIP
71	45	F	CML chronic phase	1	MTX	0	Yes	A 1175	Relapse
88	41	M	ALL 4th remission	1	MTX	0	No	A 972	—
89¶	42	M	CML blast crisis	2	MTX	0	n.e.	D 71	IIP, relapse
109	46	M	CML chronic phase	3	MTX	II	Yes	A 715	—
112	43	M	CML chronic phase	3	MTX	II	Yes	D 334	IIP, encephalitis
133¶	40	F	CML chronic phase	4	MTX	0	n.e.	D 46	CMV IP
134	48	F	CML accel. phase	4	MTX, CSA	0	No	D 173	IIP
139¶	45	M	CML accel. phase	4	MTX, CSA	III	Yes	D 95	Septic shock
146	47	M	CML chronic phase	4	MTX, CSA	0	No	A 386	—
147	45	F	CML chronic phase	4	MTX, CSA	0	No	A 358	—
148	44	M	ALL 1st remission	4	MTX	n.e.	n.e.	D 17	Aspiration pneumonia
149	47	F	CML chronic phase	4	MTX, CSA	0	n.e.	D 57	IIP
153¶	46	M	CML chronic phase	4	MTX, CSA	II	Yes	D 182	Cerebral bleeding
158	45	M	AML 2nd remission	4	MTX, CSA	II	Yes	A 295	—
164	49	M	CML chronic phase	4	MTX, CSA	0	No	A 253	—

*AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; accel. denotes accelerated.
†1, cyclophosphamide (Cy) 60 mg/kg i.v. × 2 + 8.6 Gy single-dose total body irradiation (TBI) delivered from a linear accelerator (Linac) at a dose rate of 12 cGy/min; 2, Cy × 2 + 8.6 Gy single-dose translational TBI delivered from a cobalt−60 (^{60}Co) source at an instantaneous dose rate of 18 cGy/min; 3, Cy × 2 + 4 × 2.5 Gy TBI (Linac) over 4 days (dose rate 12 cGy/min); 4, Cy × 2 + 4 × 2.5 Gy translational TBI (^{60}Co) at an instantaneous dose rate of 12 cGy/min over 4 days with lung shielding (lung dose 8 Gy ± 7%).
‡CSP, cyclosporine after grafting; MTX, methotrexate after grafting.
§D, dead; A, alive as of 13 May 1987.
‖CMV IP, cytomegalovirus interstitial pneumonia; IIP, idiopathic interstitial pneumonia.
¶Donor differed from recipient for at least one HLA class I or class II antigen.
**Patient died too early to be evaluable for acute or chronic graft-versus-host disease (GvHD); n.e., not evaluable.

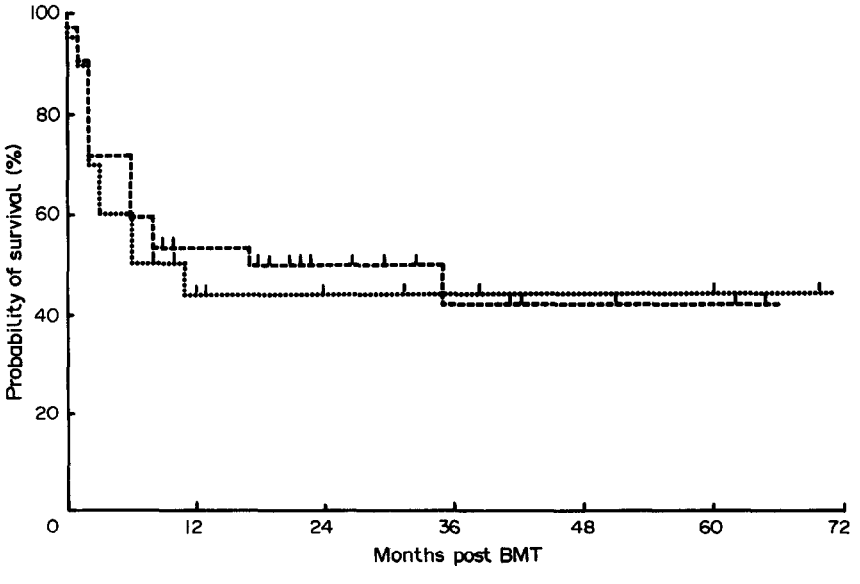

Fig. 1. Kaplan–Meier product-limit estimates of survival from date of transplantation in patients between ages 40 and 49 (dotted line) and ages 30 and 39 (dashed line). Tick marks indicate surviving patients. All analyses are based on survival as of 13 May 1987.

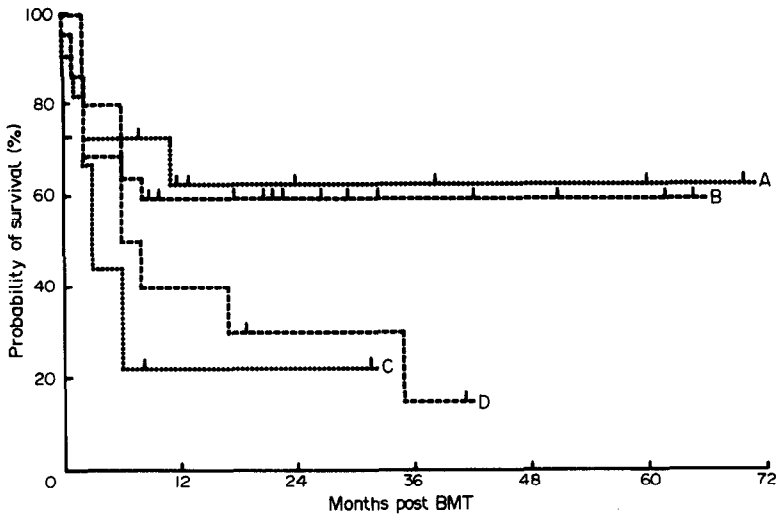

Fig. 2. Kaplan–Meier product-limit estimates of survival in patients between 40 and 49 years of age (dotted line; curves A and C) and in patients between 30 and 39 years of age (dashed line; curves B and D), categorized by recipient risk (standard risk group: patients who received an HLA-genotypically identical allogeneic transplant for acute leukaemia in first remission or for chronic myeloid leukaemia in first chronic phase; high risk group: patients who were grafted in advanced stages of acute leukaemia or chronic myeloid leukaemia or with marrow from an HLA-partially compatible donor). The difference between patients with standard risk criteria (curves A and B) as compared to those with high risk criteria (curves C and D) is statistically significant at 3.5 years after transplantation (P = 0.04, log-rank test).

lings, regardless of age. In contrast to the data of Klingemann *et al.* [14], who described an inferior outcome of allogeneic BMT for patients grafted in remission of AL, as compared to the first chronic phase of CML, survival rates in our analysis appear to be comparable with 66% vs. 55%, respectively. Thus, previous remission-induction chemotherapy does not seem to add further risk to older patients undergoing BMT.

Table 3. Incidence of acute and chronic graft-versus-host disease (GvHD) in patients between 40 and 49 years of age (group 1) and those between 30 and 39 years of age (group 2)

	Group 1	Group 2	
Proportion of patients with GvHD (%)*			
Acute Grade I–II	3/15 (20)	5/28 (18)	n.s.§
Acute Grade III–IV	0/15 (0)	4/28 (14)	n.s.§
De novo and secondary chronic†	4/11 (36)	15/23 (65)	n.s.§
Cumulative incidence of acute and chronic GvHD (%)‡	27	63	n.s.‖

*Percentages are based on the total number of patients with evidence of engraftment, who had been grafted with marrow from an HLA-genotypically identical sibling donor.
†Percentages are based on the total number of patients at risk at 90 days after transplantation.
‡By Kaplan–Meier product-limit estimate.
§By Fisher's exact test.
‖Test of equality by Mantel–Cox test.

It is generally accepted that the increased risk of developing GvHD is a major contributing factor to greater morbidity and mortality after allogeneic BMT in older patients [3]. As opposed to other reports, we were not able to find a correlation between the age of the marrow recipient and the risk of developing GvHD by multivariate analysis in 97 consecutive patients with AL or CML. The strongest predictive factor for GvHD was a sex difference between donor and recipient. This was most pronounced in male patients, who received marrow from a female donor. The second most important predictive factor was CML as the primary disease [16]. It is tempting to speculate that the relatively low incidence of grade II–IV acute GvHD in the older patient group is at least in part a consequence of the strict gnotobiotic measures, which were maintained for at least 50 days post BMT. Studies in mice revealed that a germ-free intestinal milieu had a protective influence with regard to the development of 'secondary disease' [17]. The positive effect of intestinal decontamination was further supported by a prospective clinical trial of Storb *et al.*, who found a lower frequency of GvHD and a better survival for patients with aplastic anaemia treated in laminar air-flow rooms with gut decontamination [18].

The most serious complication for patients undergoing BMT for haematological malignancies is interstitial pneumonia [4]. In our group of younger patients, the incidence of IP was somewhat lower than in the older patient group, but this difference

Table 4. Frequency of major transplantation-associated complications in patients between ages 40 and 49 (group 1) as compared to patients between ages 30 and 39 (group 2)

	Group 1	Group 2	
Proportion of patients with major transplantation-associated complications (%)			
Idiopathic IP*	6/20 (30)	7/32 (22)	n.s.§
CMV-IP	1/20 (5)	0/32 (0)	
Other pulmonary complications†	1/20 (5)	2/32 (6)	
Severe infections‡	1/20 (5)	2/32 (6)	
Cerebral bleeding	1/20 (5)	0/32 (0)	
Cardiac failure	0/20 (0)	2/32 (6)	

*IP denotes interstitial pneumonia.
†Aspiration pneumonia in group 1, bacterial and mycotic pneumonia in group 2.
‡Included are patients with severe infections as primary cause of death (septicaemia in group 1, generalized toxoplasmosis in group 2).
§By Fisher's exact test.

was not significant. It is of note that all but one patient developed non-infectious forms of IP. It remains unclear to what extent the predominance of non-infectious IP is the result of the high proportion of patients pretreated with busulfan. Five of 12 patients (42%), who had received busulfan as treatment of their primary disease, developed IP as compared to one of eight patients (12%) who did not. A possible connection between prior busulfan therapy and the development of IP has been suggested by Thomas *et al.* [5].

Klingemann *et al.* described a high number of early infectious complications leading to death in patients between 45 and 50 years of age [14]. In contrast, the incidence of life-threatening infectious complications in our study was low and limited to patients with a partially compatible donor. This may, again, point out the positive effect of a protective environment.

Despite the limited number of patients, these results encourage further studies of allogeneic marrow transplantation as treatment of haematologic malignancies for selected patients in the fifth decade of life. Patients in an early stage of their disease who have an HLA-identical sibling donor seem to benefit from this treatment modality, since the rate of transplantation-associated complications and the long-term results are comparable to younger patients.

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