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Results of allogeneic bone marrow transplantation for acute leukemia have improved in Europe with time – a report of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

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Summary:

To evaluate whether the results of bone marrow transplantation have improved in Europe with time, we analyzed the outcome for 2195 patients with acute leukemia. 1405 had acute myeloid leukemia (AML) and 790 had acute lymphoblastic leukemia (ALL), and were allografted in first complete remission between September 1979 and December 1991 with marrow from an HLA-identical sibling donor. We found a continuing improvement more evident since 1987 for AML and since 1986 for ALL. A substantial reduction in the 3 years transplant related mortality (TRM): 26 *vs* 39% for AML ($P = 10^{-4}$), and 25 *vs* 39% for ALL ($P = 10^{-4}$), has resulted in an increase of the 5-year actuarial leukemia-free survival (LFS). 57 *vs* 45% for AML ($P < 10^{-4}$) and 54 *vs* 45% ($P = 10^{-4}$) for ALL. Four important changes have occurred. (1) Graft-versus-host disease (GVHD) prevention has involved an increased use of cyclosporin A (CsA) alone and subsequently its use in combination with methotrexate: this was associated with lower TRM both in AML and ALL; (2) Use of total body irradiation as pretransplant regimen has decreased; (3) a shorter interval from remission to BMT is more common; (4) an older population of patients has undergone BMT. Multivariate analyses were performed separately in AML and ALL. In AML four variables significantly influenced TRM favorably: year of BMT ($P = 10^{-4}$), younger age at BMT ($P = 10^{-4}$), prevention of GVHD including CsA ($P = 0.008$), sex match other than female donor to male recipient ($P = 0.002$). The relapse incidence (RI) was lower in patients with FAB M1-2-3 *vs* M4-5 ($P = 0.0004$). The LFS improved by year of BMT ($P = 0.0004$), younger age at BMT ($P = 10^{-4}$), prevention of GVHD including CsA ($P = 0.01$), FAB M1-2-3 ($P = 0.03$). In ALL, three variables were associated with a lower TRM: year of BMT ($P = 10^{-4}$), younger age at BMT ($P = 10^{-4}$), sex combination other than female to male ($P = 0.008$). The LFS was better after 1986 ($P = 0.0004$) and in younger patients ($P = 10^{-4}$). However a better outcome after 1986/87 was observed in patients receiving the same GVHD prophylaxis: therefore, other unidentified factors resulting in better patient care have also contributed to this. The improved results of allogeneic BMT are entirely related to a reduction in TRM without loss of the antileukemic effect since relapse incidence has not changed over the years.

Keywords: allogeneic BMT; acute leukemia; improvement; EBMT

In the last 15 years allogeneic bone marrow transplant has been increasingly used in patients with acute leukemia with an HLA compatible sibling.[1–3] This approach significantly reduces the risk of relapse in some diseases. However, transplant related mortality has limited benefit, giving rise to debate on merit of BMT particularly in first remission[4–6] since improved results have also been reported with chemotherapy[7–9] or autologous bone marrow transplantation.[10–13] There is currently no consensus on how to treat patients in first remission; several randomized trials have been devised to compare the three modalities: allogeneic BMT, autologous BMT and chemotherapy.[13]

We report a retrospective analysis of patients with acute leukemia in first remission (CR) in which we evaluated the outcome of allogeneic BMT in Europe with time.

Patients and methods

The Acute Leukemia Working Party of the European Group for Bone Marrow Transplantation (EBMT) has collected data from European centers since 1979. Data on patient and donor age and sex, patient disease, stage of the disease, date of transplant (BMT), details on conditioning regimen, method of graft-versus-host disease (GVHD) prophylaxis, incidence of acute and chronic GVHD, relapse, and final outcome were obtained from each center for every patient by annual questionnaire. Information on surviving patients is updated every year.

The present analysis concerns 2195 patients, 1405 with acute myeloid leukemia (AML) and 790 with acute lym-

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phoblastic leukemia (ALL) ($n = 790$) allografted in first remission from September 1979 to December 1991 using an HLA-identical sibling donor.

The endpoints of the study were leukemia-free survival (LFS), relapse incidence (RI) and transplant related mortality (TRM).

LFS was defined as survival without evidence of leukemia.

TRM was defined as death while in complete remission; patients were censored at time of relapse or lost to follow-up.

For the RI, patients dying of either direct toxicity of the procedure or any other cause not related to leukemia were censored.

All analyses were performed with the BMDP statistical package. Differences between groups were studied using the χ^2 statistics for qualitative variables. Kaplan–Meier curves for LFS, RI, and TRM were calculated using the product-limit method.[14] The results were expressed as percentage ± standard error. The significance of differences between the curves was estimated by the log-rank test (Mantel–Cox). We analyzed AML and ALL separately.

We evaluated the influence on LFS, RI and TRM of several characteristics of the disease by univariate analysis: year of transplant, age, sex, FAB classification for AML, interval between diagnosis and BMT, pretransplant regimen (total body irradiation (TBI) *vs* no TBI), sex match, GVHD prevention (cyclosporin A (CsA), methotrexate (MTX), CsA-MTX, T depletion, other), score of acute GVHD (0–1 *vs* > 1), incidence of chronic GVHD.

All variables differing significantly between the two groups were included in a multivariate analysis.[15] In multivariate analysis the year of transplant was analyzed as a continuous variable.

Results

Improvement with time

We analyzed the outcome for patients year by year, and although we have found a continuous improvement over the years, a more consistent improvement in the results was recorded since 1987 for AML and since 1986 for ALL (Table 1). To assess the reason for this improvement, we compared the characteristics of the patients in the two cohorts: For AML, 648 patients were grafted before 1987 and 757 after 1987. For ALL, 248 patients were grafted before 1986 and 542 after 1986. For AML, the TRM at 3 years decreased from 39% before 1987 to 26% after 1987 ($P < 10^{-4}$). The LFS increased from 45% before 1987 to 57% after 1987 ($P < 10^{-4}$) (Figure 1). For ALL, the TRM at 3 years decreased from 39% before 1986 to 25% after 1986 ($P < 10^{-4}$) and the LFS increased from 45% before 1986 to 54% after 1986 ($P = 0.004$) (Figure 2).

The relapse incidence did not change over the years either in AML or ALL (Figures 3 and 4, respectively).

Table 1 LFS and TRM 2 years after allogeneic BMT according to the year of transplant

	AML			*ALL*		
	No. of patients	*LFS*	*TRM*	*No. of patients*	*LFS*	*TRM*
<1982	114	45 ± 5	44 ± 5	18	39 ± 11	48 ± 12
1982–84	240	47 ± 3	39 ± 3	143	48 ± 4	43 ± 4
1985	149	50 ± 4	33 ± 4	87	52 ± 5	37 ± 5
1986	145	49 ± 4	35 ± 4	83	60 ± 5	23 ± 5
1987	136	55 ± 4	29 ± 4	104	50 ± 5	21 ± 4
1988	188	58 ± 4	26 ± 3	96	60 ± 5	24 ± 4
1989	133	65 ± 4	18 ± 3	77	61 ± 6	24 ± 5
1990	148	65 ± 4	17 ± 3	83	58 ± 6	19 ± 4
1991	152	54 ± 5	25 ± 4	99	53 ± 6	33 ± 6
1992	106	70 ± 6	19 ± 5	92	65 ± 5	23 ± 6

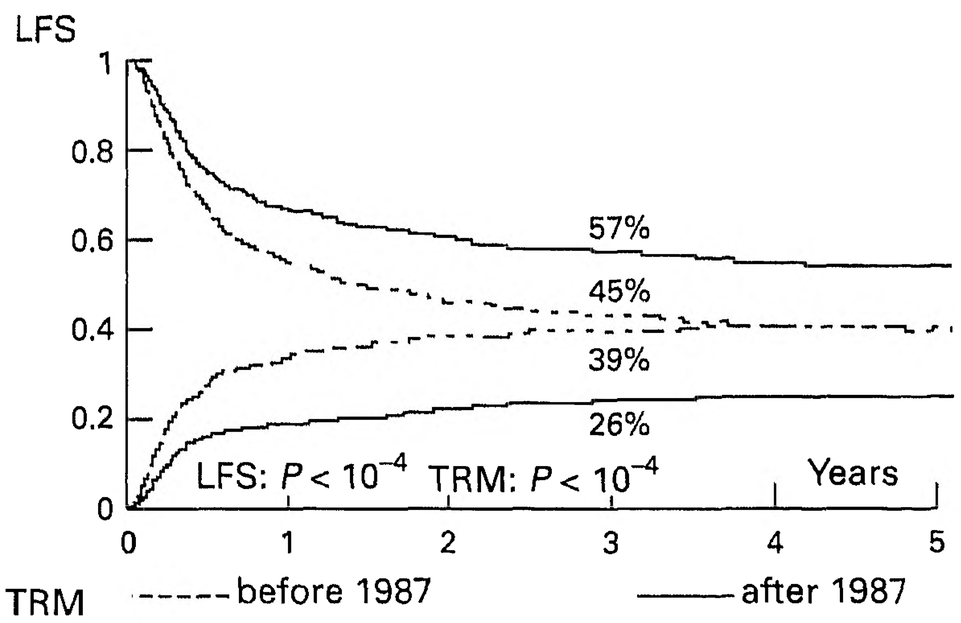

Figure 1 Leukemia-free survival and transplant-related mortality of patients with AML allografted in CR1.

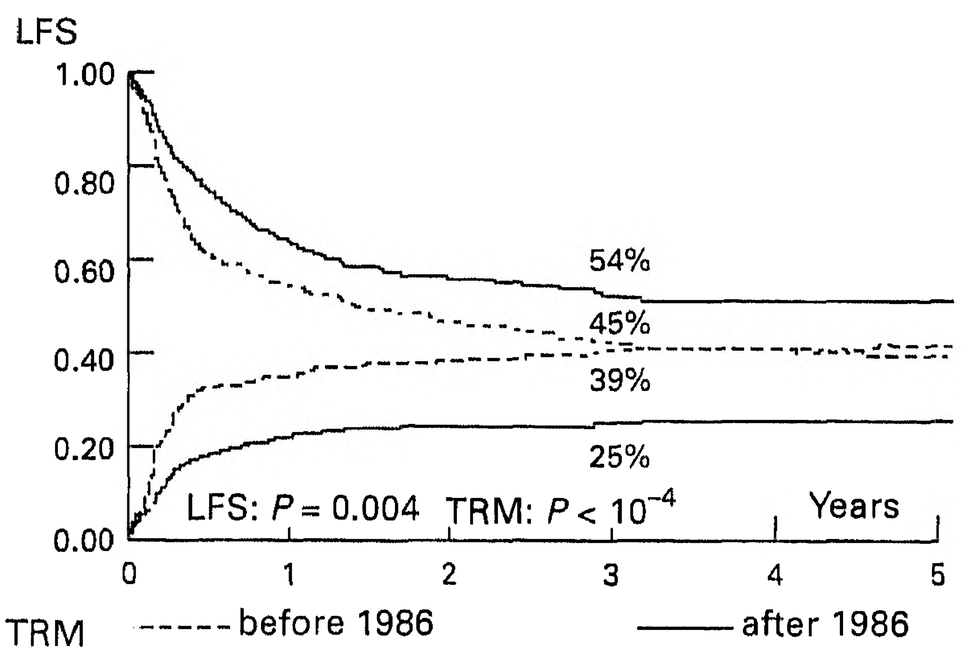

Figure 2 LFS and TRM of patients with ALL allografted in CR1.

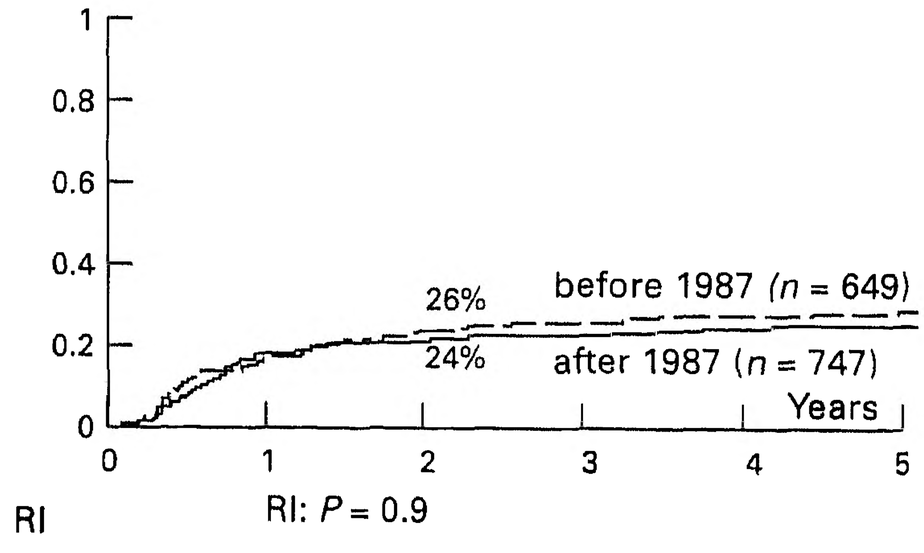

Figure 3 Relapse incidence in patients allografted for AML in CR1.

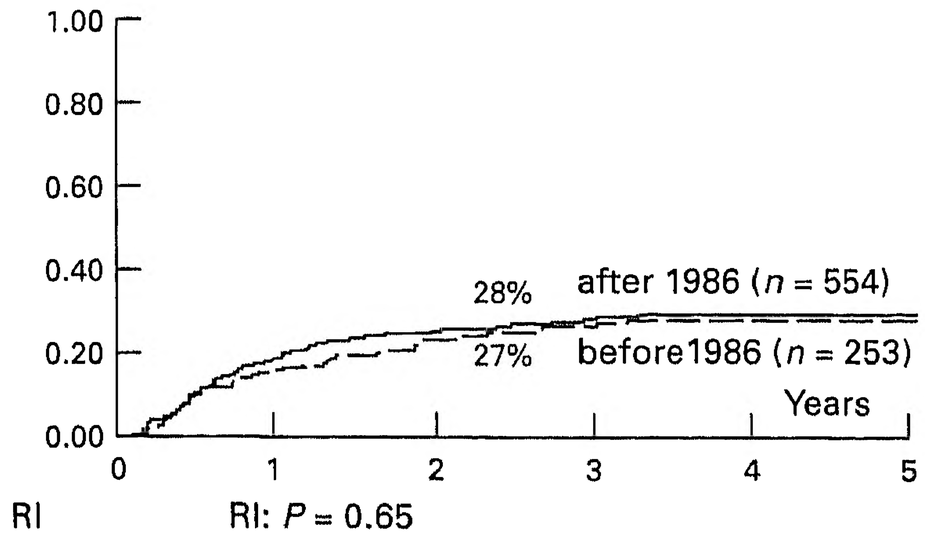

Figure 4 Relapse incidence in patients allografted for ALL in CR2.

Changes in treatment strategies

The two cohorts of patients differed in four characteristics (Table 2 and 3): in the second period, patients were older, the interval from diagnosis to BMT was shorter, TBI was used less frequently, and GVHD prophylaxis consisted of more CsA + MTX. The distribution of other variables was even, including the time to reach CR, and use of T cell depletion.

Univariate analysis

By univariate analysis, we evaluated the influence on LFS, RI and TRM of several disease characteristics: year of transplant, age, sex, FAB classification for AML, interval between diagnosis and BMT, pretransplant regimen (total body irradiation (TBI) *vs* no TBI), sex match, GVHD prevention (cyclosporin A (CsA), methotrexate (MTX), CsA-MTX, T depletion, other), score of acute GVHD (0–1 *vs* > 1), incidence of chronic GVHD.

Table 2 Distribution of patients with AML allografted in first remission

	Before January 1987	*After January 1987*	P
No. of patients	648	757	
Follow-up (months)	84 (2–167)	29 (1–73)	0.0001
Age at transplant (years)	25(1–52)	29(1–56)	< 0.0001
Sex ratio			
Male	325	392	0.54
Female	323	365	
FAB classification			
M4-5(%)	35	36	0.65
Sex matching (donor–recipient)(%)			
M/M	28	30	0.73
F/M	22	22	
M/F	26	23	
F/F	24	25	
TBI (%)	98	72	< 0.0001
GVHD prevention (%)			
CsA	31	11	< 0.0001
MTX	31	1	
CsA + MTX	6	54	
T depletion ± other	22	20	
Other	10	14	
Interval from diagnosis to BMT (days)	163 (31–3910)	150 (49–3776)	0.01
Acute GVHD score < 1(%)	31	25	0.02
Chronic GVHD(%)	19	11	< 0.0001

Table 3 Distribution of patients with ALL allografted in first remission

	Before January 1986	*After January 1986*	P
No. of patients	248	542	
Follow-up (months)	93(10–168)	38(2–85)	< 0.0001
Age at transplant (years)	21(1–43)	23(1–51)	0.07
Male/female	162/86	360/182	0.76
Sexmatching (donor–recipient) (%)			
M/M	36	37	0.94
F/M	30	28	
M/F	16	18	
F/F	17	17	
TBI (%)	99	94	0.001
GVDH prevention (%)			
CsA	35	9	<0.0001
MTX	23	3	
CsA +MTX	2	49	
T depletion ± other	28	22	
Other	12	16	
Interval from diagnosis to BMT (days)	169(53–2756)	141(57–3595)	0.0004
Acute GVHD score > 1 (%)	28	25	0.29
Chronic GVHD (%)	16	9	0.003

Risk factors for acute myeloid leukemia (AML)

The following prognostic factors were identified in AML: TRM was higher in older patients ($P < 10^{-4}$) and in the female donor to male recipient combination ($P = 0.01$). It was lower in the absence of acute or chronic GVHD ($P < 10^{-4}$) and in patients receiving cyclosporin A alone or combined with methotrexate for GVHD prevention ($P < 10^{-4}$). The RI was higher in M4 and M5 ($P = 0.002$) and in the absence of severe acute ($P = 0.03$) or chronic ($P < 10^{-4}$) GVHD. As a result, a younger age of the recipient, a FAB classification other than M4 and M5, the absence of severe acute GVHD and prevention of GVHD with CsA + MTX, all resulted in a better LFS ($P = 0.0005$, $P = 0.04$, $P < 10^{-4}$, $P < 10^{-4}$, respectively).

Risk factors for acute lymphoblastic leukemia (ALL)

The following prognostic factors were identified in ALL: TRM was higher in older patients ($P < 10^{-4}$) and in the female donor to male recipient combination ($P = 0.008$), and lower in patients receiving CsA alone or in combination with MTX. It was lower in the absence of acute GVHD ($P < 10^{-4}$). The RI was higher in the absence of severe acute ($P = 0.01$) or chronic ($P = 0.04$) GVHD. As a result, a younger recipient age and the absence of severe acute GVHD resulted in better LFS ($P < 10^{-4}$ for both).

Impact of the use of MTX, CsA and CsA + MTX and T cell depletion on TRM, RI and LFS

In AML the actuarial 3 years TRM was 45, 32, 21 and 39% with MTX, CsA, CsA + MTX and T cell depletion

respectively ($P < 10^{-4}$); the RI was not significantly different; the LFS was 43, 49, 62 and 44% ($P < 10^{-4}$).

In ALL the actuarial 3 years TRM was 41, 34, 24 and 29% with MTX, CsA, CsA + MTX and T cell depletion respectively ($P = 0.04$); the RI was 21, 25, 30 and 31% ($P = 0.46$); the LFS was 47, 49, 53 and 49% ($P = 0.27$).

Other reasons for the improvement

To further evaluate whether the improvement with time also resulted from reasons independent of factors that changed over time, we analyzed the outcome of a more homogenous subgroup: patients less than 40 years old receiving the same GVHD prophylaxis.

In AML, comparison of TRM for the two periods in the groups receiving the same prophylaxis, CsA alone and T cell depletion, showed a trend in the direction of a lower TRM in the latter period ($P = 0.053$, $P = 0.06$ respectively). We could not compare the TRM before and after 1987 in patients receiving the CsA + MTX combination because the number of patients treated before 1987 was too small ($n = 37$).

With ALL, comparison of TRM for the two periods in the groups receiving the same prophylaxis showed a significant ($P = 0.02$) reduction in those receiving T depleted marrow and a trend ($P = 0.17$) in those receiving CsA alone. Only six patients received CsA + MTX before 1986, so that evolution of TRM over years for patients receiving this combination was not possible.

Causes of transplant related mortality

We have analyzed, year by year, the following causes of death: interstitial pneumonitis, acute and chronic GVHD, veno-occlusive disease, infection, graft failure and hemorrhagic death. Other less frequent causes were grouped as miscellaneous. The relative distribution of each of these causes of TRM did not vary over the years. Instead, it was global TRM that was reduced.

Multivariate analyses

All variables found to have an impact on outcome and variables differing in distribution among the two cohorts were included in the multivariate analysis: year of BMT, sex, age, interval between diagnosis and BMT, acute GVHD prevention (CsA and CsA + MTX *vs* other), FAB classification for AML (M4-5 *vs* other), TBI (yes *vs* no).

Table 4 summarizes the results of multivariate analyses in AML and ALL. In AML, four variables favorably influenced TRM: year of BMT, younger age at BMT, prevention of GVHD including CsA, sex match other than female donor to male recipient. The RI was lower in patients with FAB M1-2-3 *vs* M4-5. LFS was improved by year of BMT, younger age at BMT, prevention of GVHD including CsA, FAB M1-2-3.

In ALL, three variables were associated with a lower TRM: year of BMT, younger age at BMT, sex combination other than female to male. The LFS was better after 1986 and in younger patients (Table 4).

Discussion

The aim of this study was to determine whether outcome has improved during the last decade for patients with acute leukemia allografted in first remission. There has been a continuous improvement which became more obvious after 1986/7: overall, the chance of being disease-free 5 years after allogeneic BMT using an HLA compatible sibling donor was 57% after 1987 *vs* 45% before 1987 for AML, 54% after 1986 *vs* 45% before 1986 for ALL. This was due to a decrease in TRM with no change in relapse rate. The fact that the European centers succeeded in reducing the toxicity of the procedure without loss of its antileukemic effect should be considered a relevant step forward in the clinical practice of allogeneic BMT. The decrease in TRM itself was at least in part due to to a reduction in the incidence and severity of acute GVHD in AML and chronic GVHD in both AML and ALL. The relative prevalence of the causes of death did not vary over the time period studied; rather, reduction of mortality arose from a global diminution of severe complications of BMT.

Four important changes have occurred: increased use of cyclosporin A, initially alone and subsequently in combination with methotrexate, decreasing use of total body irradiation as pretransplant conditioning, shorter interval from remission to BMT, and an older population of patients undergoing BMT. The older age of patients transplanted after 1986–1987 would have been expected to produce a higher TRM; this was not the case, further emphasizing improvements achieved. Earlier transplantation after 1986–1987 indicates selection of a group of patients, *per se* at greater risk of relapse compared with previous years; instead, there was no increased risk of relapse. Since there is increasing evidence that very prolonged LFS can be obtained in selected AML subgroups with chemotherapy,[21,22] it is likely that in recent years patients undergoing BMT bear worse risk factors than in the previous time cohort. Altogether, these data show that with allogeneic BMT, the interval between diagnosis and BMT does not have the same relevance as in the autografting setting;[10] secondly this was associated with reduced TRM, confirming that a shorter disease duration is associated with lower morbidity at transplant, as already reported for CML patients.[16]

Cyclosporin A alone or in combination with methotrexate was associated with reduced TRM and better LFS. This was observed both in AML and ALL but the effect of the combination of CsA + MTX is more noticeable in AML. Since the introduction of CsA and CsA + MTX is closely linked with year of transplant it is difficult to establish the respective impact on results. Nevertheless, a progressive improvement relating to year of BMT is observed by analyzing only patients who received either CsA alone or those receiving T cell depleted marrow.

Since better GVHD prevention alone did not account for the improvement, it is likely that several factors together account for the more recent improved results. The expertise of individual centers may have improved globally with better supportive care and improved prevention of major complications such as cytomegalovirus,[17] pneumonitis and veno-occlusive disease of the liver. Centers may also have

Table 4 Factors found by multivariate analysis to influence leukemia-free survival, relapse incidence and transplant related mortality in the evolution of allogeneic bone marrow transplantation for acute leukemia in Europe

AML			*ALL*		
Variables	*RR*	P	*Variables*	*RR*	P
LFS					
Year of BMT (continuous)	0.94	<0.0001	Year of BMT (continuous)	0.93	0.01
Age at BMT (continuous)	1.02	<0.0001	Age at BMT (continuous)	1.03	<0.0001
CsA or CsA + MTX *vs* other	0.8	0.02			
M4-5 *vs* other	1.24	0.13			
RI					
M4-5 *vs* other	1.63	< 0.0001	No factor significant		
TRM					
Year of BMT (continuous)	0.89	<0.0001	Year of BMT (continuous)	0.9	<0.0001
Age at BMT (continous)	1.03	<0.0001	Age at BMT (continuous)	1.04	<0.0001
CsA or CsA + MTX *vs* other	0.77	0.03	Female donor to male recipient *vs* other	1.5	0.09
Female donor to male recipient *vs* other	1.47	0.002			

RR = relative risk.

found an optimal balance for combination of conditioning therapy and GVHD prophylaxis.

In this European series of patients, the combination CsA + MTX was not associated with increased risk of relapse: this is in keeping with some[18] and in contrast with other reports.[19] Severe GVHD dramatically increases TRM and, in spite of the beneficial effect of reducing relapse risk it remains associated with poorer LFS.

In keeping with previous reports,[2] the present analysis confirms that BMT is better tolerated by younger patients, that the risk of relapse is higher for M4 and M5 and that the TRM is higher following BMT with a female donor to a male recipient. In this study the subtype M4-5 was also associated with worse LFS.

In conclusion, the present study shows that the outcome for patients with acute leukemia undergoing allogeneic BMT from their HLA identical sibling has improved considerably over the years both in AML and ALL. This confirms the place of allogeneic BMT in the treatment of acute leukemia, and currently about 1/3 patients who complete their post-remission treatment undergo allogeneic transplant.[13] Only the results of allogeneic BMT in the past 5 years should be considered from now on, because of the recent improvements in results. Nonetheless, since other treatment modalities,[10,13,20–23] have also shown improved results, the final 'best choice' therapy still remains a matter of debate.

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