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Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation

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Summary:

The purpose of this study was to determine the long-term results of allogeneic bone marrow transplantation for chronic myeloid leukemia. A retrospective analysis was carried out of the outcome of 373 consecutive transplants performed at 38 European institutions between 1980 and 1988 and reported to the registry of the European Group for Blood and Marrow Transplantation. All transplants were carried out for first chronic phase of chronic myelogenous leukemia using unmanipulated marow cells from HLA-identical sibling donors. The probability of survival and leukemia-free survival at 8 years were 54% (95% CI: 49–59) and 47% (95% CI: 41–52) respectively. The probabilities of developing acute GVHD (II–IV) at 100 days and chronic GVHD at 4 years after transplant were 47% (95% CI: 41–53) and 52% (95% CI: 46–58) respectively. The probabilities of transplant-related mortality and leukemic relapse 8 years after BMT were 41% (95% CI: 36–48) and 19% (95% CI: 14–25), respectively. Transplant within 12 months of diagnosis was associated with reduced transplant-related mortality (34 *vs* 45%, $P = 0.013$) and resulted in improved leukemia-free survival (52 *vs* 44%, $P = 0.03$). The probability of relapse was significantly reduced in patients who developed chronic GVHD (RR = 0.33, $P = 0.004$). The probability of relapse occurring more than 2 years after transplant was increased more than five-fold in patients transplanted from a male donor (RR = 5.5, $P = 0.006$). Sixty-seven patients in hematologic remission were studied for residual disease by two-step RT/PCR for BCR-ABL mRNA and 61 (91%) tested negative. We conclude that bone marrow transplantation can induce long-term survival in approximately one-half of CML patients; the majority of survivors have no evidence of residual leukemia cells when studied by molecular techniques. The probability of late relapse is increased with use of a male donor.

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Since its introduction in the early 1970s, bone marrow transplantation (BMT) for hematological malignancies has gained wide acceptance. It is generally considered as the only form of therapy with the capacity to cure chronic myelogenous leukemia (CML). During the last decade new approaches such as the combined use of cyclosporin A (CsA) and methotrexate (MTX) for graft-versus-host disease (GVHD) prophylaxis have reduced treatment-related mortality (TRM) and improved outcome.[1,2] Other developments such as T cell depletion have advanced our understanding of the role donor cells play in the elimination of residual leukaemia cells after transplant and have resulted in novel treatment strategies for relapse.[3–7] The inception of centralized data bases, such as the European Group for Blood and Marrow Transplantation (EBMT) registry, in the late 1970s have made it possible to analyze prognostic variables in large series of patients for their impact on TRM, survival, leukemia-free survival (LFS) and relapse. Knowledge of these parameters can assist in the selection of patients for BMT and contribute to improved survival. The present study extends a previous analysis of transplant for CML in Europe and focuses on the clinical and molecular outcome of a subset of 'good risk' patients transplanted in first chronic phase using unmanipulated marrow cells from a HLA-identical sibling donor.[8] Almost 50% of the patients survive free of their leukemia after marrow transplant and appear to be 'cured'. We draw attention to an increased risk of leukemic relapse with the use of male donors and the detection of residual leukemia cells by reverse-transcription polymerase chain reaction (RT/PCR) in a minority of long-term survivors.

Patients and methods

Data collection

A retrospective analysis was carried out of patients reported to the data base of the Chronic Leukemia Working Party

of the EBMT in Leiden between 1980 and 1988. Data were collected by questionnaire and included details of patient and donor age, sex and histocompatibility, WBC at diagnosis, duration of disease at the time of BMT, conditioning regimen, GVHD prophylaxis and outcome. The follow-up was updated from October 1993.

Patients

The study population is a subset of a previous transplant cohort reported by EBMT in 1993.[8] This study focused on the long-term outcome of a homogenous group of patients transplanted for CML. The present study comprised a cohort of 373 patients transplanted in first chronic phase of CML from an HLA-identical sibling donor (male, $n = 208$; female, $n = 165$) using unmanipulated marrow cells. The conditioning regimen included in all cases cyclophosphamide and total body irradiation (TBI). Patients conditioned with a non-TBI-conditioning regimen were excluded from the present analysis. GVHD prophylaxis consisted of CsA only ($n = 211$), CsA/prednisolone ($n = 21$) or CsA/MTX ($n = 141$). T cell-depleted transplants and patients receiving MTX only as GVHD prophylaxis were excluded from this analysis. The median recipient age was 31.0 years (range 2–50). Three hundred and nineteen patients were older than 20 years of age and 52 patients were younger. The median donor age was 30.5 years (range 1–62). The transplants were carried out at 38 European institutions between 1980 and 1988. The time frame 1980 to 1988 was selected in order to allow for a median follow-up of 7 years. The participating institutions and the number of patients transplanted per center are listed in Appendix 1. Each team confirmed that all patients fulfilling the aforementioned criteria had indeed been reported to the EBMT. This study therefore represents a consecutive series of patients with CML transplanted under similar and standard conditions. Patient and donor characteristics are further detailed in Table 1.

Definition of endpoints

Primary outcome variables, ie survival, leukemia-free survival (LFS), transplant-related mortality (TRM), acute and chronic GVHD and relapse, were all calculated from BMT. Leukemia-free survival was defined as survival without cytogenetic or hematologic evidence of leukemia. Acute and chronic GVHD were classified according to standard criteria as previously described.[9,10] Patients were evaluable for acute and chronic GVHD if they had survived at least 10 and 90 days respectively after marrow transplantation. Relapse was defined as the detection of Philadelphia-positive metaphases in the marrow or abnormal blood/bone marrow counts or morphology consistent with CML. Disease recurrence within 2 years after BMT was classified as early relapse; late relapse was defined as recurrence of CML more than 2 years post-BMT. Transient relapse was diagnosed if there was recurrence of CML, as defined by cytogenetic or morphological techniques, which resolved spontaneously without therapeutic intervention. Patients with transient relapse were analyzed with the non-relapse group. TRM was defined as death due to causes other than disease recurrence; patients were censored at the time of relapse or at last follow-up.

Molecular detection of BCR/ABL fusion gene

RT/PCR for the BCR-ABL gene rearrangement was carried out on peripheral blood or bone marrow cells of 67 patients at eight institutions. All these centers used a sensitive two-step PCR approach.[11]

Statistical analyses

Outcome probabilities were calculated by the Kaplan–Meier method and comparisons were made using the log rank test.[12] The primary outcome variables were analyzed according to patient and donor sex, donor–recipient sex combinations, method of GVHD prophylaxis (CsA/MTX *vs* CsA alone *vs* CsA/prednisolone), patient age (20 *vs* >20 years), donor age (30 *vs* >30 years), (WBC at diagnosis ($<30 \times 10^9$/l *vs* $>30 \times 10^9$/l) and time interval from diagnosis to transplant (<12 months *vs* >12 months). Variables significant in univariate analyses at the $P < 0.2$ level were further examined using proportional hazards regression analysis employing a backward stepping procedure to identify the most statistically significant model. Interaction terms were added to the final model, but never reached statistical significance. In the analysis of early relapse, patients surviving more than 2 years were censored at 2 years. In the analysis of late relapses, all patients surviving less than 2 years were excluded. Acute and chronic GVHD were entered as time-dependent variables. All P values are two-sided. 95% confidence intervals are quoted in parentheses.

Results

Overall results

Of the 373 patients who received a transplant between 1980 and 1988, 203 patients are still alive and 170 have died. One hundred and seventy-eight patients are in continued complete remission. The overall actuarial probabilities of survival and LFS at 8 years were 53.7% (CI: 49–59) and 46.7% (CI: 41–52) respectively (Figure 1 and Table 1). The median LFS was 58 months. The median survival had not been attained at a median follow-up of 84 months (range: 35–154). The overall probability of TRM at 8 years was 40.6% (CI: 36–46) (Table 1 and Figure 2). One hundred and fifty-five patients died a transplant-related death, while 15 died of relapse. The latest death occurred at 72 months post-BMT. The main causes of death were GVHD and interstitial pneumonitis. These accounted for 54% of all deaths. Twenty-seven patients died more than 2 years after transplant. Leukemic relapse accounted for 41% of these late deaths. The overall probabilities of developing acute GVHD (II–IV) at 100 days and chronic GVHD (limited/extensive) at 4 years after transplant were 46.6% (CI: 41–52) and 52.1% (CI: 45–59) respectively (Table 2). Relapse of CML occurred in 40 patients. In a further seven cases a transient cytogenetic relapse was observed. Twenty-four patients experienced relapse 2 years after BMT; 16

Table 1 Unadjusted probabilities (± s.e.) for survival, LFS, TRM and relapse at 8 years after HLA-identical sibling BMT for CML in first chronic phase

		Outcome							
	No.	*Survival*	*P*	*LFS*	*P*	*TRM*	*P*	*Relapse*	*P*
Overall	373	53.7 ± 3		46.7 ± 3		40.6 ± 3		18.9 ± 3	
Recipient sex									
Male	208	48.4 ± 4		40.7 ± 4		46.7 ± 4		23.1 ± 4	
Female	165	60.4 ± 4	0.027	54.3 ± 3	0.014	34.6 ± 5	0.05	14.3 ± 4	0.041
Recipient–donor sex									
M/M	120	49.6 ± 5		37.9 ± 5		43.3 ± 5		31.3 ± 6	
M/F	88	46.7 ± 6		44.3 ± 6		49.1 ± 6		10.4 ± 5	
F/M	86	56.1 ± 6	0.05	47.4 ± 5	0.027	38.5 ± 5	0.049	20.0 ± 6	0.024
F/F	79	65.1 ± 6		61.7 ± 6		30.0 ± 5		9.1 ± 4	
GVHD prophylaxis									
CsA	211	50.3 ± 4		44.7 ± 3		45.5 ± 4		13.4 ± 3	
CsA/MTX	141	60.9 ± 4	0.17 *0.06	50.0 ± 5	0.53 *0.18	32.9 ± 4	0.10 *0.04	25.6 ± 5	0.07 *0.02
Other	21	42.3 ± 11		42.3 ± 11		46.6 ± 12		20.7 ± 11	
Duration of disease									
<12 months	139	61.1 ± 4		51.9 ± 4		34.3 ± 4		18.8 ± 4	
⩾12 months	222	49.3 ± 3	0.01	44.2 ± 3	0.03	44.6 ± 3	0.013	17.8 ± 4	0.65
Recipient age									
⩽20 years	52	69.2 ± 6		63.0 ± 7		28.9 ± 6		9.1 ± 5	
>20 years	319	50.8 ± 3	0.09	43.7 ± 3	0.07	42.9 ± 3	0.18	21.0 ± 3	0.12
WBC at diagnosis									
⩽30 × 10^9/l	57	56.5 ± 7		51.4 ± 7		37.3 ± 7		19.8 ± 7	
>30 × 10^9/l	272	55.4 ± 3	0.62	48.0 ± 3	0.45	39.6 ± 3	0.70	17.6 ± 3	0.51
Donor sex									
Male	206	52.3 ± 4		41.9 ± 4		41.1 ± 4		23.6 ± 4	
Female	167	55.5 ± 4	0.60	52.7 ± 4	0.27	40.0 ± 4	0.74	9.7 ± 3	0.026
Donor age									
⩽30 years	181	55.4 ± 4		47.1 ± 3		37.8 ± 4		20.8 ± 4	
>30 years	181	52.6 ± 4	0.61	46.4 ± 3	0.98	45.6 ± 3	0.33	16.4 ± 4	0.19

*P value for comparison between CsA alone and CsA/MTX.
No. indicates the number of patients for which data were available in the registry for analysis.

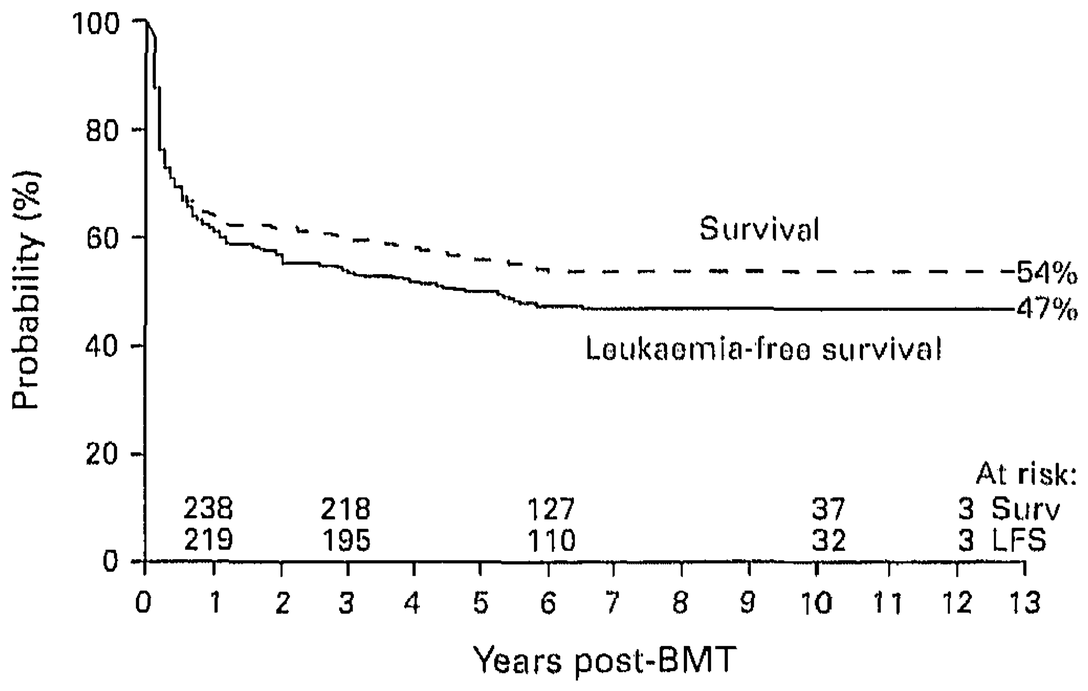

Figure 1 Probability of survival and LFS after HLA-identical sibling BMT for CML in first chronic phase.

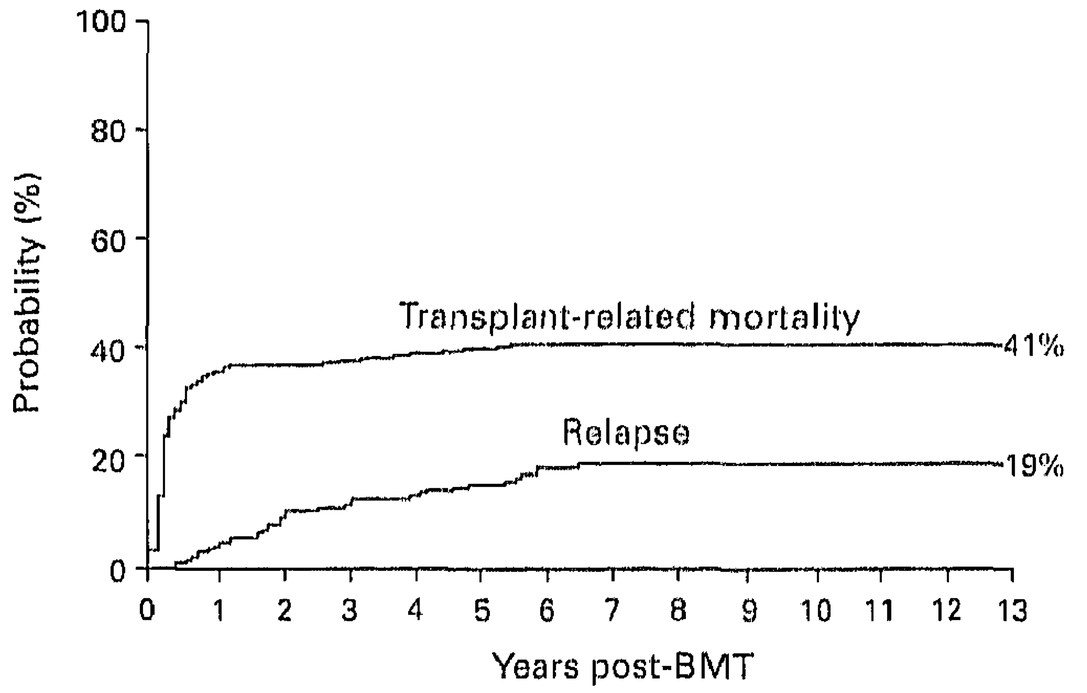

Figure 2 Probability of TRM and relapse after HLA-identical sibling BMT for CML in first chronic phase.

patients had relapse >2 years post-BMT. The latest documented relapse was at 6.5 years. The probabilities of relapse at 2 and 8 years were 10.0% (CI: 7–15) and 18.9% (CI: 14–25) respectively (Table 1 and Figure 2).

Prognostic variables

Male recipients had significantly lower LFS compared to females (40.7 *vs* 54.3%, $P = 0.014$). This could not be attributed to an increase in acute GVHD and both sexes had a similar probability of developing acute GVHD (45.4 *vs*

Table 2 Unadjusted probabilities (± s.e.) for acute GVHD (II–IV) at 100 days and chronic GVHD (limited/extensive) at 4 years after HLA-identical sibling BMT for CML in first chronic phase

	Outcome					
	No.	*Acute GVHD*	*P*	*No.*	*Chronic GVHD*	*P*
Overall	361	46.6 ± 3		230	52.1 ± 3	
Recipient sex						
Male	203	45.4 ± 4		129	50.6 ± 5	
Female	158	48.1 ± 4	0.42	101	53.9 ± 5	0.61
Recipient–donor sex						
M/M	118	44.2 ± 5		80	42.0 ± 6	
M/F	85	47.0 ± 6		49	64.8 ± 7	
F/M	82	53.3 ± 6	0.64	49	49.0 ± 7	0.19
F/F	76	42.4 ± 6		52	58.3 ± 7	
GVHD prophylaxis						
CsA	204	49.8 ± 4		129	58.5 ± 5	
CsA/MTX	135	40.1 ± 4	0.032 (0.0002)[a]	86	40.7 ± 5	0.14 (0.05)[a]
Other	21	57.1 ± 11		15	66.6 ± 12	
Duration of disease						
≤12 months	137	41.2 ± 4		96	46.9 ± 5	
>12 months	216	51.6 ± 3	0.079	133	54.4 ± 4	0.38
Recipient age						
≤20 years	50	45.2 ± 6		32	40.8 ± 9	
>20 years	309	47.1 ± 3	0.63	196	54.1 ± 4	0.59
WBC at diagnosis						
≤30 × 10^9/l	55	37.5 ± 7		37	47.5 ± 8	
>30 × 10^9/l	266	49.8 ± 3	0.078	177	53.7 ± 4	0.39
Donor sex						
Male	200	48.0 ± 4		129	44.7 ± 5	
Female	161	45.8 ± 4	0.33	101	61.3 ± 5	0.036
Donor age						
≤30 years	176	46.0 ± 4		115	49.9 ± 5	
>30 years	174	48.1 ± 3	0.83	115	56.8 ± 5	0.20

[a]*P* value for comparison between CsA alone and CsA/MTX.
No. indicates the number of patients for which data were available in the registry for analysis.

48.1%, $P = 0.42$). The difference in LFS was explained by an increase in both TRM (45.7 *vs* 34.6%, $P = 0.05$) and relapse (23.1 *vs* 14.3%, $P = 0.04$) in males. Patient sex remained a significant variable for both LFS and TRM in multivariate analysis (Table 3).

Recipient–donor sex combinations impacted significantly on transplant outcome after transplant. The LFS of female recipient–female donor pairs was 61.7% compared to only 37.9% for male–male pairs with an intermediate outcome for sex-mismatched combinations (Figure 3). Female–

Table 3 Multivariate analyses-'best' models for various outcomes after stepwise selection procedure

Outcome	*Prognostic variable*	*RR (95% CI)*	*P value*	*Favorable*
LFS[a]	Recipient sex	0.65 (0.49–0.88)	0.0043	Female
	AGVHD	0.36 (0.27–0.49)	0.00001	Grade 0–I
TRM	Recipient sex	0.64 (0.45–0.90)	0.010	Female
	aGVHD	0.25 (0.17–0.37)	0.00001	Grade 0–I
	GVHD prophylaxis	0.71 (0.50–1.01)	0.053	CsA/MTX
aGVHD	GVHD prophylaxis	0.70 (0.50–0.97)	0.028	CsA/MTX
	Duration of disease	0.75 (0.54–1.03)	0.069	≤12 months
cGVHD	GVHD prophylaxis	0.59 (0.39–0.88)	0.008	CsA/MTX
Relapse	Donor sex	0.44 (0.20–0.98)	0.032	Female
	cGVHD	0.33 (0.14–076)	0.0044	Limited/extensive
Early relapse (≤2 years)	cGVHD	0.35 (0.13–0.97)	0.030	Limited/extensive
Late relapse (>2 years)	Donor sex	0.18 (0.04–0.80)	0.006	Female
	cGVHD	0.21 (0.05–0.94)	0.015	Limited/extensive

[a]LFS is the probability of survival without relapse or death.

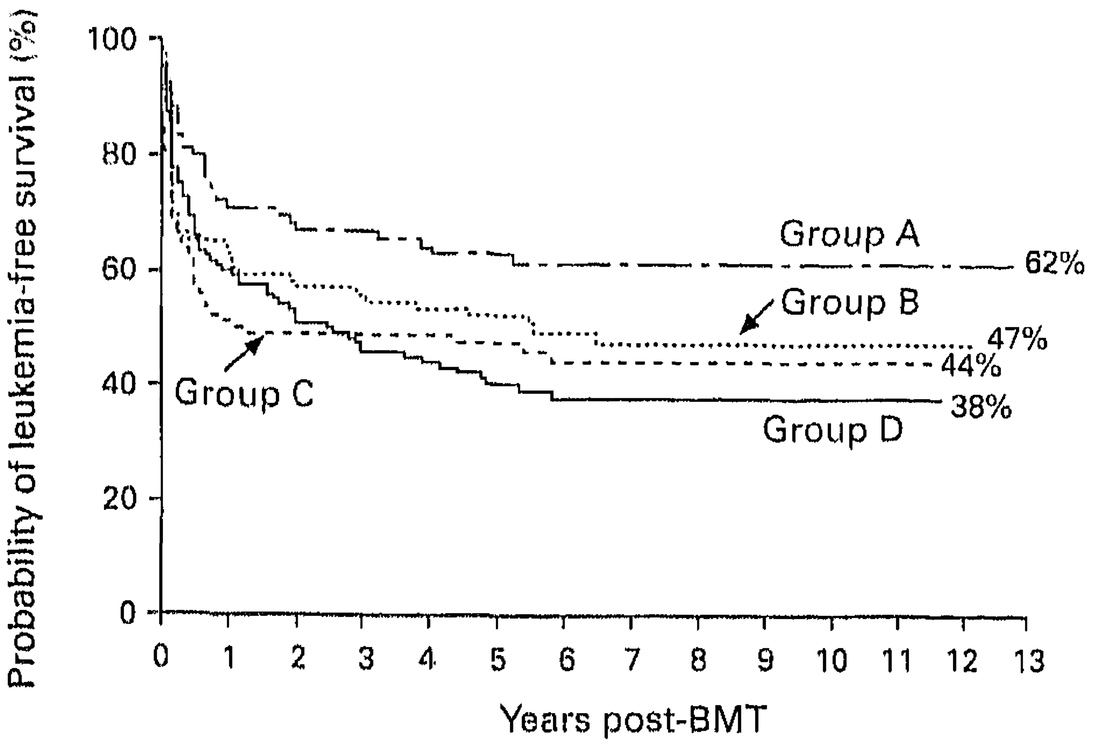

Figure 3 *Probability of LFS after HLA-identical sibling BMT for CML in first chronic phase according to donor/recipient sex. Group A: female donor and recipient ($n = 79$), group B: male donor–female recipient ($n = 86$), group C female donor–male recipient ($n = 88$) and group D: male donor and recipient ($n = 120$).*

female pairs benefited from low TRM (30.0%) and relapse rate (9.1%). In contrast male–male pairs did not only have increased TRM (43.3%), but also experienced more leukemic relapses (31.3%) (Table 1). However, the probability of leukemia relapse was not increased in male–female pairs.

Patients transplanted within 12 months of diagnosis had significantly better LFS (51.9 *vs* 44.2%, $P = 0.03$) which was due to a decrease in TRM (34.3 *vs* 44.6%, $P = 0.013$). There was a trend towards less acute GVHD if the transplant was carried out within 1 year of diagnosis (41.2 *vs* 51.6%, $P = 0.079$). The combined impact of duration of disease and GVHD prophylaxis (CsA only *vs* CsA/MTX) on LFS was also studied, but no significant differences were observed.

Acute GVHD grade II–IV affected LFS adversely in multivariate analysis (RR = 0.36, $P = 0.00001$) which was due to a significant increase in TRM (II–IV *vs* 0–I, RR = 4.0). Recipient age did not influence the probabilities of acute GVHD II–IV or chronic GVHD. There was a trend towards improved survival if the transplant was carried out with immunosuppression consisting of CsA/MTX (60.9 *vs* 50.3%, $P = 0.06$). However, there was no significant difference in LFS (50.0 *vs* 44.7%, $P = 0.18$) between the CsA and CsA/MTX group. GVHD prophylaxis with CsA/MTX reduced both acute GVHD (49.8 *vs* 40.1%, $P = 0.0002$) and TRM (45.5 *vs* 32.9%, $P = 0.04$) in comparison to CsA only. In multivariate analysis the risk of developing acute GVHD II–IV remained reduced in the CsA/MTX group (CsA *vs* CsA/MTX; RR = 0.7, $P = 0.028$) and was also associated with less TRM (RR = 0.71, $P = 0.53$). However, the relapse rate in patients treated with CsA/MTX was significantly increased (25.6 *vs* 13.4%, $P = 0.02$) (Figure 4). There was also a difference in chronic GVHD, but this was of borderline significance ($P = 0.05$).

Chronic GVHD and male donor sex were significant independent variables for relapse in the proportional hazards model (Table 3). Chronic GVHD (limited/extensive) reduced the relative risk of both early and late relapse (RR = 0.35, $P = 0.03$ and RR = 0.21, $P = 0.015$, respectively). Male donor sex was a significant variable for late relapse

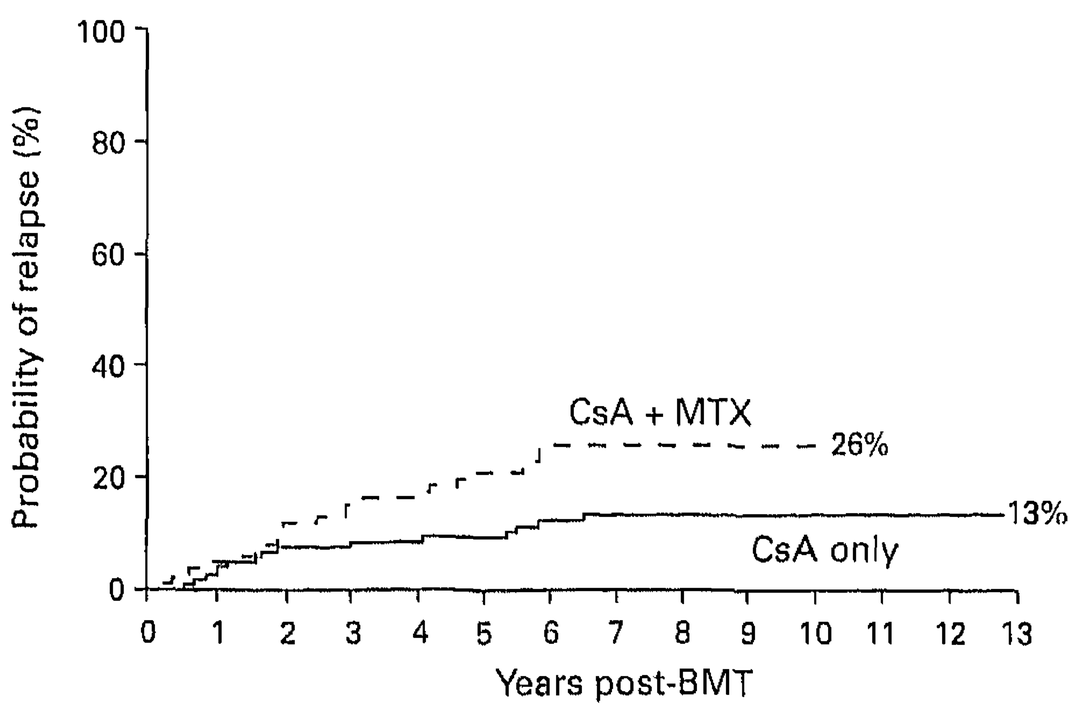

Figure 4 Relapse after HLA-identical sibling BMT for CML in first chronic phase according to GVHD prophylaxis.

(RR = 5.5, $P = 0.006$). Fourteen of the 16 patients with late relapse were transplanted from a male donor. The combined influence of these variables was that patients with no chronic GVHD and a male donor had an overall probability of relapse of 34.9% compared to only 5.1% for those with any chronic GVHD and a female donor ($P = 0.001$) (Figure 5). The duration of disease prior to transplant did not affect relapse, even if the analysis was confined to patients with no acute or chronic GVHD. The probabilities of 3-year survival after early and late relapse had occurred were 38.0% (CI. 21–57) and 70% (CI: 44–88), respectively.

RT/PCR for BCR/ABL fusion gene

Sixty-seven patients were studied by two-step RT/PCR for BCR-ABL mRNA at a median of 114 months post-BMT (range: 34–161). These patients were tested in eight different centers (Appendix 1). Sixty-one patients (91%) were PCR negative when last tested. Six patients were PCR positive at 39, 77, 84, 86, 126 and 138 months post-BMT. These patients remain in complete remission as defined in the Materials and methods section.

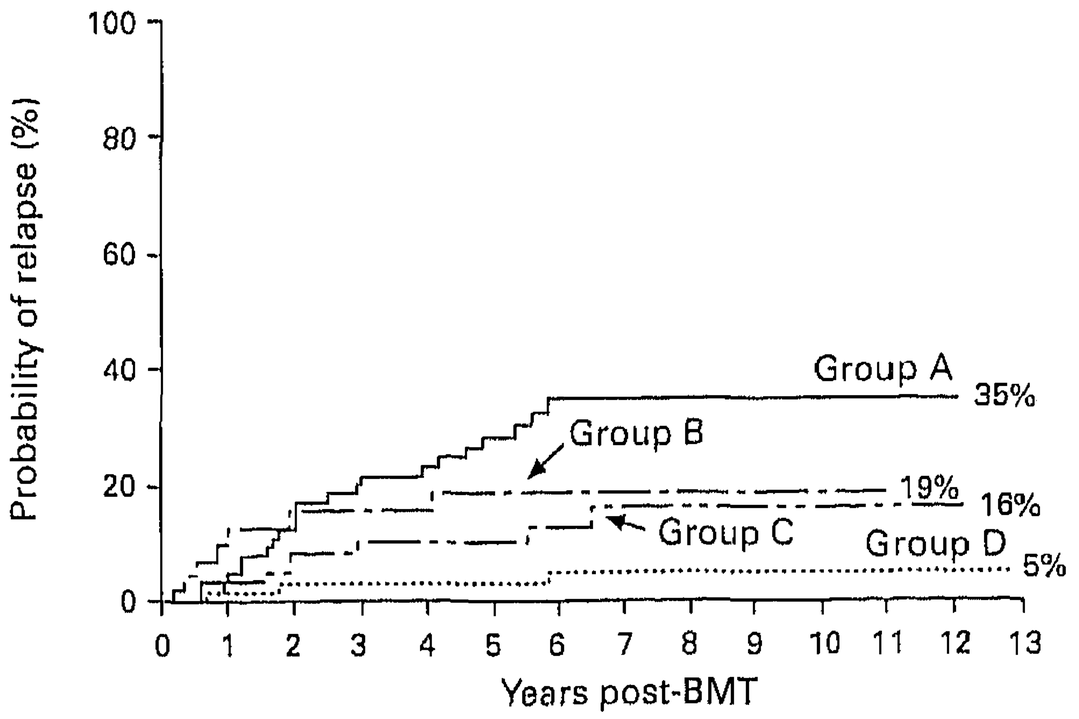

Figure 5 Relapse after HLA-identical sibling BMT for CML in a first chronic phase according to donor sex and chronic GVHD. Group A: male donor–no cGVHD ($n = 73$), group B: female donor–no cGVHD ($n = 41$), group C: male donor–limited or extensive cGVHD ($n = 72$) and group D: female donor–limited or extensive cGVHD ($n = 82$).

Discussion

The present study of a large, homogeneous cohort of patients with CML in first chronic phase indicates that allogeneic marrow transplantation results in long-term disease-free survival in nearly half of the patients. This data is similar to the outcome reported in other large series.[13,14] The median survival in this study had not yet been attained at 8 years. This compares favorably to median survivals ranging from 66 to 72 months reported in recent large scale studies of patients treated conservatively with interferon-α.[15–17] Furthermore, over 90% of patients tested were negative for the leukemia-specific BCR-ABL fusion message by RT/PCR. This is in contrast to the findings during interferon-α therapy where molecular studies can detect persisting leukemia cells in virtually all patients.[18–20] The data from this multicentre study support the notion that allogeneic marrow transplantation is the only therapy which can restore normal hematopoiesis to a substantial number of patients with CML.

The present study reports parameters which influence LFS and which may assist in the timing of transplant and donor selection. Recipient sex and acute GVHD proved to be significant determinants of LFS in multivariate analysis. Female recipients who did not develop acute GVHD (II–IV) post marrow transplant achieved a leukemia-free survival of nearly 70%. Conversely, a LFS of only 38% was observed in male recipients of male donor marrow which was due to an increase in both TRM and rate of leukemic relapse. The optimal timing of the transplant was found to be within 1 year from diagnosis where a small, but significant survival benefit was observed, primarily due to a reduction in TRM. However, we could not confirm previous findings that this survival benefit was particularly evident in patients who received CsA/MTX as GVHD prophylaxis.[13,21]

It has been previously reported that transplantation for CML in accelerated or blastic phase carries an increased risk of leukemic relapse.[8] In the present study, which was confined to CML in chronic phase, the probability of leukemic relapse was 19%. Disease-related variables, such as WBC at diagnosis, were not associated with relapse, even if the analyses were adjusted for the method of GVHD prophylaxis and the incidence of acute or chronic GVHD. However, chronic GVHD and male donor sex were strongly associated with relapse. The probability of relapse for patients transplanted with marrow cells from a female donor and who developed chronic GVHD was only 5%. In contrast, the relapse rate in patients with a male sibling donor and no subsequent chronic GVHD reached 35%. Interestingly, the absence of chronic GVHD was a risk factor for both early and late relapse, whilst male donor sex only increased the risk of late relapse. It was particularly striking that 14 out of 16 patients who relapsed more than 2 years after transplant were transplanted with marrow cells from a male donor. The increased number of late relapses observed with the use of male donors could not only be accounted for by a reduction in chronic GVHD for both factors proved significant in multivariate analysis. These findings support the idea that immunological control of residual leukemia by donor cells is of paramount importance to prevent relapse of CML after marrow transplant. It seems reasonable to speculate that the low relapse rate in male–female pairs is due to recognition of the Y minor histocompatibility antigen on leukemia cells by lymphoid cells from the female donor. Surprisingly, a low relapse rate was also observed in female–female pairs, which could be due to recognition of antigenic differences by female donor cells previously sensitized during pregnancy. However, it should be acknowledged that the registry did not contain details of the pregnancy record of the donors which would have allowed for testing of this hypothesis.

We observed that patients who were surviving more than 2 years post-BMT continued to relapse at a rate of approximately 1.5% per year until 6.5 years when the last relapse was observed. Late relapses after marrow transplant for CML may be more frequent than has been assumed hitherto. Enright *et al*[22] reported six relapses more than 5 years post-BMT in a cohort of 179 patients transplanted from a sibling donor. These findings imply that continued monitoring for late disease recurrence is warranted. In our study residual leukemia cells were found by RT/PCR for the BCR-ABL gene rearrangement in approximately 10% of disease-free survivors. Molecular quantification of residual disease in two of these long-term survivors confirmed that the leukemic clone persisted at low levels more than 10 years after transplant.[23] However, it is at present not certain if these patients indeed harbor Philadelphia-positive clonogenic precursor cells and if these patients are still at risk of relapse. Recently, attention has been drawn to the detection of the BCR-ABL fusion message in apparently normal individuals. If proven correct, this observation casts doubt on the significance of positive PCR findings in long-term survivors of marrow transplantation.[24]

GVHD and/or interstitial pneumonitis were responsible for 54% of all deaths. The current study confirms that post-transplant immunosuppression with CsA/MTX is more effective in reducing acute GVHD and TRM compared to GVHD prophylaxis with CsA only.[1,2] Although there was a trend towards better survival in the CsA/MTX group, these benefits did not translate into an improved LFS due to an increased relapse rate. New therapeutic approaches for the management of relapse have become available in recent years. The initial experience with adoptive immunotherapy consisting of lymphocyte transfusion from the original marrow donor suggest that approximately 70% of patients with relapsing disease can be salvaged. It seems likely therefore that in coming years more emphasis will be placed on reducing GVHD and acute toxicity at the time of the *per primum* transplant procedure with the option of subsequent immune modulation with donor cells in case of relapse. The present cohort did not have the benefit of recent advances in the management of cytomegalovirus infection which is an important cause of interstitial pneumonitis after transplant.[25] Early detection and effective treatment of reactivation of cytomegalovirus with ganciclovir has now become common practice and will serve to prevent CMV pneumonitis and further improve outcome in future transplant cohorts.

Acknowledgements

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