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Syngeneic transplants

Stem cell transplantation from identical twins in patients with myelodysplastic syndromes

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Summary:

In a multicentre retrospective EBMT database study, we analysed factors influencing outcome in 38 patients with MDS/sAML who were transplanted with stem cells from their syngeneic twin and compared those to 1444 patients who were transplanted from an HLA-identical sibling. The median time to leukocyte and platelet engraftment was faster in the twin group: 14 *vs* 17 ($P = 0.02$) and 16 *vs* 26 days ($P = 0.09$), respectively. The 5 years cumulative incidence of treatment-related mortality (TRM) was higher in the sibling than in the twin group (38 *vs* 27%; $P = 0.05$). The 5 year cumulative incidence of relapse was 32% (95% CI: 29–35%) for the siblings and 39% (95% CI: 26–60%; $P = 0.6$) for the twins. A trend for better 5-years disease-free and overall survival was observed in the twin group: 34% (95% CI: 14–54%) *vs* 28% (95% CI: 25–31%; $P = 0.2$) and 36% (95% CI: 15–57%) *vs* 32% (95% CI: 29–35%; $P = 0.09$), respectively. In a multivariate analysis, stem cell transplantation from identical twins had a lower TRM: HR: 0.4 (95% CI: 0.2–0.9; $P = 0.03$). The relapse rate was similar for both groups with a HR of 1.2 (95% CI: 0.07–2.1; $P = 0.5$), with a better survival for the twins: HR 0.6 (95% CI: 0.4–1.0; $P = 0.07$). We conclude that twin transplantation in MDS/sAML is associated with a similar relapse risk, a lower TRM and a trend for better overall survival in comparison to transplantation from HLA-identical siblings.
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The myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders characterized by ineffective haematopoiesis and high percentage of progression to acute myeloid leukaemia. According to the International Prognostic Scoring System, the median survival of patients with MDS ranges between 5 months and 5.7 years.[1] Allogeneic stem cell transplantation is probably the most effective curative approach in these patients, and this treatment should be proposed in younger patients if an HLA-matched donor is available.[2–8] The transplantation of immunocompetent donor lymphocytes might contribute via a graft-versus-leukaemia/MDS effect to the curative potential of this treatment. However, donor lymphocytes may induce graft-versus-host disease which contributes to the high transplant-related mortality (TRM) of up to 60% after allogeneic transplantation in patients with MDS.[3,4,8] In early studies of the International Bone Marrow Transplant Registry, transplantation from an identical twin resulted in significantly less TRM in patients with acute leukaemia and chronic myeloid leukaemia. On the other hand, a higher relapse rate was observed in AML, CML and in ALL resulting in a similar leukaemia-free survival in comparison to HLA-identical siblings since the increased relapse rate in twins is counterbalanced by the higher treatment-related mortality after transplantation from HLA-identical sibling.[9] This retrospective multicenter study compared the results of syngeneic transplantation in MDS patients of the European Blood and Marrow Transplantation Group to the results of patients transplanted from an HLA-identical sibling in terms of relapse, TRM as well as disease-free and overall survival.

Patients and methods

Between 1978 and 2001, 38 patients with myelodysplastic syndromes or secondary AML underwent syngeneic stem cell transplantation and were reported to the EBMT registry. The outcome of these patients was compared to the results of 1444 patients transplanted during the same time period from their HLA-identical sibling. Diagnoses in the twin group were: RA/RARS: 33%; RAEB/CMML: 20%; RAEB-t/sAML: 47%. In the HLA-identical sibling group: RA/RARS: 13%, RAEB/CMML: 25%; RAEB-t/sAML: 61%. Median patient age was 43 years in the twin group and 37 years in the sibling group. Time from diagnosis to transplantation was 7.8 months in the twin group and 9.5 months in the sibling group. At the time of transplantation, 24% in the twin group and 35% in the sibling group were in first complete remission. Peripheral blood stem cells served as graft source in 43% of the twin group and 30% in the sibling group, whereas bone marrow was used in 57% of the twin group and 70% of the sibling group. In all, 36% of the twin group and 48% of the sibling group received a TBI-containing conditioning regimen. Details of the patients from both groups are listed in Table 1.

Study end points

Primary end points of this retrospective study were TRM, relapse rate, disease-free survival and overall survival after syngeneic transplantation in MDS/sAML patients. Haemopoietic recovery of leucocytes and platelets was also described. The secondary aim was to compare the results from identical twin stem cell transplantation with the results from HLA-identical sibling transplantation within a multivariate analysis with respect to TRM, relapse rate, overall and disease-free survival. Haemopoietic recovery was defined as the first of three consecutive days with an absolute neutrophil count of 0.5/nl, the date of platelet recovery was defined as the first of 7 consecutive days with a platelet count >20/nl without transfusion. Criteria for relapse were haematologic relapse. For analysis of disease-free survival, treatment was considered as failure at time of clinical or haematological relapse or at the time of death from any cause. Patients who were alive and in complete remission were censored at time of last follow-up; for overall survival, the event was death from any cause. Surviving patients were censored at the date of last contact.

Statistical analyses

Time intervals for survival, relapse-free survival, relapse rate and TRM were calculated and expressed as the number of months between stem cell transplantation and the event of interest. For the Kaplan–Meier curves (used in univariate descriptions) and Cox models (used to estimate hazard ratio's) relapsed patients were censored for TRM at time of relapse and *vice versa*. Univariate comparison of Kaplan–Meier curves was performed using the two-tailed log-rank test. For ordered categorical variables, the trend version of the log-rank test was used. The association of various risk factors such as age, remission status at transplantation, stem cell source, time from diagnosis to transplantation, stage of the disease and TBI containing conditioning with the outcomes OS (overall survival), RFS (relapse-free survival), RI (relapse incidence) and TRM (transplant-related mortality) was quantified using the hazard ratio's estimated in Cox models.

For the purpose of comparison with other publications and to obtain valid (nonbiased) estimates for the actual probability of the competing risks of relapse and death in remission, estimates for RI and TRM were made using cumulative incidence estimates. The sum of the RI and TRM cumulative incidences equals (complement of the) RFS. Calculations were performed in SPSS version 11. The

Table 1 Characteristics of MDS/sAML patients transplanted with stem cells from an identical twin or HLA-identical sibling

	MDS in twins n = 38	*MDS in siblings n = 1444*	*P-value*
Classification			
RA/RARS	$n=10$ (33%)	$n=191$ (13%)	0.06
RAEB/CMML	$n=6$ (20%)	$n=366$ (25%)	
RAEB-t/sAML	$n=14$ (47%)	$n=887$ (61%)	
Missing	$n=8$		
Mean age (years)	43.5 (6–71)	37.3 (1–69)	0.01
Interval Dx–Tx (mean)	7.8 months	9.5 months	0.3
CR_1 at transplantation	24% ($n=8$)	35% ($n=466$)	0.2
No CR at transplantation	76% ($n=25$)	65% ($n=871$)	
Peripheral blood stem cells	43% ($n=17$)	30% ($n=421$)	0.07
Bone marrow	57% ($n=21$)	70% ($n=1007$)	
Conditioning			
TBI	36% ($n=13$)	48% ($n=664$)	0.2
Non-TBI	64% ($n=21$)	52% ($n=719$)	

RA = refractory anaemia; RAEB = refractory anaemia with excess of blasts; RAEB-t = refractory anaemia with excess of blasts in transformation; sAML = secondary acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; Dx = diagnosis; TX = transplantation; CR = complete remission; TBI = total body irradiation; MDS = myelodysplastic syndrome.

cumulative incidences were calculated in NCSS version 2001.

Since the hazard ratio's of the various risk factors involved in the analyses can be validly estimated using the Cox model, all inferences in univariate and multivariate analyses concerning such risk factors are performed in the framework of Cox models. The cumulative incidence approach is not really needed (nor currently feasible) when estimating the relative effect of the risk factor multivariately: only when estimating the height of the survival curve itself, does one have to revert to the cumulative incidence estimate of that curve. Hence, the sections on relapse and death-in-remission start with the (10 year) cumulative incidence estimates but revert to the usual K–M and Cox estimates when addressing the relative effects of the various risk factors.

Comparison of baseline characteristics and risk factors between twins and siblings was done by a *t*-test for continuous variables and a χ^2-test for categorical ones. All tests are two-sided and use a cutoff value of 0.05 for significance.

Results

Engraftment

One graft failure (3%) was observed in the twin group and 88 graft failures (6%) in the sibling group (n.s.). Haematopoietic engraftment was observed in 95% in the twin group and in 92% in the sibling group. The median time to achieve a neutrophil count $\geqslant 0.5$/nl was 14 days in the twin group and 17 days in the sibling group ($P = 0.02$). A sustained platelet count $\geqslant 20$/nl was reached after a median of 16 days in the twin group and 26 days in the sibling group ($P = 0.09$) (see Table 2).

Transplant-related mortality

Based on a cumulative incidence calculation in a competing risk setting (for relapse and death-in-remission), the 5-year cumulative incidence for TRM (=death-in-remission) is 38% (95% CI: 36–41%) for the siblings and 27% (95% CI: 13–55%) for the twins. Figure 1 shows these estimates together with those for relapse incidence.

All other estimates below are based on Kaplan–Meier and Cox survival analyses (Figures 2–6).

The hazard ratio for TRM comparing the twins to the siblings was (univariately) 0.49 (95% CI: 0.23–1.0), $P = 0.06$ indicating a two-fold reduction in TRM rate among twins compared to siblings. After multivariate adjustment for age, source of stem cells, stage, interval diagnosis-transplant and TBI the estimated TRM was significantly lower in the twins (HR = 0.42, 95% CI: 0.20–0.89, $P = 0.03$).

In the twin group, TRM was mainly due to multiorgan failure and bacterial/fungal infections. Within the twin group, there was a trend to a higher TRM in patients conditioned with a TBI-containing regimen (62 *vs* 20%) ($P = 0.09$). In the twin group neither stem cell source, stage

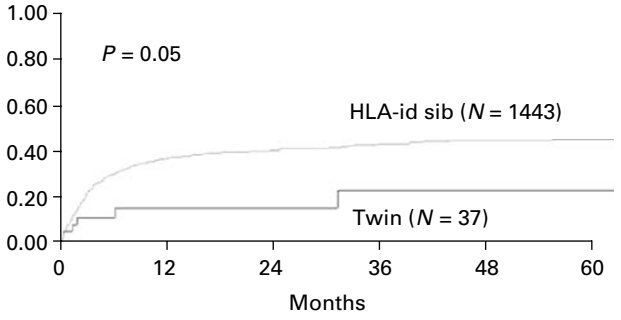

Figure 1 Transplant related mortality after stem cell transplantation from twin or HLA-identical sibling.

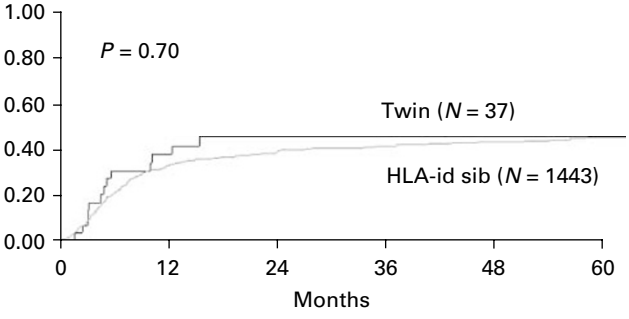

Figure 2 Incidence of relapse.

Table 2 Results

	MDS in twins n = 38	*MDS in siblings n = 1444*	*P-value*
Graft failure	3% ($n = 1$)	6% ($n = 88$)	0.5[a]
Engraftment	95% ($n = 34$)	92% ($n = 1266$)	
Days until leucocytes >1.0/nl (median)	14 days	17 days	0.02[b]
Days until platelets >20/nl (median)	16 days	26 days	0.09[b]
7-year probability of overall survival	36% (95% CI: 15–57)	32% (95% CI: 29–35%)	0.09[c]
Median survival (months)	41 months	14 months	
5-year cumulative incidence of TRM	27% (95% CI: 13–55%)	38% (95% CI: 36–41%)	0.05[c]
5-year cumulative incidence of relapse	39% (95% CI: 26–60%)	32% (95% CI: 29–35%)	0.6[c]
5-year probability of disease-free survival	34% (95% CI: 14–54%)	28% (95% CI: 25–31%)	0.2[c]

[a]χ^2-test;
[b]Mann–Whitney test;
[c]Log-rank test.

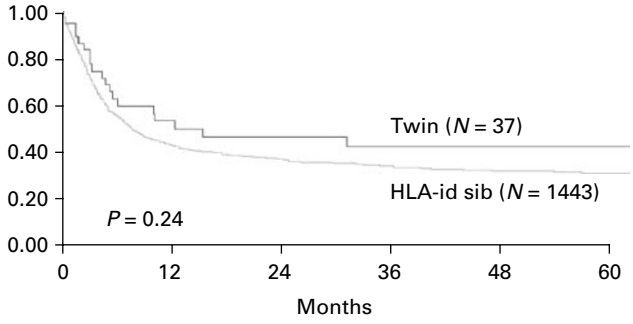

Figure 3 Disease-free survival.

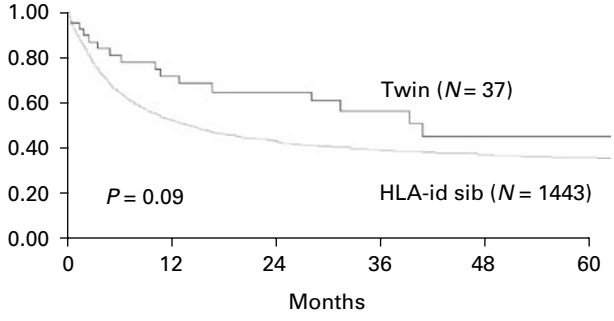

Figure 4 Overall survival.

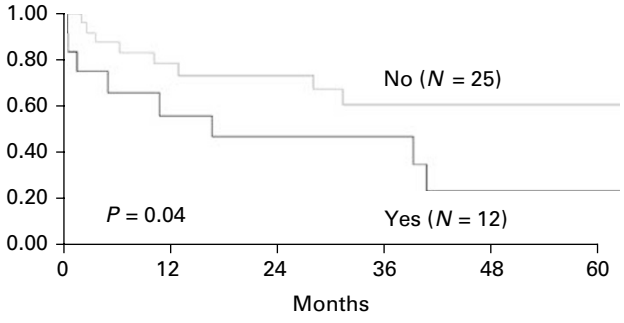

Figure 5 Overall survival after stem cell transplantation in twins according to TBI containing conditioning regimen.

of disease (RA/RARS *vs* RAEB/CMML *vs* RAEB-t/sAML), time from diagnosis to transplant (< *vs* >6 months) or being in first complete remission *vs* nonbeing in first complete remission influenced the TRM (Table 2). In a multivariate analysis including the HLA-identical sibling transplants, TRM was significantly lower in the twin group (HR: 0.4: 95% CI: 0.2–0.9; $P=0.03$) and in patients who were transplanted with peripheral blood stem cells as the stem cell source (HR: 0.8: 95% CI: 0.6–0.96; $P=0.02$). TRM increased with patient age (HR 1.02: 95% CI: 1.021–1.028; $P\leqslant0.001$) (see Tables 2–4).

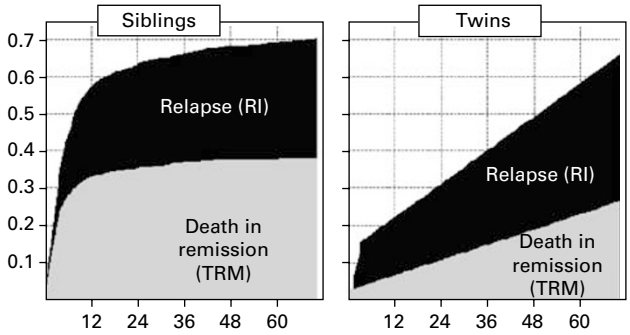

Figure 6 Cumulative incidence estimates using a competing risk model for relapse and death in remission.

Relapse

Based on a cumulative incidence calculation in a competing risk setting (between relapse and death-in-remission), the 5-year cumulative incidence for relapse (=relapse incidence) is 32% (95% CI: 29–35%) for the siblings and 39% (95% CI: 26–60%) for the twins ($P=0.6$).

All other estimates below in this section are based on Kaplan–Meier and Cox survival analyses.

The hazard ratio for relapse comparing the twins to the siblings was (univariately) 1.1 (95% CI: 0.64–1.9), $P=0.70$ indicating a virtually identical relapse rate among twins and siblings. After multivariate adjustment for age, source of stem cells, stage, interval diagnosis-transplant and TBI the estimated was virtually the same (HR = 1.2).

Within the subgroup of twins a univariate analysis showed that early transplantation (< *vs* >6 months after diagnosis) was associated with an increased relapse rate (58 *vs* 20%) ($P=0.03$), while TBI- or non-TBI-containing conditioning regimens, stem cell source, stage of disease (RA/RARS *vs* RAEB/CMML *vs* RAEB-t/sAML) or complete *vs* noncomplete remission at time of transplantation did not influence relapse rate in the twin group. The relapse rate in patients who were transplanted with stem cells from an HLA-identical sibling was almost identical at 45% (95% CI: 41–49%) ($P=0.6$). Within a multivariate analysis of all patients, relapse rate was influenced by stage of disease (RAEB-t/sAML: HR 2.57: 95% CI: 1.8–3.7; $P\leqslant0.01$) and by the use of PBSC as stem cell source (HR 0.73: 95% CI: 0.6–0.9; $P=0.01$). Furthermore, increasing age significantly influenced relapse rate (HR 1.01: 95% CI: 1.0–1.03; $P=0.001$). Having an identical twin as donor did not significantly influence relapse rate on multivariate analysis significantly (HR 1.2: 95% CI: 0.07–2.1; $P=0.5$) (see Tables 2–4).

Disease-free survival

There was a trend to better 5-years disease-free survival in the twin group in comparison to the sibling group: 34 (95% CI: 14–54%) *vs* 28% (95% CI: 25–31%) ($P=0.2$). Within the twin group neither conditioning regimen, source of stem cells, stage of disease, time of transplantation or disease status at transplantation had a significant negative influence on disease-free survival. In a multivariate analysis

Table 3 Univariate analysis of outcome after transplantation from an identical twin 5 years after transplantation

	N	*OS (5-years) (%)*	*P-value*	*TRM (5 years) (%)*	*P-value*	*Relapse (5 years) (%)*	*P-value*	*DFS (5 years) (%)*	*P-value*
TBI	12	11	0.03	62	0.09	62	0.3	10	0.07
Non-TBI	25	61		20		35		50	
PBSC	16	45	0.8	34	0.7	35	0.7	42	0.9
BM	21	35		37		48		32	
RA/RARS	13	40	0.6	33	0.2	40	0.9	40	0.6
RAEB/CMML	6	35		38		60		24	
RAEB-t/sAML	14	40		34		45		37	
DX to TX									
< 6 months	23	20	0.5	55	0.5	58	0.03	20	0.2
>6 months	14	55		35		20		55	
CR_1	8	50	0.8	30	0.5	45	0.9	40	0.9
Untreated	11	45		18		55		50	
Others	14	40		15		35		38	

OS = overall survival; TRM = treatment-related mortality; DFS = disease-free survival.

Table 4 Multivariate analysis of all patients including twins (OS, DFS, TRM, relapse)

	Overall survival		*Disease-free survival*		*TRM*		*Relapse*	
	HR (95% CI: %)	*P-value*	*HR (95% CI: %)*	*P-value*	*HR (95% CI: %)*	*P-value*	*HR (95% CI: %)*	*P-value*
Twin transplantation	0.6 (0.4–1.0)	0.07	0.73 (0.48–1.15)	0.12	0.43 (0.2–0.9)	0.03	1.2 (0.7–2.1)	0.5
PBSC	0.8 (0.7–0.9)	0.04			0.783 (0.6–0.96)	0.02	0.73 (0.6–0.9)	0.01
RAEB-t/sAML	1.3 (1.07–1.63)	0.01	1.37 (1.12–1.68)	0.003			2.57 (1.8–3.7)	<0.001
Age	1.02 (1.01–1.025)	<0.001	0.88 (0.77–1.0)	0.06	1.02 (1.021–1.028)	<0.001	1.01 (1.0–1.02)	0.001

advanced disease (RAEB-t/sAML: HR 1.37: 95% CI: 1.12–1.68; $P = 0.03$) and increasing age (HR 1.02: 95% CI: 1.01–1.02; $P \leqslant 0.001$) significantly influenced disease-free survival, while a better but statistically insignificant disease-free survival was observed for twin transplantation on multivariate analysis (HR 0.73: 95% CI: 0.48–1.15; $P = 0.12$) (Tables 2–4).

Overall survival

The estimated 5-year overall survival was 36% (95% CI: 15–57%) in the twin and 32% (95% CI: 29–35%) in the sibling group ($P = 0.09$).

On univariate analysis of the twin group only a TBI-containing regimen resulted in a lower probability of overall survival (11 *vs* 61%) ($P = 0.03$) while stem cell source, disease stage and time to transplantation did not influence overall survival. On multivariate analysis including all patients a better overall survival was noted for patients who were transplanted with peripheral blood stem cells (HR 0.8: 95% CI: 0.7–0.9; $P = 0.04$) while increasing age (HR 1.02: 95% CI: 1.01–1.025; $P \leqslant 0.001$) and advanced disease (RAEB-t/sAML: HR 1.3: 95% CI: 1.07–1.63; $P = 0.01$) resulted in a lower overall survival. Transplantation from identical twins resulted in a better overall survival (HR 0.6: 95% CI: 0.4–1.0; $P = 0.07$) (see Tables 2–4).

Discussion

In this first study of syngeneic stem cell transplantation in MDS/sAML patients, we compared the results of 38 patients with MDS/sAML after twin transplantation with 1444 MDS/sAML patients who were transplanted with stem cells from their HLA-identical sibling. To counterbalance the higher percentage of patients with advanced disease in the HLA-identical sibling group and the higher median age of the patients in the twin group, we performed a multivariate analysis adjusting for factors such as age, disease stage and stem cell source. Furthermore, to exclude some bias due to lacking data of disease classification among the twin group ($n = 8$) the statistical results did not change if all missing patients were evaluated as advanced disease (RAEB, RAEB-t or sAML). The most striking result was the absence of an increased relapse rate after syngeneic transplantation in comparison to transplantation from an HLA-identical sibling (39 *vs* 32% at 5 years). This is in contrast to the reported results in acute and chronic leukaemia.[9] In acute lymphoblastic and myeloid leukaemia, the relapse rate after syngeneic stem cell transplantation was 36 and 52% in comparison to 26 and 16% after HLA-identical transplantation.[9] Even after HLA-identical or matched unrelated stem cell transplantation the relapse rate in MDS/sAML patients is

high. Several authors have reported a relapse rate between 23 and 48% after HLA-identical stem cell transplantation[4,7,8,10] and a relapse rate between 14 and 41% after unrelated stem cell transplantation.[3,4,11] A strong association between relapse and disease status, age, prognostic score and chromosomal abnormalities has been observed in the largest studies.[2,6,8,10,12,13] In two studies, a reduced incidence of relapse was observed in patients who experienced acute graft-versus-host disease,[3,11] suggesting a graft-versus-MDS/sAML effect after allogeneic stem cell transplantation. The sensitivity of MDS cells to alloreactive T cells could be demonstrated in relapsed patients after allogeneic stem cell transplantation by adoptive transfer of donor lymphocytes from HLA-matched related donors.[14,15] Some well-documented reports of graft-versus-host disease after syngeneic stem cell transplantation indicate at least a weak immune response against the genetically identical twin.[16–18] In our series, acute graft-versus-host disease grade I of the skin after syngeneic transplantation was observed in four patients (11%). The fact that after autologous stem cell transplantation in MDS the relapse rate is up to 55%[4] may further support a supposed graft-versus-MDS effect after syngeneic transplantation. However, the high relapse rate after autologous transplantation may at least in part be due to malignant cell contamination of the graft, as has been shown in gene-marking studies.[19] It has been shown in syngeneic mice model that interleukin 2 and cyclosporin after twin transplantation reduce relapse rate by a graft-versus-leukaemia effect without graft-versus-host disease.[20] Further attempts to reduce relapse rate are being made by intensifying the conditioning regimen.[21] In a univariate analysis of the twin transplants, use of a TBI-containing regimen resulted in a lower overall survival due to higher nonrelapse mortality and higher relapse rate. Recently, encouraging results have been reported for a busulphan-containing regimen,[22] and a National Marrow Donor Program (NMDP) study reported an improved DFS, less graft-versus-host disease and less relapse after unrelated stem cell transplantation in MDS with a busulphan/cyclophosphamide conditioning regimen.[3] In our study only increasing age, more advanced disease and the bone marrow as stem cell source increased relapse probability, while transplantation from an identical twin did not result in a higher relapse rate. The importance of PBSC as stem cell source for HLA-identical sibling transplantation in MDS/sAML patients with respect to TRM, relapse and event-free survival has been reported by the EBMT recently.[23] As expected from syngeneic transplantation in other hematological diseases[9,21,24–26] nonrelapse mortality was lower after the twin transplantation than after HLA-identical transplantation. Therefore, the lower treatment mortality and the similar relapse rate resulted in a strong tendency for better overall and disease-free survival after syngeneic transplantation, which, however, did not reach statistical significance. We conclude that syngeneic stem cell transplantation should be the treatment of choice for all patients with an identical twin who are eligible for a high-dose chemotherapy treatment, even high-risk patients.

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Appendix

List of participating centres in the MDS twin study.

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D Blaise, Institut Paoli Calmettes, Marseille, France [230]	3
T de Witte, Univ. Med. Cent. St Radboud, Nijmegen, The Netherlands [237]	3
E Hellström-Lindberg, G Gahrton, Huddinge University Hospital, Huddinge, Sweden [212]	2
R Powles, Royal Marsden Hospital, Sutton, UK [218]	2
T Littlewood, The Oxford Radcliffe Hospital, Oxford, UK [255]	2
B Chapuis, Hopital Cantonal Universitaire, Geneva, Switzerland [261]	2
V Koza, Charles University Hospital, Pilsen, Czech Republic [718]	2
A Gratwohl, Kantonsspital, Basel, Switzerland [202]	1
R Barge, Leiden University Medical Centre, Leiden, The Netherlands [203]	1
D Bunjes, Medizinische Klinik und Poliklinik, Ulm, Germany [204]	1
A Devergie, Hopital St Louis, Paris, France [207]	1
JL Harousseau, Hotel Dieu, Nantes, France [253]	1
B Simonsson, University Hospital, Uppsala, Sweden [266]	1
J Reiffers, Hopital Haut-Leveque, Pessac, France [267]	1
EP Alessandrino, Policlinico San Matteo, Pavia, Italy [286]	1
B Hertenstein, Medical School of Hannover, Hannover, Germany [295]	1
H-J Kolb, Klinikum Grosshadern, München, Germany [513]	1
M Attal, Hopital de Purpan, Toulouse, France [624]	1
A Vitek, Inst. of Hematology and Blood Transf., Prague, Czech Republic [656]	1
MA Sanz, Servicio de Hematologia, Valencia, Spain [663]	1
J Holowiecki, Silesian Medical Academy, Katowice, Poland [677]	1
JM Moraleda, Unidad de Transplante de Médula Osea, Murcia, Spain [735]	1
AC Newland, The Royal London Hospital, London, UK [768]	1
J Finke, University of Freiburg, Freiburg, Germany [810]	1