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Haematopoietic stem cell transplantation for patients with myelodysplastic syndromes and secondary acute myeloid leukaemias: a report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

Theo de Witte,[1] Jo Hermans,[2] Jaak Vossen,[3] Andrea Bacigalupo,[4] Giovanna Meloni,[5] Niels Jacobsen,[6] Tapani Ruutu,[7] Per Ljungman,[8] Alois Gratwohl,[9] Volker Runde,[10] Dietger Niederwieser,[11] Anja van Biezen,[12] Agnes Devergie,[13] Jan Cornelissen,[14] Jean-Pierre Jouet,[15] Renate Arnold[16] and Jane Apperley[17] [1]*Department of Haematology, University Hospital St Radboud, Nijmegen, The Netherlands,* [2]*Departments of Medical Statistics and* [3]*Paediatrics, Leiden University Medical Centre, The Netherlands,* [4]*Department of Haematology, Ospedale San Martino, Genova, Italy,* [5]*Department of Haematology, University La Sapienza, Roma, Italy,* [6]*Rigshospitalet, Copenhagen, Denmark,* [7]*Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland,* [8]*Department of Haematology, Huddinge Hospital, Stockholm, Sweden,* [9]*Division of Haematology, Department of Internal Medicine, Kantonsspital Basel, Switzerland,* [10]*Department of Bone Marrow Transplantation, University Hospital, Essen, Germany,* [11]*Department of Internal Medicine, University Hospital, Leipzig, Germany,* [12]*Chronic Leukaemia Working Party Registry, Leiden, The Netherlands,* [13]*Department of Haematology, Hôpital St Louis Paris, France,* [14]*University Hospital Rotterdam, The Netherlands,* [15]*Department of Haematology, Hôpital C. Huriez, Lille, France,* [16]*University Hospital Charité, Berlin, Germany, and* [17]*Department of Haematology, Imperial College School of Medicine, London, UK*

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Summary. Allogeneic stem cell transplantation from an HLA-identical sibling donor is a curative treatment option for a young patient with myelodysplastic syndrome, limited by age and lack of sibling donors. Alternative stem cell sources have been used more recently, such as unrelated donors, non-identical family members or autologous transplants. This analysis of 1378 transplants reported to the European Group for Blood and Marrow Transplantation (EBMT) addresses the outcome of the varying procedures according to the known risk factors. The estimated disease-free survival (DFS) and estimated relapse risk at 3 years were both 36% for 885 patients transplanted with stem cells from matched siblings. In the multivariate analysis, age and stage of disease had independent prognostic significance for DFS, survival and treatment-related mortality. Patients transplanted at an early stage of disease had a significantly lower risk of relapse than patients transplanted at more advanced stages. The estimated DFS at 3 years was 25% for the 198 patients with voluntary unrelated donors, 28% for the 91 patients with alternative family donors and 33% for the 126 patients autografted in first complete remission. The non-relapse mortality was 58% for patients with unrelated donors, 66% for patients with non-identical family donors and 25% for autografted patients. The relapse rate of 18% was relatively low for patients with non-identical family donors, 41% for patients with unrelated donors and 55% for patients treated with autologous stem cell transplantation. Both allogeneic and autologous stem cell transplantation have emerged as treatment options for patients with myelodysplastic syndromes. Transplantation with an HLA-identical sibling donor is the preferred treatment option. Patients without an HLA-identical sibling donor may be treated with either autologous stem cell transplantation or an alternative donor transplantation. Patients younger than 20 years may be treated with an unrelated donor transplantation. Patients older than 40 years, and probably also patients between 20 and 40 years, may benefit most from an autologous stem cell transplantation.

Keywords: myelodysplastic syndromes, secondary leukaemia, autologous stem cell transplantation, allogeneic stem cell transplantation

Correspondence: Professor Dr T. de Witte, Department of Haematology, University Hospital St Radboud, 8 Geert Grooteplein, 6525 GA Nijmegen, The Netherlands. E-mail: t.dewitte@hemat.azn.nl

The prognosis of the myelodysplastic syndromes (MDS) varies from a few months to many years. Refractory anaemia (RA) and RA with ring sideroblasts (RARS) are characterized by a low risk of transformation to acute myeloid leukaemia (AML) and a median survival usually in excess of 30 months (Mufti *et al*, 1985). In contrast, the median survival of patients with refractory anaemia and excess of blasts (RAEB) or RAEB in transformation (RAEBt) is less than 12 months (Bennett *et al*, 1982; Kantarjian *et al*, 1986). The karyotype is an additional prognostic factor for survival in MDS (Yunis *et al*, 1986; Geddes *et al*, 1990; de Witte *et al*, 1990a). A recent international workshop has proposed a scoring system based on cytogenetic abnormalities, marrow blasts and peripheral blood cytopenias, which identifies patients in whom median survival is <1 years (Greenberg *et al*, 1997).

In view of the lack of curative therapies, allogeneic bone marrow transplantation (BMT) is the treatment of choice for young patients with histocompatible siblings. The first cases were transplanted more than 10 years ago (Appelbaum *et al*, 1984; de Witte *et al*, 1984). Subsequent publications have addressed the role of allogeneic transplantation for MDS in adults (Appelbaum *et al*, 1990; Anderson *et al*, 1993; O'Donnell *et al*, 1995) and children (Guinan *et al*, 1989; Locatelli *et al*, 1997). National and international bone marrow transplant registries have collected data on patients transplanted for myelodysplasia (de Witte *et al*, 1990b). Results of allogeneic BMT depend on the same risk factors as defined for conventional treatment, such as the presence of cytogenetic abnormalities (De Witte *et al*, 1991; Sutton *et al*, 1996), age (de Witte *et al*, 1991; Sutton *et al*, 1996) and the percentage of blasts in the bone marrow (Anderson *et al*, 1993; O'Donnell *et al*, 1995; Sutton *et al*, 1996). Recently, donors other than HLA-identical siblings and autologous cells have been used as alternative sources of stem cells.

This report describes an analysis of the data from 1378 patients transplanted for MDS or secondary acute myeloid leukaemia (MDS-AML). We focused on prognostic factors, such as source of transplant (matched sibling vs. mismatched family donor or voluntary unrelated donor and autologous transplant), age of recipient, duration of disease before BMT conditioning, primary vs. therapy-related MDS and stage of disease.

PATIENTS AND METHODS

All consecutively reported transplants from 1983 to 1998 were included in this analysis. If a patient received a second transplant for transplant failure or relapse, then the data from the second transplant were analysed combined with those from the first procedure. For example, a patient who died because of complications after the second transplant for treatment of relapse was defined as treatment failure due to relapse. A patient who died because of complications after the second transplant performed for treatment of rejection was defined as treatment failure due to treatment-related complications. Patients with myeloproliferative syndromes and secondary acute lymphoblastic leukaemia were excluded from this analysis. Patients who developed MDS or AML after autologous stem cell transplantation were also excluded from this analysis.

The data from the 10 patients transplanted for chronic myelomonocytic leukaemia (CMMoL) and from the 22 patients with unclassifiable MDS were not analysed separately in view of the low numbers.

All EBMT transplant centres have committed themselves to report the minimal essential data (Med-A forms) of all consecutive transplants at the time of the transplantation. Updates of the data on the Med-A forms have been performed on a regular basis. The follow-up of the patients ends at the time of death or the last reported date of being alive. An increasing number of national registries report all transplants within the respective country to the megafile of the EBMT. The EBMT commenced a centre review process in 1996, in which individual teams are audited for the quality of their data returns.

The present analysis focused on the four main end-points: disease-free survival, overall survival, relapse incidence and transplant-related mortality. The analysis concentrated on well-recognized risk factors, i.e. age of recipient, primary vs. therapy-related MDS, disease stage at transplantation, time from diagnosis to transplant and year of transplantation. Complete cytogenetic data have been reported for a small minority of patients. Therefore, cytogenetic characteristics had to be excluded from this analysis.

Definitions. The classification of MDS and acute myeloid leukaemia (AML) was performed according to the criteria of the French–American–British (FAB) working group (Bennett *et al*, 1982). AML that developed after pre-existing myelodysplasia with a duration of at least 3 months was defined as secondary acute myeloid leukaemia (MDS-AML).

MDS without a previous history of other haematological conditions, such as aplastic anaemia, or MDS without a history of exposure to cytotoxic or immunosuppressive therapy for malignancies, autoimmune diseases or organ transplantation were defined as primary MDS.

MDS/AML occurring after other haematological conditions such as aplastic anaemia or MDS/AML occurring after exposure to cytotoxic or immunosuppressive therapy for malignancies, autoimmune diseases or organ transplantation were defined as therapy-related MDS/AML (tMDS/AML). Patients with blast crisis evolving from myeloproliferative disorders have been excluded from this analysis.

The early stage of MDS was defined as untreated RA/RARS or MDS in first complete remission (CR-1); intermediate stage as untreated RAEB(t) or MDS in second complete remission (CR-2); advanced stage as remaining MDS.

Treatment-related mortality (TRM) or non-relapse mortality was defined as mortality after stem cell transplantation not occurring after relapse.

Statistics. The time intervals for survival, disease-free survival, relapse rate and risk of transplant-related mortality were calculated from the day of stem cell transplantation. Relapsed patients were censored for transplant-related mortality from time of relapse. Actuarial curves were calculated according to the Kaplan–Meier technique (Peto, 1984). The differences between curves were tested statistically

using the two-tailed log-rank test (Breslow). For ordered variables, the log-rank test for linear trend was used (Breslow, 1984). The prognostic value of covariables was studied by Cox's regression.

RESULTS

Transplantation activity for MDS in Europe

A total of 193 European teams had reported data from 1378 patients by 15 December 1997. Surveys of transplant activity in Europe indicated that 142 and 216 procedures were performed in 1992 and 1994 (Gratwohl & Hermans, 1994; Gratwohl *et al*, 1996). Approximately 150 transplants were reported annually to the EBMT registry from 1992 to 1994, thus confirming that data were available from more than 90% of all transplants for MDS performed in Europe. The reported number of transplants for patients with MDS doubled in the period 1992–94 compared with the period 1989–92. Transplantation for MDS using unrelated donors has occurred more recently and has surpassed transplantation with mismatched family members. In the period 1992–94, 25 transplants were performed using non-identical family donors and 82 transplants with unrelated donors. Only 15 autologous stem cell transplantations (ASCTs) were performed before 1989, but this application has acquired more acceptance recently. The number of reported ASCTs for patients with MDS was 64 in the period 1992–94. Since 1994, more autologous transplants have been performed with mobilized peripheral stem cells than with those from marrow.

Transplantation with histocompatible siblings

The most frequent form of transplantation for MDS was transplantation with stem cells from HLA-identical siblings. A total of 885 patients were transplanted with matched sibling stem cells. Overall, 400 patients (45%) were alive at the time of most recent reporting, and 187 patients were alive with a follow-up of more than 3 years. Forty-five of these surviving patients (11%) have relapsed. The major cause of failure after transplantation was treatment-related mortality. A total of 324 patients died because of treatment-related complications and 161 patients died after relapse. The actuarial probability of disease-free survival at 3 years was 36%, and the relapse risk was 36% (Figs 1 and 2, Table I).

A number of possible prognostic factors were studied by univariate analysis, i.e. type of MDS, age, disease stage, interval from diagnosis to transplantation and year of transplant. The 3-year disease-free survival of patients transplanted for primary MDS was 37%. This was not significantly different from a DFS of 32% for patients who had developed AML after MDS (Table I). The treatment-related mortality was the same for both groups, but the risk of relapse was significantly higher ($P < 0{\cdot}001$) for the patients transplanted after development of AML. Sixty-seven patients were transplanted for therapy-related MDS ($n = 30$) or t-AML ($n = 37$). Patients transplanted for t-MDS/AML had a similar outcome after transplantation to

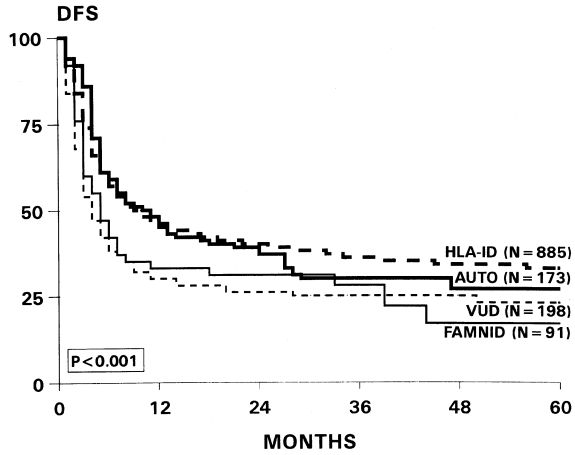

Fig 1. Disease-free survival (DFS) of patients with myelodysplastic syndromes transplanted with stem cells from: histocompatible siblings (HLA-ID); genotypically non-identical relatives (FAMNID); volunteer unrelated donors (VUD); autologous stem cells (AUTO).

patients transplanted for primary MDS and MDS-AML (Table I).

Age has a significant effect on outcome. Patients aged < 20 years had a DFS of 45%, which compared favourably with the outcome in patients transplanted between 20 and 40 years (37%) and patients older than 40 years at the time of transplant (31%). These significantly ($P < 0{\cdot}001$) better results can be explained by a lower treatment-related mortality in the younger patients. The risk of relapse was similar for all three age categories (Table I).

The stage of disease and disease status are important prognostic factors for outcome after transplantation. A total of 215 patients received the transplant as primary treatment, and 670 patients were transplanted after intensive chemotherapy. The DFS of the 72 patients transplanted with RA/RARS or the 230 patients transplanted in CR-1 were significantly better ($P < 0{\cdot}001$) than the DFS when the

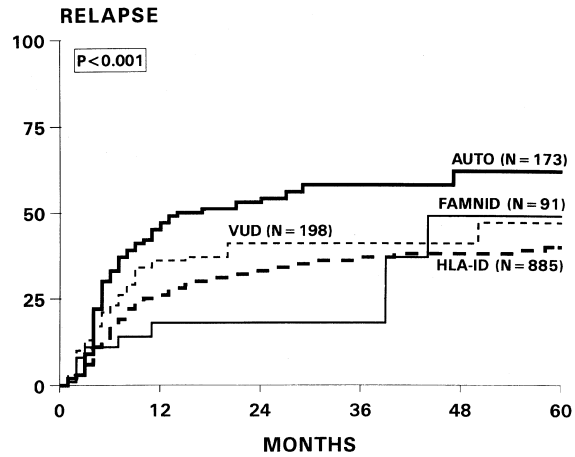

Fig 2. Relapse risk of patients with myelodysplastic syndromes transplanted with stem cells from: histocompatible siblings (HLA-ID); genotypically non-identical relatives (FAMNID); volunteer unrelated donors (VUD); autologous stem cells (AUTO).

Table I. Three-year actuarial probability of disease-free survival (DFS), survival, treatment-related mortality (TRM) and relapse of HLA-identical donor transplants in MDS.

Patient categories	Number	DFS	Survival	TRM	Relapse
All patients	885	36	41	43	36
Diagnosis					
Primary MDS	712	37	42	43	35
MDS-AML	106	32	37	38	49
tMDS/AML	67	35	35	46	36
P-value		0·18	0·39	0·69	< 0·001
Age (years)					
< 20	163	45	53	30	36
20–40	388	37	41	43	35
> 40	329	31	35	50	39
P-value		0·001	< 0·001	< 0·001	0·92
Stage at transplantation					
Untreated					
RA/RARS	72	55	53	37	13
RAEB(t)/MDS-AML	111	28	31	52	43
Treated					
CR-1	230	44	49	37	30
No CR-1	440	32	38	45	42
P-value		< 0·001	0·002	0·02	< 0·001
Early stage	302	47	50	37	26
Intermediate stage	125	29	33	49	43
Advanced stage	458	32	37	46	42
P-value		< 0·001	< 0·001	0·005	< 0·001
Interval: diagnosis–transplantation					
12 months	665	34	39	43	40
> 12 months	194	43	48	43	24
P-value		0·27	0·48	0·41	0·001
Year of transplant					
Before 1989	156	31	35	50	39
1989–91	166	39	43	36	39
1992–94	325	40	43	42	31
P-value		0·06	0·05	0·04	0·41

Early stage, RA/RARS (untreated) or patients transplanted in CR-1; intermediate, untreated RAEB(t) or patients transplanted in CR-2; advanced stage, remaining patients.

transplant was performed for more advanced stages of MDS (Table I). The risk of relapse was only 13% for RA or RARS and 30% for CR-1. This contrasts with the relapse risks of 43% and 42% when the transplant was performed for more advanced MDS or after failure of chemotherapy respectively (Table I). The survival and DFS of patients transplanted at an early stage were significantly ($P < 0·001$) better than the DFS of patients transplanted at a later phase of the disease (Fig 3, Table I). The survival and DFS of intermediate-risk and more advanced risk patients did not differ significantly. Both the higher relapse risk and the higher treatment-related mortality contributed to this impaired DFS for patients transplanted at an advanced phase of the disease (Fig 4).

The interval from diagnosis to transplant did not affect the survival and DFS significantly, except for relapse. Several analyses on subgroups of patients did not reveal an advantage of transplantation within 6 or 12 months after diagnosis (data not shown). One explanation may be that the majority of patients (665 out of 885 patients) were transplanted within 1 year of diagnosis.

In general, the results of allogeneic transplantation have improved over the years (Bortin *et al*, 1992). For this reason, we compared the treatment outcomes of patients transplanted in three periods, namely before 1989, 1989–91 and 1992–94 (Table I). The 3-year survival and DFS were better in patients transplanted after 1989. This resulted from a decrease in treatment-related mortality over recent years.

Multivariate analysis of prognostic variables

In view of the results from the univariate analyses (Table I), the multivariate analysis for DFS, survival and treatment-related mortality was restricted to the following variables: age, stage of disease at transplant and year of transplantation. Both age and stage of disease had independent prognostic significance for all three end-points (Table II). Increasing age had a gradually worsening effect. Early stage disease had a significantly improved outcome compared

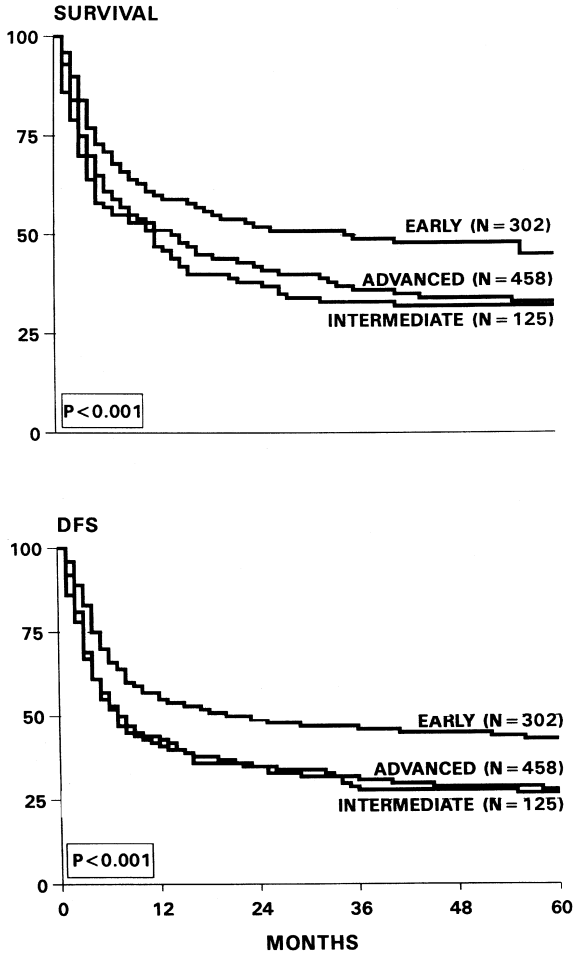

Fig 3. Survival and disease-free survival (DFS) of patients transplanted with stem cells from histocompatible siblings in early stage (untreated RA/RARS or CR-1), intermediate stage (untreated RAEB/RAEBt or CR-2) and advanced stage (untreated MDS-AML or no CR-1/CR-2) disease.

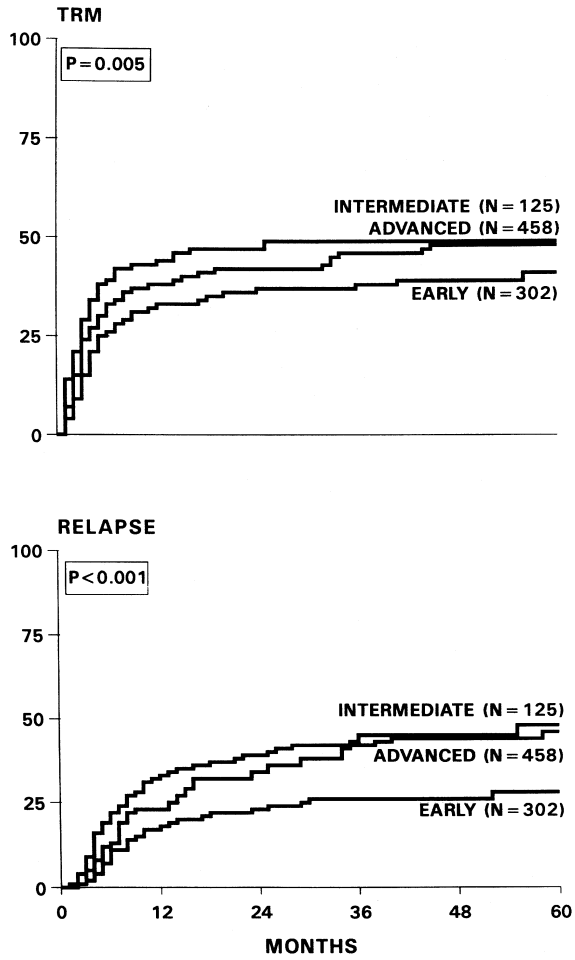

Fig 4. Treatment-related mortality (TRM) and relapse risk of patients transplanted with stem cells from histocompatible siblings, in early stage (untreated RA/RARS or CR-1), intermediate stage (untreated RAEB/RAEBt or CR-2) and advanced stage (untreated MDS-AML or no CR-1/CR-2) disease.

with transplant for intermediate and advanced stage disease. The year of transplant had no or only a marginal effect on DFS and survival, whereas the treatment-related mortality of patients transplanted before 1989 was significantly higher than the TRM of patients transplanted after 1989 (Table II) The relapse risk was analysed using the variables diagnosis, stage at transplant and interval from diagnosis to transplantation (Table III). The risk of relapse was higher when MDS had progressed to AML, but the risk of relapse was not higher for patients with therapy-related MDS than for patients with primary MDS. Patients transplanted in early disease had a significantly lower risk of relapse than patients transplanted at more advanced stages. Patients transplanted more than 1 year after diagnosis had a significantly lower relapse risk, similar to the univariate analysis (Table III).

Transplantation with voluntary unrelated donors

The DFS of the 198 patients transplanted with voluntary unrelated donors was 25% (Fig 1). This was lower than the DFS observed after matched-sibling transplantation despite the younger age in this type of transplant. The TRM was 58% and the relapse risk 41% (Fig 2, Table IV). Age had a remarkable impact on treatment outcome. The DFS was 36% when patients were younger than 20 years at the time of transplant and 19% and 11% when patients were between 20 and 40 years or older than 40 years respectively. Treatment-related mortality was high in all age groups, but was age dependent (Table IV).

Transplantation with genotypically non-identical related donors

The 3-year DFS of the 91 patients transplanted with stem cells from alternative family donors was 28% (Fig 1, Table IV). The main cause of failure was a treatment-related mortality of 66%, higher than in any other type of transplantation. The relapse rate of 18% was low (Fig 2, Table IV). Age had no significant influence on treatment outcome when genotypically non-identical family members

Table II. Multivariate analysis in patients transplanted with stem cells from HLA-identical siblings.

		DFS			Survival			TRM		
Number		RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Age (years)										
< 20	163	1·00			1·00			1·00		
20–40	388	1·41	1·10–1·82	0·007	1·64	1·25–2·16	< 0·001	1·83	1·28–2·64	0·001
> 40	329	1·76	1·36–2·27	< 0·001	2·07	1·56–2·73	< 0·001	2·47	1·71–3·57	< 0·001
Stage										
Early	299	1·00			1·00			1·00		
Intermediate	125	1·63	1·25–2·13	0·003	1·61	1·22–2·13	< 0·001	1·54	1·11–2·15	0·01
Advanced	456	1·57	1·29–1·91	< 0·001	1·47	1·19–1·80	< 0·001	1·34	1·04–1·72	0·02
BMT year										
Before 1989	156	1·00			1·00			1·00		
1989–91	166	0·78	0·59–1·02	0·07	0·76	0·58–1·01	0·06	0·64	0·45–0·91	0·01
1992–94	325	0·79	0·62–1·01	0·06	0·78	0·61–1·00	0·05	0·74	0·55–0·99	0·04
After 1994	235	0·83	0·63–1·09	0·17	0·76	0·57–1·02	0·07	0·69	0·49–0·97	0·03

Early stage, RA/RARS (untreated) or patients transplanted in CR-1; intermediate stage, untreated RAEB(t) or patients transplanted in CR-2; advanced stage, remaining patients.DFS RR, relative risk of disease-free survival: time to relapse or death; Survival RR, relative risk of survival time to death; TRM RR, relative risk of time to death related to treatment; CI, confidence intervals.

served as donors. Other factors, such as degree of mismatch and stage of disease, apparently had a more important effect.

Autologous stem cell transplantation

The 3-year DFS of the 173 patients transplanted with autologous stem cells was 30% (Table IV, Fig 1). The treatment-related mortality of 29% was lower than in other forms of transplantation. The majority of autologous transplants were performed in CR-1. The DFS of the 126 patients transplanted in CR-1 was 33%. Treatment failure resulted mainly from a high relapse risk of 55%. Non-relapse mortality was 25%. The DFS of patients transplanted beyond CR-1 was 18%. Age had a borderline significant effect on treatment outcome. The DFS was 46% when patients were younger than 20 years at the time of transplant. The DFS was 29% when the patients were older than 40 years. This difference can be explained by a higher treatment-related mortality in the older age group (Table IV). The relapse incidence was similar for all age groups.

DISCUSSION

Most patients with MDS are too old to be considered for intensive treatment such as stem cell transplantation. In patients younger than 60 years, allogeneic stem cell transplantation has become a curative treatment option. The EBMT reported its first analysis on a large group of patients in 1990 (de Witte *et al*, 1990b). The results were encouraging, but the follow-up was limited. Now, we present the long-term results of more than 1000 patients transplanted for MDS. In addition, this analysis presents data from patients transplanted with sources of haematopoietic stem cells other than histocompatible sibling donors.

Young patients with RA and RARS are considered good candidates for allogeneic BMT. Relapses are rare, provided that the pretransplant conditioning includes a marrow ablative regimen (Appelbaum *et al*, 1990). Disease-free survival in this analysis was 55%, in accordance with other reports (Appelbaum *et al*, 1990; de Witte *et al*, 1990b, Mattijssen *et al*, 1997). The high treatment-related mortality suggests that early transplantation is indicated before there is sensitization as a result of transfusion of blood products, before the development of iron overload and opportunistic infections and before transformation to more

Table III. Multivariate analysis in patients transplanted with stem cells from HLA-identical siblings; relative risk (95% confidence intervals)of relapse.

		Relapse incidence		
		RR	95% CI	*P*
Diagnosis				
Primary MDS	690	1·00		
MDS-AML	103	2·29	1·57–3·36	< 0·001
Therapy-related	66	1·14	0·68–1·91	0·62
Stage				
Early	299	1·00		
Intermediate	125	2·25	1·41–3·59	0·001
Advanced	456	2·43	1·72–3·41	< 0·001
Interval: diagnosis–BMT				
12 months	665	1·00		
> 12 months	194	0·62	0·42–0·91	0·01

Early stage, RA/RARS (untreated) or patients transplanted in CR-1; intermediate stage, untreated RAEB(t) or patients transplanted in CR-2; advanced stage, remaining patients.

Table IV. Three-year actuarial probability of disease-free survival (DFS), survival, treatment-related mortality (TRM) and relapse of patients treated with voluntary unrelated donor (VUD) transplants, genotypically non-identical related donor transplants (Fam-nonid) in MDS/sAML and autologous transplants: the influence of age on treatment outcome.

Patient category	Number	DFS	Survival	TRM	Relapse
VUD transplants	198	25	26	58	41
< 20 years	84	36	36	45	35
20–40 years	81	19	22	65	44
> 40 years	33	11	13	73	59
P-value		0·03	0·03	0·004	0·01	0·39
Fam-nonid. transplants	91	28	31	66	18
< 20 years	36	14	23	81	27
20–40 years	32	41	41	47	22
> 40 years	23	27	27	71	5
P-value		0·14	0·44	0·10	0·67
Autologous transplants	173	30	32	29	58
CR-1	126	33	38	25	55
No CR-1	47	18	14	51	64
P-value	12	0·06	0·01	0·07	0·32
< 20 years*	48	46	58	17	44
20–40 years*	66	36	41	15	58
> 40 years*		29	29	39	51
P-value		0·08	0·05	0·22	0·27

*Only patients in first complete remission.

advanced stages of MDS or AML. This analysis could not show a clear benefit of transplantation within 12 months when an HLA-identical sibling donor was available (Table I). This observation may be explained by the inclination of physicians to transplant high-risk patients earlier than low-risk patients because the multivariate analysis showed a lower relapse risk when patients were transplanted more than 12 months after diagnosis (Table III). However, the TRM appeared to be lower in patients transplanted within 3 months after diagnosis in an earlier multivariate analysis by the EBMT (Runde *et al*, 1998). Postponement of allogeneic stem cell transplantation may be justified in patients with a relatively good prognosis. These patients are characterized by an absence of profound cytopenias and an absence of poor prognostic cytogenetic characteristics (Greenberg *et al*, 1997).

An increase in the proportion of marrow blasts to more than 5% had a negative impact on DFS after transplantation. The DFS was 55% when patients were transplanted for RA or RARS compared with a DFS of 28% in patients with more than 5% marrow blasts. This inferior outcome resulted mainly from an increased risk of relapse. A recent analysis by the EBMT of 131 MDS patients treated by HLA-identical sibling BMT confirmed that bone marrow blast count is the most important risk factor for increased relapse and decreased survival (Runde *et al*, 1998). One of the analyses from Seattle (Appelbaum *et al*, 1990) reported an actuarial relapse risk of 45% in 30 patients transplanted with RAEB or RAEBt.

The results of allogeneic BMT as primary therapy appeared to be worse for patients with overt AML after MDS than for patients transplanted at earlier stages of MDS-AML (de Witte *et al*, 1990b; Sutton *et al*, 1996; Anderson *et al*, 1997; Runde *et al*, 1998). Disease-free survival was approximately 20% when patients were transplanted for MDS-AML (de Witte *et al*, 1990b; Anderson *et al*, 1997; Runde *et al*, 1998). The alternative approach is to offer allogeneic BMT to these patients as consolidation therapy in complete or partial remission after intensive AML-type remission-induction chemotherapy (Armitage *et al*, 1981; de Witte *et al*, 1990a; Fenaux *et al*, 1991). The 3-year DFS was 44% for 230 patients transplanted in complete remission after chemotherapy. Patients not in first remission after chemotherapy responded less well and showed a 3-year DFS of 32%. The issue as to whether patients with MDS-AML or RAEBt should receive remission-induction therapy before the transplant procedure is controversial. Some patient categories may be identified that are unlikely to enter CR after intensive chemotherapy. These patients are characterized by a prolonged history of MDS, by hypocellular marrow or by multiple chromosomal abnormalities. In these cases, allogeneic BMT may be considered as first-line therapy (Marmont & Tura, 1986; Anderson *et al*, 1997). Only large prospective studies may resolve this issue. In the report from Seattle (Anderson *et al*, 1997), no significant difference in outcome was observed between patients treated with immediate transplantation and patients treated after remission-induction therapy. However, the numbers are limited, and only six of the 20 patients treated with chemotherapy before the transplant procedure received the transplant in CR-1 (Anderson *et al*, 1997).

Increasing numbers of patients with malignancies are treated successfully with radiochemotherapy. Therefore, there are a number of patients who present with treatment-related MDS. In several reports, patients transplanted for t-MDS tended to have a lower DFS than patients transplanted for primary MDS (Longmore *et al*, 1990; Anderson *et al*, 1997). A previous report from the EBMT (Runde *et al*, 1998) showed an identical DFS, but the relapse rate was slightly higher in the therapy-related group. This analysis and another recent report (Ballen *et al*, 1997) confirm an identical DFS and relapse risk of patients transplanted for t-MDS to that for patients with primary MDS.

Two-thirds of the patients with MDS who may benefit from allogeneic BMT lack a suitable family donor. The development of efficient, worldwide registries of HLA-typed volunteer unrelated donors (VUDs) has made allogeneic BMT with fully or partially matched unrelated donors a realistic alternative. Three recent analyses reported an 18–38% DFS (Kernan *et al*, 1993; Anderson *et al*, 1996; Arnold *et al*, 1998). Non-relapse mortality was higher than that of HLA-identical related recipients. Increasing age was significantly associated with increased risk of death from non-relapse causes (Anderson *et al*, 1996; Arnold *et al*, 1998). The DFS of 36% in patients younger than 20 years is very encouraging and similar to the results obtained with histocompatible sibling transplantation. On the other hand, the poor outcome of the 22 patients older than

40 years transplanted with stem cells from unrelated donors indicates that these patients should not be transplanted unless substantial improvements in the technology have been achieved.

Autologous stem cell transplantation (ASCT) may be an alternative option for patients ineligible for allografting. A primary requisite for ASCT is a complete remission with sufficient numbers of stem cells. Multidrug chemotherapy, such as that applied to induce CR in primary AML, is effective in MDS with CR rates varying from 15% to 64% (Mertelsmann *et al*, 1980; Armitage *et al*, 1981; Preisler *et al*, 1986; Michels *et al*, 1989; de Witte *et al*, 1990a, O'Donnell *et al*, 1995; Parker *et al*, 1997). The experience with ASCT in patients with MDS is limited (Geller *et al*, 1988; Laporte *et al*, 1993). A recent report from the EBMT showed a DFS of 28% for 55 patients with MDS and 51% for a matched group transplanted for *de novo* AML (de Witte *et al*, 1997). In this report, the 3-year DFS of the 126 patients transplanted in CR-1 was 33%, and the actuarial relapse rate was 55%. Patients younger than 40 years had a better DFS than patients aged ≥ 40 years. This difference could be explained by the higher non-relapse mortality in the older age group.

Myelodysplastic syndromes are clonal stem cell disorders. This may raise concern about the presence of sufficient numbers of residual normal stem cells to perform ASCT. Chemotherapy induces cytogenetically normal CRs in the majority of patients (de Witte *et al*, 1995). In addition, the peripheral stem cell harvests of three patients with MDS appeared to be polyclonal, when assessed by polymerase chain reaction (PCR) techniques based on X-chromosome inactivation patterns (Delforge *et al*, 1995). Preliminary data indicate that repopulation after transplantation with mobilized peripheral stem cells was much faster than autologous bone marrow transplantation (Carella *et al*, 1996; Demuynck *et al*, 1996).

Both allogeneic and autologous stem cell transplantation have emerged as treatment options for patients with myelodysplastic syndromes. The DFS of the patients transplanted with matched sibling stem cells was superior to that of patients transplanted with other sources of stem cells (Fig 1). Therefore, transplantation with an HLA-identical sibling donor is the preferred treatment option. Young patients, patients transplanted at an early stage of the disease and those transplanted more recently benefited more clearly from an HLA-identical sibling transplantation than the other patients. Patients without an HLA-identical sibling donor may be treated with either autologous stem cell transplantation or an alternative donor transplantation. Autologous stem cell transplantation requires a CR that has been maintained for at least several months. Multivariate analysis cannot yet identify which patient should be treated with which treatment modality. Careful interpretation of the data from this analysis indicates that young patients (< 20 years) may be treated with an unrelated donor transplantation. This approach results in a 3-year DFS of 36% (Table IV). Patients older than 40 years, and probably also patients between 20 and 40 years, will benefit most from an autologous stem cell transplantation. Only data from large numbers of patients with sufficient follow-up data may allow a multivariate analysis, which may answer these questions.

PARTICIPATING EBMT TRANSPLANT CENTRES, PHYSICIAN (NUMBER OF CASES)

University Hospital, Nijmegen, T. de Witte (57); University Hospital, Leiden, R. Willemze/J. Vossen (52); Ospedale San Martino, Genova, A. Bacigalupo (44); University of degli Studi La Sapienza, Rome, W. Arcese (34); Rigshospitalet, Copenhagen, N. Jacobsen (32); Helsinki University Central Hospital, Helsinki, T. Ruutu (31); Hopital St. Louis, Paris, A. Devergie (28); Karolinska Institute, Huddinge, G. Gahrton (28); Kantonsspital, Basel, A. Gratwohl (27); AZR/DDHK, Rotterdam, J. Cornelissen (26); Hopital Claude Hurez, Lille, F. Bauters (25); University Hospital Gasthuisberg, Leuven, M. Boogaerts (24); Hopital Henri-Mondor, Creteil, M. Kuentz (23); University Hospital, Essen, V. Runde (22); Klinikum Grosshadern, Munich, H. J. Kolb (22); Charing Cross–Hammersmith Hospital, London, D. Samson/J. Apperley (22); University of Ulm, Ulm, D. Bunjes (21); Hopital Saint Antoine, Paris, N. Gorin (21); Cliniques Universitaires St Luc, Brussels, A. Ferrant (21); Hopital Jean Minjoz, Besancon, J.Y. Cahn (20); Royal Free Hospital, London, H. Prentice (19); Hospital University of 'Marqués de Valdecilla', Santander, A. Iriondo (19); Medical School of Hannover, Hannover, B. Hertenstein (18); Heinrich-Heine-Universität, Düsseldorf, W. Schneider (17); University Hospital, Utrecht, L. Verdonck (16); Pitie-Salpetriere, Paris, V. Leblond (16); Hopital du Haut Leveque, Pessac, J. Reiffers (16); Policlinico San Matteo (Paediatric), Pavia, F. Locatelli (15); Institute of Haematology and Blood Transfusion, Praha, A. Vitek (15); CHU Sart-Tilman, Liege, Y. Beguin (15); Policlinico San Matteo (Adult), Pavia, E. Alessandrino (14); Great Ormond Street Hospital, London, P. Veys (12); Clinica Medica Universita, Torino, M. Aglietta (11); University Hospital, Uppsala, B. Simonsson (11); University Hospital (Paediatrics), Tübingen, D. Niethammer (11); Hopital E. Herriot, Lyon, M. Michallet (11); Hospital Clinic, Barcelona, E. Carreras (10); King Faisal Specialist Hospital, Riyadh, P. Ernst (10); Hospital Universitario La Fe, Valencia, M. Sanz (10); University Hospital (Adults), Tubingen, H. Einsele (9); Hopital Hotel Dieu, Paris, B. Rio (8); Royal Infirmary, Glasgow, I. Franklin (8); Ospedale Civile, Pescara, G. Torlontano (8); Hotel Dieu, Nantes, J. Harousseau (8); Hadassah University Hospital, Jerusalem, S. Slavin (8); Hop. Cantonal Universitaire, Geneva, B. Chapuis (8); Pesaro Hospital, Pesaro, G. Lucarelli (8); University Hospital VUB, Brussels, R. Schots (8); Institut Gustave Roussy, Villejuif, O. Hartmann (8); Hospital San Orsola, Bologna, S. Tura (7); Hopital Caen, Caen, X. Troussard (7); Ospedale Maggiore die Milano, Milano, G. Lambertenghi-Deliliers (7); Ospedale San Gerardo (Paediatrics), Monza, C. Uderzo (7); Heartlands Hospital, Birmingham, D. Milligan (7); Ospedale di Careggi, Firenze, A. Bosi (7); A.Z. St. Jan, Brugge, D. Selleslag (7); Universitatskrankenhaus Eppendorf, Hamburg, H. J. Schmoll (7); Evangelismos Hospital, Athens, A. Skandalis (7); K. Marcinkowski University (Haematology), Poznan, J.

Hansz (7); Hospital Universitario 'Virgen del Rocio', Sevilla, J. Rodriguez Fernandez (7); University Hospital, Zurich, J. Gmur (6); Rikshospitalet, Oslo, S. Evensen (6); Hopital de Nancy, Nancy, F. Witz (6); Hospital Santa Creu i Sant Paul, Barcelona, S. Brunet (6); Hopital A. Michallon, Grenoble, L. Molina (6); AZM, Maastricht, H. Schouten (6); University of Cambridge, Cambridge, R. Marcus (6); Klinik fur KMT, Hamatologie und Onkologie, Idar-Oberstein, A. Fauser (6); Centre Henry Becquerel, Rouen, H. Tilly (6); Hopital Necker-Enfants Malades, Paris, A. Bezyn (5); Royal Mardsden Hospital, Sutton Surrey, R. Powles (5); University of Turku Central Hospital, Turku, K. Remes (5); Inst. Paoli I. Calmettes, Marseille, D. Blaise (5); Hopital Nord, St. Etienne, J. Stephan (5); Christian-Albrechts-University, Kiel, N. Schmitz (5); Centre Jean Perrin, Clermont-Ferrand, R. Plagne (5); Institute G. Gaslini, Genova, G. Dini (5); University Hospital Centre-Rebro, Zagreb, B. Labar (5); Royal Manchester Children's Hospital, Pendlebury, A. Will (5); The George Papanicolaou General Hospital, Thessaloniki, A. Fassas (5); Hopital de Purpan, Toulouse, M. Attal (5); Hopital de Hautepierre, Strasbourg, B. Lioure (5); S. Bortolo Hospital, Vicenza, F. Rodeghiero (5); Hopital Debrousse, Lyon, G. Souillet (5); Charité-Virchow Klinikum, Berlin, R. Arnold (5); Kinderpoliklinik Universität of München, München, C. Bender-Götze (5); University College Hospital, London, A. Goldstone (4); University of Vienna, Vienna, H. Greinix (4); Hopital Cochin, Paris, F. Dreyfus (4); University Hospital of Lund, Lund, A. Bekassy (4); Centro Leucemie Infantili, Padova, C. Messina (4); Centor Porto, Porto, F. Campilho (4); Inst. Portugues Oncologia, Lisboa, M. Abecasis (4); Bristol Hospital for Sick Children, Bristol, J. Cornish (4); R G Vall Hebron, Barcelona, A. Julia (4); Ospedale 'Bianchi-Melacrino-Morelli', Reggio Calabria, P. Iacopino (4); University Hospital, Udine, M. Baccarani (4); Nottingham City Hospital, Nottingham, N. Russell (4); King's Healthcare NHS Trust, London, G. Mufti (4); St James Hospital Trinity College, Dublin, S. McCann (3); San Camillo Hospital, Rome, A. De Laurenzi (3); Spedali Civile, Brescia, T. Izzi (3); Sahlgrenska University Hospital/East, Göteborg, A. Fasth (3); Ospedale di Niguarda, Milano, R. Cairoli (3); Royal Liverpool University Hospital, Liverpool, R. Clarke (3); National Institute of Haematology, Budapest, E. Kelemen (3); Hopital Erasme, Brussels, W. Feremans (3); University Hospital, Bratislava, M. Mistrik (3); University of Verona, Verona, F. Benedetti (3); CHRU, Angers, M. Boasson (3); Heinrich-Heine-University (Paediatrics), Düsseldorf, S. Burdach (3); Hospital Infantil La Fe, Valencia, V. Castel (3); Hopital d'Enfants CHU de Dijon, Dijon, D. Caillot (3); Perth Royal Infirmary, Perth, R. Herrmann (3); Hospital Clinico, Salamanca, D. Caballero (3); Hopital Robert Debre, Paris, E. Vilmer (3); University Hospital, Innsbruck, D. Niederwieser (2); Royal Victoria Infirmary, Newcastle, S. Proctor (2); University of Ulm (Paediatrics), Ulm, W. Friedrich (2); Hopital d'Enfants de la Timone, Marseille, C. Coze (2); Universita Cattolica S. Cuore, Rome, G. Leone (2); Clinica Paediatrica, Trieste (2); Hospital Mat Infantil Vall d'Hebron, Barcelona, J. Ortega (2); Poole Hospital, Dorset, D. Spence (2); Hospital Aranzazu, San Sebastian, R. Lasa Isasti (2); Klinikum Nürnberg, Nürnberg, H. Wandt (2); Ospedale Bergamo, Bergamo, T. Barbui (2); Hopitaux de Brabois (Paediatrics), Nancy, P. Bordigoni (2); Sahlgrenska University Hospital (Haematology), Göteborg, J. Carneskog (2); Hospital Son Dureta, Palma de Mallorca, J. Besalduch (2); St László Hospital, Budapest, T. Masszi (2); Antartida Hospital Privado, Buenos Aires, L. Feldman (2); University of Jena, Jena, F. Zintl (2); Tel Aviv University, Tel Hashomer, I. Ben-Bassat (2); Schneider Children's Medical Centre of Israel, Petach-Tikva, I. Yaniv (2); Universita Tor Vergata/St Eugenio Hospital, Rome, S. Amadori (2); Clinica Corachan, Barcelona, A. Granena (2); Hospital of Manchester, Manchester, G. Morgensterne (2); Policlinico Monteluce, Perugia, M. Martelli (2); Universita di Palermo, Palermo, A. Cajozzo (2); Institut Jules Bordet, Brussels, P. Stryckmans (2); Children's Hospital, Helsinki, U. Pihkala (1); Hospital Reina Sofia, Cordoba, A. Torres Gomez (1); AMC/Emma Kinderziekenhuis, Amsterdam, H. vd Berg (1); The Oxford Radcliffe Hospital, Oxford, T. Littlewood (1); Hopital La Miletrie, Poitiers, F. Guilhot (1); The London Clinic, London, D. Guéret-Wardle (1); Hospital Clinico Universitario, Valencia, J. Garcia-Conde (1); Ospedale Regina Margherita, Torino, R. Miniero (1); HCI International Medical Centre, Clydebank, D. Spence (1); Queen Elizabeth Medical Centre, Birmingham, J. Murray (1); UCT Medical School, Cape Town, N. Novitzky (1); St Anna Kinderspital, Vienna, H. Gadner (1); Polish Academy of Sciences, Wroclaw, A. Lange (1); St George's Hospital, London, J. Marsh (1); Hopital Huguenin, St. Cloud, X. Janvier (1); Klinikum Benjamin Franklin, Berlin, W. Knauf (1); Ibni Sina Hospital, Ankara, H. Koc (1); Karolinska Hospital, Stockholm, M. Björkholm (1); Children University Hospital, Brussels, C. Devalck (1); The New Children's Hospital, Sydney, P. Shaw (1); Marmara University of Hastanesi, Istanbul, T. Akoglu (1); Charles University Hospital, Pilsen, V. Koza (1); Clinca Puerta de Hierro, Madrid, M. Fernandez (1); Hospital Nino Jesus of Madrid, Madrid, L. Madero (1); Orebro Medical Centre Hospital, Orebro, U. Tidefelt (1); University Hospital. Linköping, G. Juliusson (1); Stadt Kliniken Oldenburg, Oldenburg, B. Metzner (1); Hospital Duran i Reymais, Barcelona, A. Granena (1); Istanbul Medical School, Istanbul, Y. Tangun (1); Our Lady's Hospital for Sick Children, Dublin, A. O'Meara (1); The Children's Hospital, Sheffield, E. Vandenberghe (1); University Hospital, Homburg, L. Trumper (1); Ospedale di Torrette, Ancona, P. Leoni (1); Ospedale 'San Francesco', Nuoro, A. Gabbas (1); Hopital Saint Louis (Adults), Paris, C. Gisselbrecht (1); University of Erlangen-Nuremberg, Erlangen, M. Gramatzki (1); Ospedale Regionale Microcitimie, Cagliari, A. Cao (1); Riyadh Armed Forces Hospital, Riyadh, M. Aldouri (1); Derriford Hospital, Plymouth, M. Hamon (1).

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