

## Outcome of allogeneic stem cell transplantation in patients with myelofibrosis

M Ditschkowski, DW Beelen, R Trenschele, M Koldehoff and AH Elmaagacli

Department of Bone Marrow Transplantation, University Hospital of Essen, Hufelandstr. 55, 45122 Essen, Germany

### Summary:

Myelofibrosis, either *de novo* or following pre-existing hematologic diseases, can be cured by allogeneic hematopoietic stem cell transplantation (SCT), but SCT is associated with significant morbidity and mortality, making the choice and timing of transplantation difficult. In all, 20 patients (seven female and 13 male), with a median age of 45 years (range 22–57 years), with idiopathic myelofibrosis ( $n = 12$ ), post-thrombocytopenic ( $n = 3$ ) or post-polycythemic ( $n = 2$ ) myeloid metaplasia or leukemic transformation ( $n = 3$ ), underwent allogeneic SCT at our center between 1994 and 2003. With regard to the pre-transplant presence of risk factors such as hemoglobin levels  $\leq 10$  mg/dl, grade III marrow fibrosis or peripheral blast counts  $> 1\%$ , patients were divided into high- and low-risk groups. The estimated 3-year survival post transplant was 38.5% for all patients. The 3-year probability of survival within the high-risk group ( $n = 11$ ) characterized by the presence of at least two risk factors was 16%. Low-risk patients ( $n = 9$ ) with at most one risk factor had an estimated 3-year survival of 67%. Thus, previously defined risk determinants for the outcome of allogeneic transplantation for myelofibrosis may provide useful information facilitating treatment strategies. Our data suggest that transplantation should be taken into consideration before poor prognostic variables develop.

*Bone Marrow Transplantation* (2004) 34, 807–813.  
doi:10.1038/sj.bmt.1704657

Published online 6 September 2004

**Keywords:** myelofibrosis; allogeneic SCT; stem cells

Myelofibrosis with myeloid metaplasia (MMM), also known as agnogenic myeloid metaplasia or idiopathic myelofibrosis (IM), is a rare hematologic disorder classified with polycythemia vera (PV) and essential thrombocythemia (ET) as a chronic myeloproliferative disease. Clinical

manifestations comprise bone marrow fibrosis, progressive anemia, extramedullary hematopoiesis, splenomegaly and leukoerythroblastic peripheral blood smear.<sup>1</sup> Bone marrow fibrosis is regarded as a reactive phenomenon caused by a clonal hematopoietic stem cell disorder.<sup>2</sup> Inflammatory cytokines released by clonal megakaryocytes and monocytes are assumed to stimulate nonclonal fibroblasts to proliferate.<sup>3–5</sup> Leukemic transformation is observed in 20% of the patients during the first 10 years after onset of MMM.<sup>6</sup>

Although MMM, having a median age at presentation of 65 years<sup>7</sup> is typically a disease affecting the elderly, almost a quarter of patients are younger than 55 years of age.<sup>6</sup> The median survival of patients with IM approximately is 3.5–5 years,<sup>2,7,8</sup> but depending on the presence or absence of prognostic determinants a wide variation can be observed. In contrast, patients with PV and ET have a life expectancy that does not seem to differ significantly from that of age- and sex-matched control groups.<sup>9</sup> However, disease progression in these patients can lead to an increase in marrow fibrosis and then consecutive shortened life expectancy.<sup>10</sup> The parameters older age, anemia, constitutional symptoms, circulating blasts  $> 1\%$ , leukocytosis or leukocytopenia and high-risk cytogenetic aberrations are described to have the most important adverse prognostic impact on survival in MMM.<sup>7,8</sup> According to Cervantes *et al.*,<sup>6</sup> young patients with MMM and poor prognostic factors are reported to have a median survival of 33 months, while low-risk patients with no or one adverse prognostic factor have a median survival of 176 months. Using the Dupriez score,<sup>7</sup> the median survival of MMM patients receiving conventional treatments is 93 months among the low-risk group, 26 months for the intermediate risk group and 13 months among high-risk patients.

Allogeneic hemopoietic stem cell transplantation (SCT) offers long-term relapse-free survival but is associated with significant mortality and morbidity.<sup>11</sup> Recent studies analyzed the results of allogeneic transplantation in MMM patients and defined variables influencing post-transplant survival. Hemoglobin levels  $< 10$  g/dl and osteomyelosclerosis before transplantation seem to affect the outcome negatively,<sup>12</sup> as well as clonal cytogenetic abnormalities or increasing severity by Dupriez classification.<sup>13</sup> The purpose of this study was to evaluate the applicability of risk factors for allogeneic SCT in MMM patients in order to estimate post-transplant survival.

Correspondence: Dr M Ditschkowski, Department of Bone Marrow Transplantation, University Hospital of Essen, Hufelandstr. 55, 45122 Essen, Germany; E-mail: markus.ditschkowski@uni-essen.de  
Received 19 February 2004; accepted 3 June 2004  
Published online 6 September 2004

## Patients and methods

A total of 20 patients (13 male and seven female) underwent allogeneic transplantation at our center between 1994 and 2003. At the time of transplantation, 12 patients had IM, three patients progressive myelofibrosis developing with ET and two patients suffered from 'spent phase' of PV. Three patients were diagnosed with leukemic transformation evolved from IM, PV and ET in each case. The clinical and demographic profile of the patients is summarized in Table 1. Elevated peripheral blast counts > 1%, documented grade 3 marrow fibrosis and hemoglobin levels  $\leq 10$  g/dl prior to transplantation were regarded as relevant risk factors supposed to influence the outcome of transplantation negatively. By the use of a numeric scoring system, we defined a low-risk group including nine patients with at most one risk determinant prior to conditioning. Presence of two or three bad prognostic factors characterized the high-risk group consisting of 11 patients.

The median time interval between the diagnosis of a myeloproliferative disorder and allogeneic SCT was 16 months in the high-risk group but only 10 months in the low-risk group. Chromosomal abnormalities pre-transplant were observed in two cases in the low-risk group and in three cases in the high-risk group. Constitutional symptoms presenting as bone pain occurred in three high-risk patients. According to the Dupriez classification,<sup>7</sup> seven patients had a low-risk score, eight patients an intermediate risk score and five patients a high-risk score. In all, 15 patients had been transfused with red blood cells or platelets or both prior to HSCT. A total of 12 patients had undergone splenectomy at various time intervals before transplanta-

tion, generally due to symptomatic splenomegaly or to avoid apprehended engraftment failure. Five patients had received hydroxyurea and three patients had been treated with intravenous standard dose polychemotherapy. One patient in each case had received anagrelide, interferon or blood letting, which is summarized under 'other treatment' in Table 1.

Donors were HLA-identical related in 13 cases and matched unrelated in 3 cases. Three patients received grafts from mismatched sibling donors, one patient was transplanted from a mismatched unrelated donor (Table 2). In all, 17 patients had conditioning regimens containing TBI, two patients received preparative treatment using polychemotherapy. Transplants consisted of unmanipulated peripheral hematopoietic blood stem cells in 14 cases, one patient received a CD34 enriched, T-cell-depleted graft and five patients were transplanted with bone marrow. While primary prophylaxis of GVHD consisted of CSA and a short-course methotrexate in 18 cases, one patient was treated with CSA plus mycophenolate mofetil.

Diagnosis of the underlying myeloproliferative disorder was based on the conventional diagnostic criteria.<sup>14,15</sup> Bone marrow biopsies of all patients were analyzed histopathologically to grade the extent of fibrosis prior to transplant. The degree of marrow fibrosis was recorded due to the histomorphometric grading scheme reported by Thiele *et al.*<sup>16</sup>

The day of graft infusion was defined as day 0 and leukocyte recovery was defined as the first of three consecutive days with absolute neutrophil counts  $> 0.5 \times 10^9/l$ . Primary graft failure was assumed if leukocyte engraftment was not reached by day 30. Platelet recovery was defined as the first of three consecutive days

**Table 1** Clinical and demographic profile of patients with myelofibrosis

	Overall patients (n = 20)	Low risk (n = 9)	High risk (n = 11)
Male/female	13/7	7/2	5/5
Age (years) at diagnosis (median; range)	37 (22–57)	35 (22–54)	37 (22–57)
Age (years) at transplantation (median; range)	45 (23–59)	41 (23–54)	46 (23–59)
Number of patients > 50 years of age at transplant	7	2	5
Time (months) from diagnosis to transplantation (median; range)	13 (3–180)	10 (3–72)	16 (4–180)
<i>Degree of marrow fibrosis at transplant</i>			
Grade 0	1	1	0
Grade I	3	2	1
Grade II	5	5	0
Grade III	11	1	10
Hemoglobin at transplant < 10 mg/dl	9	2	7
<i>Dupriez risk score at transplant</i>			
Low	7	4	3
Intermediate	8	5	3
High	5	0	5
Peripheral blasts $\geq 1\%$ at transplant	6	0	6
Constitutional symptoms	4	0	4
Clonal cytogenetic abnormalities before transplant	6	2	4
<i>Treatment before transplant</i>			
Splenectomy	12	5	7
Transfusions	15	5	10
Chemotherapy	8	3	5
Other	3	1	2

**Table 2** Transplantation characteristics of patients with myelofibrosis

	Overall patients (n=20)	Low risk (n=9)	High risk (n=11)
<i>Donor match</i>			
HLA-identical sibling	13	7	6
Mismatched sibling	3	2	1
HLA-identical unrelated	3	0	3
Mismatched unrelated	1	0	1
<i>Graft source</i>			
Bone marrow transplantation (BMT)	5	3	2
Unmanipulated peripheral blood stem cell transplantation (PBSCT)	14	6	8
CD 34 purified stem cell transplantation (SCT)	1	0	1
<i>Conditioning regimen</i>			
Total body irradiation (TBI)+ Cyclophosphamide	16	8	8
Treosulfan + Cyclophosphamide + Anti-thymocyte-globulin (ATG)	1	0	1
TBI + Cyclophosphamide + Thiotepa	1	0	1
TBI + Fludarabine	1	0	1
Melphalan + VP16 + Ara C + Cyclophosphamide + Dexamethasone	1	1	0
<i>GVHD prophylaxis</i>			
T-cell depletion	1	0	1
Cyclosporin A (CSA)+ methotrexate (MTX)	18	9	9
Cyclosporin A (CSA)+ mycophenolate	1	0	1

**Table 3** Post-transplant characteristics

	Overall patients (n=20)	Low risk (n=9)	High risk (n=11)
WBC engraftment (days after transplant) (median; range)	16 (9–25)	16 (12–23)	16 (9–27)
Platelet recovery > 20 × 10 <sup>9</sup> /l (days after transplant) (median; range)	19 (8–31)	18 (15–22)	22 (8–31)
Platelet recovery > 50 × 10 <sup>9</sup> /l (days after transplant) (median; range)	23 (9–46)	22 (18–25)	23 (9–46)
Acute GVHD (grades I–II)	13	4	9
Acute GVHD (grades III–IV)	3	2	1
Chronic GVHD	6	3	3
Graft failure	2	0	2
Complete chimerism	13	7	6
Relapse	3	1	2
Deceased patients	11	3	8
Time (months) from transplantation to death (median; range)	6.5 (1–34)	2 (2–7)	8 (1–34)

with platelet counts > 20 × 10<sup>9</sup>/l without support. Acute and chronic GVHD was graded according to the Seattle criteria,<sup>17,18</sup> and for transplant-related mortality (TRM) the time period by day +100 after transplantation was taken into consideration. For the analysis of bone marrow chimerism, we used PCR with amplified variable number tandem repeat (VNTR) DNA markers.<sup>19</sup>

Cumulative estimates were calculated by the method of Kaplan and Meier.<sup>20</sup> Comparisons between risk groups were done by log-rank test (Mantel-Haenszel) and exploratory interpretation of Fisher's exact test. Resulting probabilities were accepted as significant if they were less than 0.05 (two-sided tests).

## Results

Granulocyte engraftment was achieved in 18 of 20 patients (90%) and 19 patients experienced platelet recovery (95%). The median time to leukocyte engraftment was 16 days in both patient groups. Among the splenectomized patients, granulocyte recovery could be assessed after a median

time of 14 days, while the patients without splenectomy showed neutrophil engraftment 20 days after transplant ( $P=0.054$ ). Platelet counts above 20 × 10<sup>9</sup>/l were achieved after 18 days in the low-risk group and after 22 days in the high-risk group. Splenectomized patients demonstrated a shorter time to platelet recovery (median 17 days) as compared to patients without splenectomy (median 22 days) ( $P=0.08$ ). Failure of sustained neutrophil engraftment was observed in two of the patients (10%), with one primary and one secondary graft failure in the high-risk group after transplantation from a HLA-identical-related and a mismatched related donor, respectively. Primary graft failure occurred after conditioning with TBI and cyclophosphamide and transfusion of 3.0 × 10<sup>6</sup>/kg CD34 + peripheral blood stem cells. A patient transplanted with CD34 highly purified blood stem cells from a partially HLA-identical family member experienced secondary graft failure. This patient received successful second PBSCT from his HLA-identical sister using fludarabine and cyclophosphamide as preparative regimen.

Outcome of the 20 patients with MMM after transplantation is summarized in Table 3. Cumulative incidence of

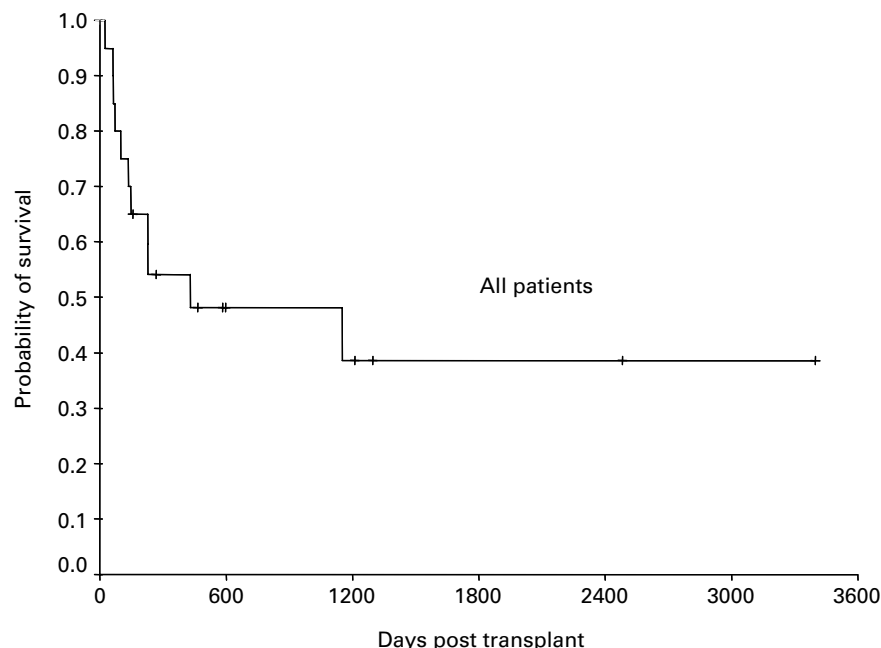
acute GVHD grades I–IV could be ascertained in 80% of all patients. Three patients (15%) developed acute GVHD grades III–IV. Within the low-risk group, the incidence rate for grades I–II GVHD was 44% (four of 9 patients) and among the high-risk patients it was 82% (nine of 11). Grades III–IV GVHD occurred in two cases (22%) within the low-risk and one case (9%) within the high-risk group. Chronic GVHD occurred in three patients of each group.

Out of 20 patients transplanted, 11 (55%) died, three (33%) in the low-risk and eight (73%) in the high-risk group ( $P=0.09$ ). Causes of death were infections ( $n=5$ ), relapse ( $n=3$ ), GVHD ( $n=1$ ), lymphoproliferative disorder ( $n=1$ ), and suicide ( $n=1$ ). Among the deceased patients, the median time of post-transplant survival was 8 months. Four patients (20%) died from direct transplant-related causes and an estimated TRM by day 100 after transplant could be assessed with  $22 \pm 14\%$  for low-risk and  $27 \pm 13\%$  for high-risk patients. All patients with transformation into secondary AML prior to transplantation died (median survival 136 days); two of them were shown to have incomplete chimerism after SCT. The probability of survival after transplantation is shown in Figure 1 for all patients and in Figure 2 for the different risk groups, showing the high-risk group including patients with leukemic transformation. Post-transplant median follow-up was 13 months (range 1–112 months) for all patients. The estimated overall survival could be assessed with  $38.5 \pm 12.6\%$  for all patients, with a median survival of 430 days (range: 26–3397 days) after transplant. Among low-risk patients, the 3-year probability of survival following transplantation was  $67 \pm 16\%$ , with a median survival of 583 days and a relapse-free survival of 51%. The estimated 3-year probability of survival among the high-risk patients could be specified with  $16 \pm 14\%$ , with a relapse-free survival of 17%. High-risk patients exclusive of patients

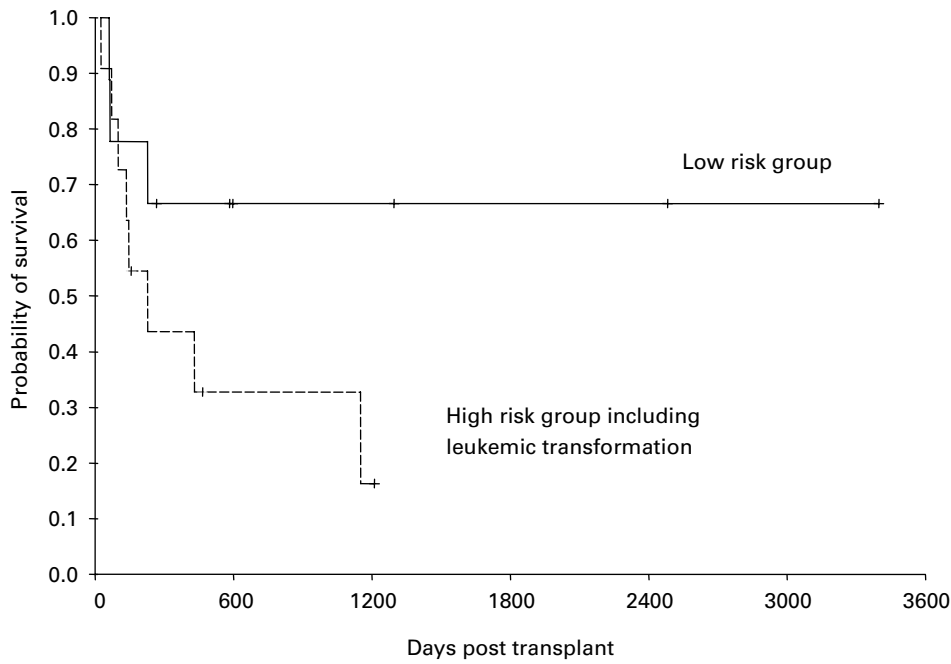
with leukemic transformation were shown to have an estimated 3-year survival of  $27 \pm 21\%$  (Figure 3). Differences regarding post-transplant survival between patient risk groups did not reach statistical significance,  $P$ -value was 0.11. Three relapses were diagnosed between 1 and 14 months post-transplant (median 3 months).

## Discussion

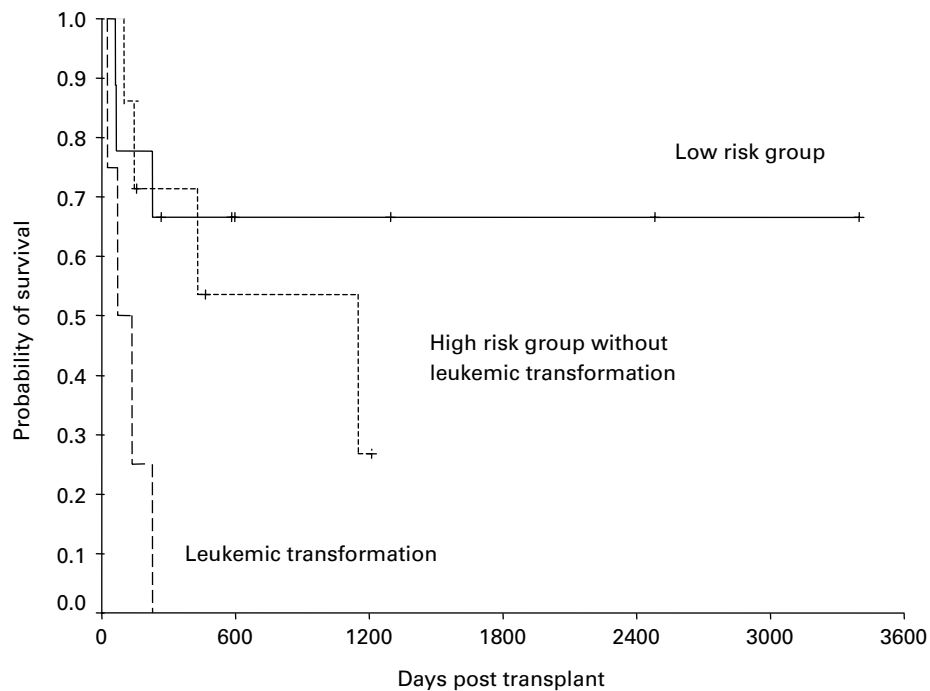
Bone marrow fibrosis in MMM is the consequence of the neoplastic proliferation of a pluripotent stem cell.<sup>2</sup> Owing to the heterogeneity in the presentation and clinical course of MMM, there is a wide variation concerning the median survival,<sup>7,8</sup> which makes the decision whether and when to transplant affected patients difficult. Several studies identified prognostic features for survival in MMM with conservative treatment and different scoring systems could be elaborated.<sup>6,7</sup> However, until now, allogeneic SCT remains the only treatment that can cure MMM, but is associated with an estimated 1-year TRM of 27%.<sup>12</sup> Previous reports demonstrated the feasibility of allogeneic SCT in MMM, showing that long-lasting complete hematologic remissions can be achieved in a substantial number of patients, which was also accompanied by regression of marrow fibrosis.<sup>11–13</sup> However, investigations on post-transplant survival in MMM demonstrated that low hemoglobin ( $\leq 10$  g/dl), osteosclerosis, clonal chromosomal aberrations, high Dupriez severity score or low platelet counts prior to transplantation were predictors for decreased survival.<sup>12,13</sup> These findings imply that those differences in post-transplant survival result from the individual risk profile, which again reflects the stage of disease. Since low hemoglobin levels and severe marrow fibrosis prior to SCT are recognized as relevant predictors



**Figure 1** Estimated overall survival for all patients ( $n=20$ ) transplanted.



**Figure 2** Kaplan-Meier estimates of post-transplant survival for low-risk ( $n=9$ ) and all high-risk ( $n=11$ ) patients.



**Figure 3** Estimated post-transplant survival for low-risk patients ( $n=9$ ), high-risk patients without leukemic transformation ( $n=8$ ), and patients with leukemic transformation ( $n=3$ ).

for decreased survival of MMM patients, we used these determinants together with the presence of peripheral blasts to assess whether risk factors were of use for an independent series of patients treated in a single center. An improvement of outcome in allogeneic transplantation for chronic myeloid leukemia originated among other

things from a precise definition of risk factors.<sup>21</sup> It can be suggested that, as for CML, pre-transplant risk evaluation in MMM may facilitate decision-making strategies concerning allogeneic SCT, which could then lead to better results in the treatment of chronic myeloproliferative disorders.

In the present study, post-transplant survival was demonstrated to be different between the two risk groups, without reaching statistical difference but showing a clear trend. Even if patients with leukemic transformation were excluded from the high-risk group, the survival estimates still clearly differed between the risk groups. Of note is that the low-risk group is composed of patients who received grafts from sibling donors, whereas four patients in the high-risk group were transplanted from unrelated donors. However, comparison between HLA-identical sibling donors, partially matched family donors and matched unrelated donors regarding transplantation outcome has shown no significant differences in overall survival after hematopoietic SCT.<sup>22</sup>

Although more than a half of the patients were characterized by grade 3 marrow fibrosis, platelet engraftment was not a problem and the median white blood cell recovery could be documented at day 16 after transplantation. This observation corroborates previous experiences demonstrating marrow fibrosis not to be a barrier to successful allogeneic stem cell engraftment.<sup>11,23</sup> Nevertheless, we observed one primary graft failure in a high-risk patient with post-thrombocytopenic myelofibrosis, who received peripheral blood stem cells from a matched unrelated donor after conditioning with TBI and cyclophosphamide. Graft failure may have resulted from a low number of transfused CD34+ cells, which was  $3.0 \times 10^6/\text{kg}$  in this case. One secondary graft failure in the high-risk group occurred after transplantation of CD34 highly purified peripheral blood stem cells. Since there is some evidence for a graft-versus-myelofibrosis effect,<sup>6,24</sup> the lack of donor lymphocytes may have contributed to graft rejection.

Owing to the high mortality rate for patients with myelofibrosis undergoing splenectomy, its role in MMM remains controversial. We observed that splenectomized patients tend to have earlier platelet and neutrophil recovery, which corroborates previous reports.<sup>12,13</sup>

In a collaborative study with a cohort of 55 patients who received allogeneic SCT from HLA-matched siblings (49 patients) or alternative donors (six patients), the 5-year probability of survival was 47% for all patients but only 23% for patients with hemoglobin levels  $< 10 \text{ g/dl}$  receiving pre-transplant RBC transfusions.<sup>12</sup> The 1-year probability of TRM was 27%. Our results are comparable and furthermore show that classification of MMM patients into risk groups depending on the presence of adverse prognostic factors is reasonable. Two or more risk factors at the time of transplant point to an advanced stage of disease comparable to accelerated or blastic phase in CML. In both entities of myeloproliferative disorders, advanced disease stages seem to go along with a decreased probability to survive allogeneic SCT. This is of clinical relevance concerning the decision for transplantation and in order to refine the prognostic accuracy. Our results support the view that allogeneic SCT for MMF should be considered before poor prognostic determinants develop. For high-risk patients with a decreased prognosis to survive transplantation, myeloablation and autologous peripheral blood stem cell rescue or reduced intensity allogeneic SCT might be more appropriate treatment options.<sup>25,26</sup>

## References

- 1 Bouroncle B, Doan CA. Myelofibrosis: clinical, hematologic and pathologic study of 110 patients. *Am J Med Sci* 1962; **243**: 697–715.
- 2 Tefferi A. Myelofibrosis with myeloid metaplasia. *N Engl J Med* 2000; **342**: 1255–1265.
- 3 Jacobson RJ, Salo A, Fialkow PJ. Agnogenic myeloid metaplasia: a clonal proliferation of hemopoietic stem cells with secondary myelofibrosis. *Blood* 1978; **5**: 189–194.
- 4 Rameshwar P, Denny TN, Stein D, Gascón P. Monocyte adhesion in patients with bone marrow fibrosis is required for the production of fibrogenic cytokines. *J Immunol* 1994; **153**: 2819–2830.
- 5 Chagraoui H, Komura E, Tulliez M et al. Prominent role of TGF-beta 1 in thrombopoietin-induced myelofibrosis in mice. *Blood* 2002; **100**: 3495–3503.
- 6 Cervantes F, Barosi G, Demory JL et al. Myelofibrosis with myeloid metaplasia in young individuals: disease characteristics, prognostic factors and identification of risk groups. *Br J Haematol* 1998; **102**: 684–690.
- 7 Dupriez B, Morel P, Demory JL et al. Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. *Blood* 1996; **88**: 1013–1018.
- 8 Cervantes F, Pereira A, Esteve J et al. Identification of 'short-lived' and 'long-lived' patients at presentation of idiopathic myelofibrosis. *Br J Haematol* 1997; **97**: 635–640.
- 9 Rozman C, Giralt M, Feliu E et al. Life expectancy of patients with chronic nonleukemic myeloproliferative disorders. *Cancer* 1991; **67**: 2658–2663.
- 10 Hoffman R, Silverstein MN. Agnogenic myeloid metaplasia. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silverstein LE (eds). *Hematology: Basic Principles and Practice*, 2nd edn. Churchill Livingstone: New York, USA, 1995, pp 1160–1174.
- 11 Anderson JE, Sale G, Appelbaum FR et al. Allogeneic marrow transplantation for primary myelofibrosis and myelofibrosis secondary to polycythaemia vera or essential thrombocytosis. *Br J Haematol* 1997; **98**: 1010–1016.
- 12 Guardiola P, Anderson JE, Bandini G et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: a European group for blood and marrow transplantation, société française de greffe de moelle, gruppo italiano per il trapianto midollo osseo, and Fred Hutchinson cancer research center. *Blood* 1999; **93**: 2831–2838.
- 13 Deeg J, Gooley TA, Flowers ME et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. *Blood* 2003; **102**: 3912–3918.
- 14 Laszlo J. Myeloproliferative disorders (MPD): myelofibrosis, myelosclerosis, extramedullary hematopoiesis, undifferentiated MPD, and hemorrhagic thrombocytopenia. *Semin Hematol* 1975; **12**: 409–432.
- 15 Murphy S, Peterson P, Iland H, Laszlo J. Experience of the polycythemia study group with essential thrombocytopenia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. *Semin Hematol* 1997; **34**: 29–39.
- 16 Thiele J, Kvasnicka HM, Fischer R. Histochemistry and morphometry on bone marrow biopsies in chronic myeloproliferative disorders – aids to diagnosis and classification. *Ann Hematol* 1999; **78**: 495–506.
- 17 Glucksberg H, Storb R, Fefer A et al. Clinical manifestations of graft-versus-host disease in human recipient of marrow from HLA-matched sibling donors. *Transplantation* 1974; **18**: 295–304.
- 18 Thomas E, Storb R, Clift RA et al. Bone-marrow transplantation. *N Engl J Med* 1975; **292**: 832–843.

- 19 Elmaagacli AH, Runkel K, Steckel N *et al*. A comparison of chimerism and minimal residual disease between four different allogeneic transplantation methods in patients with chronic myelogenous leukemia in first chronic phase. *Bone Marrow Transplant* 2001; **27**: 809–815.
- 20 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457.
- 21 Gratwohl A, Hermans J, Goldman JM *et al*. Risk assessment for patients with chronic myeloid leukemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Lancet* 1998; **352**: 1087.
- 22 Ottinger HD, Ferencik S, Beelen DW *et al*. Hematopoietic stem cell transplantation: contrasting the outcome of transplantations from HLA-identical siblings, partially HLA-mismatched related donors, and HLA-matched unrelated donors. *Blood* 2003; **102**: 1131–1137.
- 23 Soll E, Massumoto C, Clift RA *et al*. Relevance of marrow fibrosis in bone marrow transplantation: a retrospective analysis of engraftment. *Blood* 1995; **86**: 4667–4673.
- 24 Cervantes F, Rovira M, Urbano-Ispizua A *et al*. Complete remission of idiopathic myelofibrosis following donor lymphocyte infusion after failure of allogeneic transplantation: demonstration of a graft-versus-myelofibrosis effect. *Bone Marrow Transplant* 2000; **26**: 697–699.
- 25 Anderson JE, Trefferi A, Craig F *et al*. Myeloablation and autologous peripheral blood stem cell rescue results in hematologic and clinical responses in patients with myeloid metaplasia with myelofibrosis. *Blood* 2001; **98**: 586–593.
- 26 Tanner ML, Hoh CK, Bashey A *et al*. FLAG chemotherapy followed by allogeneic stem cell transplant using nonmyeloablative conditioning induces regression of myelofibrosis with myeloid metaplasia. *Bone Marrow Transplant*. 2003; **32**: 581–585.