

Different outcome of allogeneic transplantation in myelofibrosis using conventional or reduced-intensity conditioning regimens

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Myelofibrosis with myeloid metaplasia (MMM) is characterised by bone marrow fibrosis, splenomegaly, extramedullary haematopoiesis and the finding of teardrop cells and immature precursors in the peripheral blood. MMM is a rare disease and only 1:55 cases per 100 000 inhabitants are diagnosed each year in Sweden according to a recent report (Johansson *et al*, 2004).

Conventional treatment can ameliorate symptoms of the disease but has little, if any, impact on the long-term disease development or on survival. Over recent years, the single curative treatment has been allogeneic stem cell transplantation (allo-SCT) but mortality has been significant and overall survival was between 38% and 58% of transplanted patients (Guardiola *et al*, 1999; Daly *et al*, 2003; Deeg *et al*, 2003; Ditschkowski *et al*, 2004). MMM is a disease that is likely to affect the elderly with an average age at diagnosis of 65 years. Indeed, only less than a quarter of MMM patients are younger than 55 years at diagnosis, which renders the majority of patients ineligible for myeloablative transplantation. In recent

Summary

Allogeneic haematopoietic stem cell transplantation remains the only curative treatment of myelofibrosis with myeloid metaplasia (MMM). Previous reports have indicated significant treatment-related mortality (TRM) for patients transplanted after myeloablative conditioning but superior survival has been reported after reduced-intensity conditioning (RIC). We report the results of a survey of all allogeneic transplantations for MMM performed in Sweden at six transplant units between 1982 and 2004. Twenty-seven patients were transplanted; 17 with a myeloablative conditioning regimen and 10 with RIC. The median age was 50 years (5–63 years) at transplantation. After a median follow up of 55 months, 20 patients are alive. TRM was 10% in the RIC group and 30% in the myeloablative group. There was no difference in survival for high or low-risk patients according to Cervantes score or between sibling and unrelated donor transplantations.

Keywords: myelofibrosis, allogeneic transplantation, reduced intensity conditioning, Cervantes score.

years, reduced-intensity conditioning (RIC) has emerged as an option that can be offered to a larger cohort of MMM patients with significantly better outcome and less treatment-related mortality (TRM) (Devine *et al*, 2002; Hessling *et al*, 2002; Tanner *et al*, 2003; Greyz *et al*, 2004).

The risks associated with transplantation have to be balanced with the expected survival, which is highly variable for patients with MMM. Several risk scores have been developed with documented efficacy in estimating the expected survival for MMM patients. The Lille score can divide patients into low-, intermediate- and high-risk groups based on two clinical parameters; haemoglobin above or below 10.0 g/dl and leucocyte count below $4 \times 10^9/l$ or above $30 \times 10^9/l$. The risk groups have a median survival of 93, 26 and 13 months, respectively (Dupriez *et al*, 1996). The Cervantes score, uses the same cut-off level for haemoglobin in combination with occurrence of peripheral blasts and presence of constitutional symptoms (Cervantes *et al*, 1997). Although several other

prognostic factors in MMM exist, these two proposed scores provide a simple tool that enable therapeutic decisions to be made. Recently, the acquired mutation V617F in *JAK2*, which is present in approximately half of the patients with MMM, was reported to be a negative prognostic factor for survival (Campbell *et al*, 2006), but other investigators have found no evidence for correlation between *JAK2* mutation and disease progression or leukaemic transformation in MMM (Mesa *et al*, 2006a,b).

In Sweden, allo-SCT has been performed in MMM since 1982 at six different transplantation units. In 2003, The Swedish Group for Myeloproliferative Disorders decided to pursue a survey of transplants for MMM in Sweden with the aim of establishing a uniform policy for the selection of patients and choice of transplant procedure. Our study showed a marked difference in patient selection between different centres. The survey reveals, however, encouraging results for a majority of patients and this report may hopefully constitute the basis of a more uniform transplant policy in the future.

Patients and methods

Questionnaires were distributed to all six units that carry out allogeneic transplantations in Sweden in order to identify patients with primary or secondary myelofibrosis that had undergone allogeneic transplantation. Twenty-nine patients transplanted between 1982 and 2004 were reported, but two patients were excluded from the study because the diagnostic criteria for myelofibrosis were not fulfilled. Of the remaining 27 patients, 21 were males and six females. Nineteen had a primary diagnosis of MMM. Eight patients had secondary myelofibrosis including three patients with a primary diagnosis of polycythemia vera and five patients with essential thrombocythemia. Three patients had transformed to leukaemia at time of transplantation. Median age was 48 years (5–62 years) at diagnosis and 50 years (5–63 years) at transplantation. Three patients were transplanted before 1990, six patients between 1990 and 1999 and the remaining 18 patients after 2000.

The reported main indications for transplantation were anaemia ($n = 12$), thrombocytopenia ($n = 1$), highly active disease ($n = 4$), disabling symptoms ($n = 6$), increase in blast count ($n = 4$) and manifest leukaemic transformation ($n = 3$). Fifteen patients required transfusion of erythrocytes or platelets. Ten patients reported constitutional symptoms. Cytogenetic analyses were evaluable in 20 patients and clonal cytogenetic abnormalities were identified in six cases. Clinical characteristics are shown in Table I. Nineteen patients had received prior therapy including hydroxycarbamide ($n = 12$), radioactive phosphorus ($n = 2$) and interferon- α ($n = 6$). Three patients with leukaemic transformation had received induction courses for acute myeloid leukaemia. Six patients had undergone splenectomy prior to transplantation and four patients had received splenic irradiation, three as part of the

conditioning regimen for transplantation. Eight patients had not received any therapy prior to transplantation.

Data for the evaluation of the risk score were available at time of transplantation for 23 of the 24 patients without leukaemic transformation. According to Cervantes score, there were 12 high-risk (score 2–3) and 11 low-risk patients (score 0–1) and according to Lille score, there were five patients with score 0, 15 patients with score 1 and three patients with score 2. The time interval between diagnosis of the myeloproliferative disorder and transplantation was 50 (2–306) months for the whole group and there was no difference in time interval between patients with high- and low-risk score.

The donors were human leucocyte antigen (HLA) identical siblings in 19 cases and a haploidentical parent in one case. There were seven unrelated matched donors. Seventeen patients received a myeloablative regimen based on cyclophosphamide 60 mg/kg on two consecutive days and total body irradiation (TBI) 3 Gy \times 4 ($n = 11$) or busulfan 4 mg/kg/d \times 4 ($n = 6$). Ten patients received a dose-reduced conditioning regimen based on fludarabine–busulfan ($n = 8$) or fludarabine–cyclophosphamide–melphalan ($n = 2$). Average age at transplantation for the myeloablative group was 43 years (5–58 years) and in the RIC cohort it was 58 years (52–63 years). In the myeloablative group, there were 10 Cervantes score high-risk patients, five low-risk and one with leukaemic transformation. In the RIC group, there were two high-risk patients, six low-risk and two in leukaemic transformation. Peripheral blood stem cells were used in 17 cases and the remaining received purified stem cells from bone marrow.

Evaluation of spleen size and bone marrow fibrosis

Six patients were splenectomised at time of transplantation. Information about the size of the spleen before transplantation was available in 20 of the remaining 21 patients and methods for evaluation of spleen size included ultrasonography, scintigraphy and clinical examination. In two cases the spleen was not considered to be enlarged. The spleen was considered to be enlarged in 10 patients whose longest spleen axis was <20 cm. In eight patients, the longest axis exceeded 20 cm and was evaluated as massively enlarged.

For the estimation of bone marrow fibrosis, the scoring system of Bauermeister was used (Bauermeister, 1971).

Statistics

Survival was analysed with the Kaplan–Meier method. Survival differences between groups were tested with the Log-Rank statistic or the Gehan–Wilcoxon statistic (exact test). Cox regression analysis was used to evaluate the significance of prognostic factors in multivariate analysis. Student's *t*-test was used to compare time with engraftment. *P*-values <0.05 were considered significant.

Table I. Characteristics of 27 patients transplanted for myelofibrosis.

Number	Diagnosis	Age at tx	Cervantez score	Lille score	Spleen size	Bone marrow fibrosis	Previous therapy	Type of conditioning	Donor
1	MMM	56	0	0	Enlarged	II	IFN, epo, steroids	Bu + Cy	Sibling
2	ET/MMM/AML	41	Leukaemia	Leukaemia	Removed	III-IV	Hyd, AML induction	Cy + TBI	Sibling
3	PV/MMM	58	2	0	Removed	II	Hyd, ³² P, anag, IFN, Ara-C, Gem	Bu + Cy	Sibling
4	MMM	27	1	1	Removed	II	Hyd, Cy	Cy + TBI	Sibling
5	MMM	48	3	1	Normal	III-IV	No therapy	Bu + Cy	Sibling
6	MMM	47	3	1	Removed	III-IV	Hyd, IFN, IL4	Bu + Cy	Sibling
7	MMM	39	3	2	Enlarged	II	Thalidomide	Bu + Cy	URD
8	MMM	52	1	1	Enlarged	II	Hyd, epo	Bu,Cy,ATG	URD
9	ET/MMM	47	2	1	Massive	IV	Hyd, Bu, autologous tx	Cy + TBI + OKT3	URD
10	ET/MMM	51	2	2	Massive	III-IV	No therapy	Cy + TBI	URD
11	MMM	50	2	2	Removed	IV	No therapy	Cy + TBI	Sibling
12	ET/MMM	52	1	1	Massive	III-IV	IFN, epo, Ara-C, thioguanin	Flu + Bu + ATG	Sibling
13	MMM	41	1	1	Enlarged	Grade II	No therapy	Cy + TBI	Sibling
14	MMM	5	2	1	Removed	No data	No therapy	Cy + TBI	Haploid
15	MMM	63	1	1	Enlarged	III	No therapy	Flu + Bu + ATG	Sibling
16	PV/MMM	52	2	1	Massive	III	Bu, ³² P, IFN	Flu, Bu, ATG	Sibling
17	ET/MMM	39	1	1	Normal	III-IV	Anag, IFN	Flu, Bu, ATG	URD
18	MMM	54	0	0	Enlarged	III	No data	Flu, Bu	Sibling
19	MMM	26	No data	No data	No data	No data	No data	Cy-TBI	Sibling
20	MMM	41	0	0	Massive	II	Hyd	Cy + TBI	Sibling
21	MMM	58	1	0	Massive	No data	Hyd	Flu + Bu + ATG	URD
22	MMM	52	2	1	Enlarged	II	No therapy	Flu + Bu + ATG	Sibling
23	MMM	49	2	1	Enlarged	IV	No therapy	Cy + VP-16 + TBI	Sibling
24	MMM	62	1	1	Massive	II	Hyd, thalidomide	Flu + Bu + ATG	URD
25	PV/MMM/AML	60	Leukaemia	Leukaemia	Massive	IV	Hyd, AML induction	Flu + Cy + Mel + ATG	Sibling
26	PV/MMM/AML	59	Leukaemia	Leukaemia	Enlarged	III	Hyd, AML induction	Flu + Cy + Mel + ATG	Sibling
27	MMM	43	3	1	Massive	I	Hyd	Cy + TBI	Sibling

tx, transplant; MMM, myelofibrosis with myeloid metaplasia; ET, essential thrombocythaemia; PV, polycythaemia vera; AML, acute myeloid leukaemia; IFN, interferon- α ; hyd, hydroxycarbamide; aneg, anegralide; Bu, busulfan; epo, erythropoietin; Ara-C, cytarabine arabinoside; gem, gemcitabine; IL4, interleukin-4; Cy, cyclophosphamide; Flu, fludarabine; Mel, Melphalan; ATG, antithymocyte globulin; TBI, total-body irradiation; VP-16, etoposide; URD, unrelated donor.

Results

Transplantation period

Engraftment of granulocytes (neutrophils exceeding $0.5 \times 10^9/l$ for 3 d) was obtained in 25 patients and was significantly earlier in patients undergoing RIC (median 15.9 d) compared with myeloablative regimens (median 19.4 d) ($P = 0.02$). For platelets, the median time to recovery (platelet count exceeding $20 \times 10^9/l$ without transfusions) was 14.2 and 24.3 d, respectively ($P = 0.03$). There was no difference in time to engraftment for patients who had been splenectomised compared with patients whose spleen was not enlarged, enlarged or massively enlarged. There was also no difference in time to engraftment between patients with grades III and IV fibrosis in the bone marrow compared with patients with lower grades of fibrosis. In the myeloablative group, one patient never showed

granulocyte or platelet recovery and two other patients never showed platelet recovery.

Infections were seen in 14 patients, six RIC patients and eight patients that had received myeloablative conditioning. These included eight cases of cytomegalovirus (CMV) reactivation, including lethal CMV pneumonitis and colitis in one case. Aspergillosis was reported in two patients, both of whom were in the RIC group with lethal outcome for one patient. Two patients in the myeloablative group had pericarditis, with lethal outcome in one subject.

Graft-versus-host disease and donor lymphocyte infusion

Prophylaxis and treatment against graft-versus-host disease (GVHD) included cyclosporine, methotrexate and corticosteroids. Acute GVHD grade I or II was observed in 16 patients and one patient had acute GVHD grade IV. Chronic GVHD

was grades I–II was reported in 12 patients and one patient had grade III.

Three RIC patients were given donor lymphocyte infusions (DLI). One patient with evidence of graft rejection received DLI on day +63 resulting in full donor chimaerism. Two patients received DLI at 4 and 5 months respectively because of remaining mixed chimaerism. In addition, one patient, originally diagnosed with primary myelofibrosis, had a relapse (polycythemia vera) 4 years after myeloablative transplantation but achieved a complete remission after administration of DLI.

Deaths

In total, eight patients have died after transplantation, seven in the myeloablative group and one in the RIC group (Table II). Early deaths, before day +100, occurred in three patients, all of them in the myeloablative group. Two patients died of graft

failure in combination with pneumonia and veno-occlusive disease of the liver in one case. The third patient who had an early engraftment died at day +59 because of CMV pneumonitis and colitis. Another three patients, including the only death in the RIC group, died within the first year after transplantation. One patient, who never achieved platelet engraftment, died of progressive disease. Another patient died from a bacterial infection at day +221 and the RIC patient died from aspergillosis at day +117.

One patient in complete remission died 14 months after transplantation due to CMV infection with haemorrhagic-uremic syndrome and intracerebral bleeding. Of the seven patients that died from causes attributable to transplantation, three were high risk and two low risk according to Cervantez score and one patient had transformed to leukaemia. The risk score was missing for one patient.

Finally, patient 11 died in complete remission 16 years after transplantation due to pancreatic cancer.

Table II. Outcome of 27 patients transplanted for myelofibrosis.

Number	Time to death (months)	Cause of death	Follow up period (months)	Spleen size	Acute GVHD	Chronic GVHD	Size of spleen after tx	Bonemarrow fibrosis	Bone marrow fibrosis after tx
1	2	Pneumonitis, myocardial infarction,	2	Enlarged	II	0	No data	II	No data
2	5	Unknown	5	Splenectomised	I	0	Splenectomised	III–IV	III–IV
3			40	Splenectomised	I	0	Splenectomised	II	0
4			61	Splenectomised	I	Limited	Splenectomised	II	0
5			66	Normal	II	Limited	Enlarged	III–IV	0
6			55	Splenectomised	II	Limited	Splenectomised	III–IV	III–IV
7			30	Enlarged	0	0	Normal	II	I
8			14	Enlarged	0	0	Normal	II	I
9	1	Haemorrhage, pneumonia, VOD	1	Massive	0	0	No data	IV	No data
10	13	CMV, TTP, intracerebral bleeding	13	Massive	I	Limited	No data	III–IV	I
11	188	Pancreatic cancer	188	Splenectomised	I	0	Splenectomised	IV	0
12			62	Massive	0	Extensive	No data	III–IV	0
13			180	Enlarged	0	Limited	Normal	Grade II	0
14	7	Bacterial infection	7	Splenectomised	I	0	Splenectomised	No data	No data
15	4	Aspergillosis	4	Enlarged	II	0	No data	III	No data
16			19	Massive	No data	No data	Enlarged	III	0–1
17			31	Normal	I–II	0	Normal	III–IV	
18			13	Enlarged	No data	No data	No data	III	No data
19	56	Pneumonia	56	No data	No data	No data	No data	No data	0–1
20			68	Massive	I	Extensive	Normal	II	0
21			44	Massive	0	None	Enlarged	No data	0
22			870	Enlarged	I	Limited	Enlarged	II	No data
23			3264	Enlarged	I	Limited	Normal	IV	0
24			429	Massive	0	Extensive	Enlarged	II	I
25			2397	Massive	IV	Extensive	Normal	IV	0
26			1855	Enlarged	II	Extensive	Normal	III	0
27			1826	Massive	0	II	Normal	I	0

GVHD, graft-versus-host disease; tx, transplant; CMV, cytomegalovirus; TTP, thrombotic thrombocytopenic purpura; VOD, veno-occlusive disease.

Long-term outcome and response to transplantation

At present, 19 patients are alive with a median follow up of 55 months (14–180 months). All patients have platelet counts exceeding $100 \times 10^9/l$ and only one patient has a haemoglobin concentration below 11.5 g/dl. Out of the 21 unsplenectomised patients, the size of the spleen was documented before and after transplantation in 14 cases. A reduction of spleen was documented in 12 cases, as shown in Table II. In nine cases, the size of the spleen has been documented as within normal limits. A reduction of bone marrow fibrosis was seen in 17 patients and in 11 patients there is a total disappearance of fibrotic changes in the bone marrow.

Nine of 10 patients undergoing RIC transplantations are alive compared with nine of 16 after conventional myeloablative transplantation (Fig 1). There was no difference in survival between the high- and low-risk group or for the group with leukaemic transformation. Two of three patients trans-

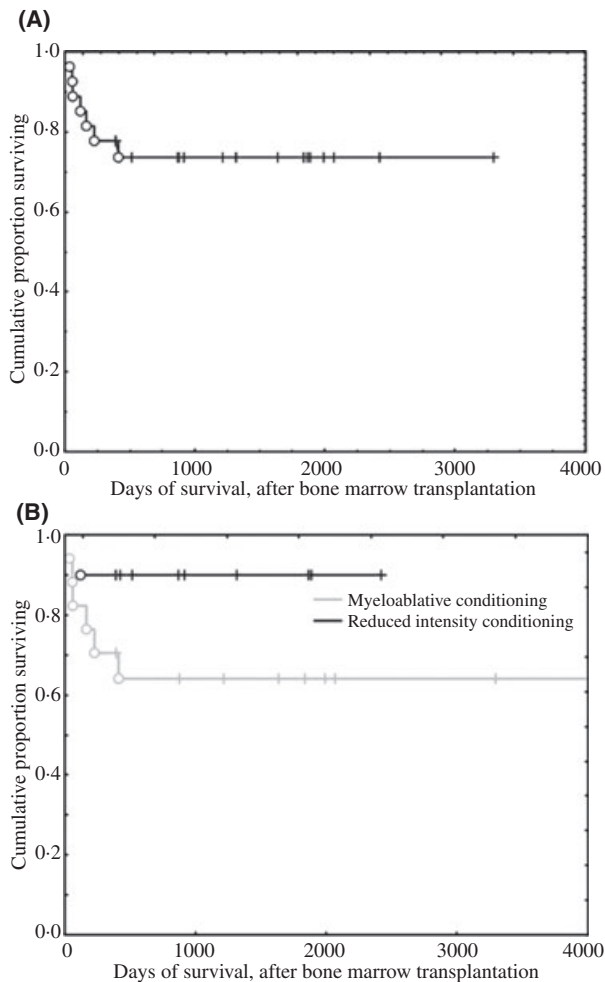


Fig 1. Survival of 27 patients with myelofibrosis with myeloid metaplasia after allogeneic stem cell transplantation. (A) Survival for the whole group. (B) Survival for 17 patients transplanted with myeloablative conditioning and 10 patients with reduced-intensity conditioning.

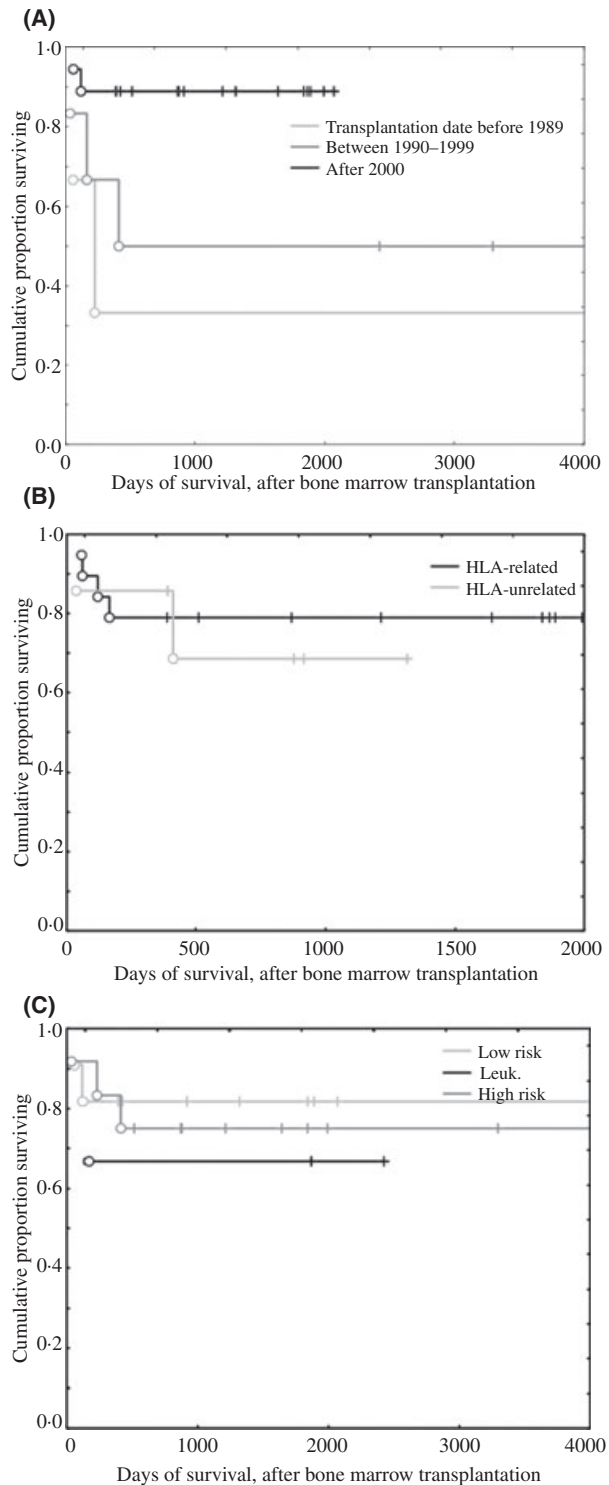


Fig 2. Allogeneic stem cell transplantation for 27 patients with myelofibrosis with myeloid metaplasia. Impact on outcome of transplantation period (A), type of donor (B) and Cervantes risk score prior to transplantation (C).

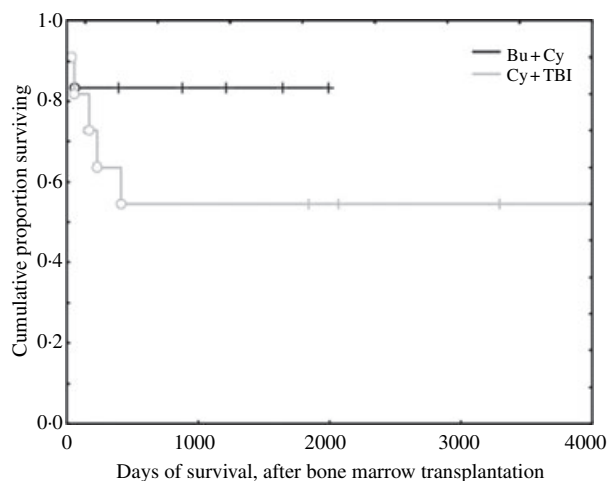


Fig 3. Impact of conditioning regimen on survival for 17 patients with myelofibrosis with myeloid metaplasia transplanted with myeloablative conditioning based on busulfan and cyclophosphamide (Bu + Cy, $n = 6$) or cyclophosphamide and total body irradiation (Cy + TBI, $n = 11$).

planted in leukaemic transformation are alive and in complete remission.

Prognostic factors influencing survival after transplantation

It is likely that patient survival has benefited from more recent transplantation procedures (Fig 2A), but the results did not appear to be dependant on whether the stem cells were obtained from HLA-identical siblings or HLA-matched unrelated donors (Fig 2B). Finally, there was a tendency for better survival in patients with low as compared with high-risk score (Fig 2C). In the myeloablative group, patients receiving cyclophosphamide-TBI conditioning had a tendency for inferior outcome compared with patients receiving busulfan and cyclophosphamide (Fig 3). However, none of the above analyses reached statistical significance.

Discussion

The aim of the present work was to analyse the frequency of allo-transplants for MMM in Sweden and to study the selection of patients and outcome after transplantation. Data were collected from all six transplantation units and covered all transplantations performed during the years 1982–2004 ($n = 27$). The transplant-related mortality in the total cohort was 25%, but results have improved substantially in patients transplanted during the last decade, particularly in RIC transplant patients, where the mortality was 10%. Our results collected from six institutions are in line with two larger series reported recently that showed long-term disease-free survival of 80–84% after RIC transplants for MMM (Kröger *et al*, 2005; Rondelli *et al*, 2005).

The current results also confirm the lower incidence of TRM with RIC compared with conventional allogeneic transplantation. Indeed, the average age of the RIC group was 14 years older than the myeloablative group. RIC, therefore, appears to be a treatment option for a substantially larger cohort of MMM patients.

Previous reports have indicated superior outcome for patients transplanted early in the course of disease and inferior survival for patients with high-risk score and extensive bone marrow fibrosis (van Besien & Deeg, 2005). The present series had more low-risk patients according to the Cervantes and Lille score in the RIC group, which might have contributed to the superior outcome for the RIC group compared with conventional transplantation. However, in our cohort there was no significant difference between the outcomes for high- and low-risk patients. Patients with low-risk disease are expected to have a good survival without treatment, which has to be balanced against the risk from transplantation. In our series, one patient with Lille score 0 and an expected median survival of 93 months died within 4 months after transplantation.

The majority of transplants in the present series were performed with HLA-identical sibling donors. Only seven unrelated donors were used but there was no significant difference in the outcome between sibling and unrelated donors. Although this series was small, the survival of 71% following unrelated donor transplantation was similar to the outcome for the whole group. Other studies have reported inferior outcome for transplants with unrelated donors (Guardiola *et al*, 2002).

In previous reports, there has been a concern that extensive bone marrow fibrosis may lead to impaired engraftment (Deeg *et al*, 2003). This notion was supported by the observation that all three patients in our series who did not obtain engraftment had bone marrow fibrosis grades III or IV. For the patients that achieved engraftment there was, however, no difference in time to engraftment when comparing patients with extensive fibrosis (grades III and IV) to those with less extensive fibrosis.

Extensive splenomegaly has also been of concern for engraftment. In our series, six patients had undergone splenectomy prior to transplantation. There was a slower engraftment in patients with massive splenomegaly (longest spleen axis >20 cm) compared with patients with a normal or less extensive splenic enlargement. Moreover, our two patients with primary graft failure had a massive splenomegaly. Thus, it might be advantageous to remove a massively enlarged spleen from high-risk patients. In spite of this, in the present series three patients with a splenic axis of 30 cm and more had a rapid engraftment indicating that engraftment can also occur when the spleen is very large.

Many different types of conditioning regimens have been applied for transplantation. Increased TRM in patients receiving TBI-based conditioning compared with myeloablative conditioning with busulfan and cyclophosphamide has been reported (van Besien & Deeg, 2005). This finding could also

find support in our series, with a trend for better survival for patients receiving busulfan-based conditioning.

In this study, 20 patients were long-term survivors after transplantation. A reduction of fibrosis and splenomegaly was noted in all patients except one who maintained fibrosis grades III–IV but displayed good recovery of peripheral blood counts. Previous studies have reported complete reversal of fibrosis within 6 months (Thiele *et al*, 2005) but in our series the reversal was slower in some cases.

It could be concluded that the present results appear to support the possibility of long-term survival and possible cure by allogeneic transplantation for patients with myelofibrosis. RIC increases the number of patients eligible for transplant and is superior to myeloablative treatment in terms of survival and morbidity. Clearly, there seems to be a graft-versus-myelofibrosis effect and our study supports the beneficial effect of DLI reported previously (Cervantes *et al*, 2000). Still, transplant-related mortality is significant and transplantation should be reserved for high-risk patients with poor prognosis in response to conventional treatment.

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