

Allogeneic Hemopoietic Stem Cell Transplantation for Myelofibrosis

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ABSTRACT

Fifty-six patients, 10–66 years of age, with idiopathic myelofibrosis (IMF) or endstage polycythemia vera or essential thrombocythemia received allogeneic hemopoietic cell transplants from related (n=36) or unrelated (n=20) donors. Forty-four patients were prepared with busulfan plus cyclophosphamide, and 12 with total body irradiation plus chemotherapy. The source of stem cells was marrow in 33, and peripheral blood in 23 patients. All but three patients achieved engraftment. While 50 patients showed complete donor chimerism, three patients were found to be mixed chimeras 26, 48, and 86 months post-transplant, respectively. Two patients died from relapse/progressive disease, and 18 from other causes. Thirty-six patients are surviving at 0.5–11.6 (median 2.8) years for a 3-year Kaplan-Meier estimate of 58% (CI 43%, 73%). Dupriez score, cytogenetic abnormalities and degree of marrow fibrosis were the most significant risk factors for post-transplant mortality. Patients conditioned with a regimen of busulfan targeted to plasma levels of 800–900 ng/mL plus cyclophosphamide had a higher probability of survival (76% [CI 62%, 91%]) than other patients. Results with unrelated donors were comparable to those with HLA-identical sibling transplants. Thus, allogeneic hemopoietic cell transplantation offers long-term relapse-free survival for patients with myelofibrosis.

INTRODUCTION

Idiopathic myelofibrosis (IMF) is characterized by a leukoerythroblastic peripheral blood smear, splenomegaly, and extramedullary hemopoiesis. With conservative management, life expectancy may range from only a few months to more than a decade.¹ Eventually, progressive hemopoietic failure or leukemic transformation leads to the patients' demise. A similar clinical picture may develop in 15–20% of patients with advanced polycythemia vera (P. vera) and 10% of patients with essential thrombocythemia (ET).^{2,3} At that stage, treatment options for those diseases are limited, and the prognosis is poor.

Anemia, thrombocytopenia, increase in immature white blood cells in circulation, and hepatomegaly are some of the poor-risk prognostic factors identified in patients with myelofibrosis.⁴⁻⁶ Patients with IMF with either a hemoglobin (Hgb) <10 g/dL or a white blood count (WBC) <4 x 10⁹/L or >30 x 10⁹/L have a median life expectancy of about 2 years.⁷ Patients who “require” splenectomy (because of massive spleen enlargement, transfusion-dependent anemia, or thrombocytopenia) also have a median life expectancy of approximately 2 years. Presumably the indications that lead to splenectomy are manifestations of disease progression.⁸ In addition, abnormal karyotype and osteomyelosclerosis are considered poor prognostic features.

As these disorders are clonal diseases of hemopoietic stem cells, it should be possible to cure them by hemopoietic cell transplantation (HCT). The marrow fibrosis is thought to be a reactive process of non-clonal fibroblasts, possibly mediated by transforming growth factor- β released by

megakaryocytes, and other signals.⁹ Thus, removal of the abnormal clone and replacement by normal precursors from healthy donors should eliminate the stimulus for a reaction of the marrow environment, and the fibrosis should regress. This notion is supported by preliminary observations.¹⁰⁻¹⁷

Here we summarize results in 56 patients with myelofibrosis treated at a single institution and transplanted from HLA-identical siblings or alternative related or unrelated donors.

PATIENTS AND METHODS

Patients

Patients with IMF or with myelofibrosis developing with P. vera or ET, and patients with myeloproliferative disorders that were not otherwise specified but were associated with myelofibrosis, were referred to the Fred Hutchinson Cancer Research Center (FHCRC) for HCT because of peripheral blood cytopenias, spent phase disease or leukemic transformation. From February 1980 through May 2002, 56 patients were transplanted, all but three of them since 1994. While 12 patients were prepared with radiation-containing conditioning regimens, 44 patients were enrolled prospectively in a trial that used busulfan (BU) in combination with cyclophosphamide (CY). Patient characteristics are summarized in Table 1. Karyotypes were normal in 28 patients, and in six patients material was insufficient for analysis. Clonal cytogenetic abnormalities in marrow cells were present in 22 patients: +8 (\pm other abnormalities) in five, 20q- or -20 in three, 13q- in one, 7q- in one, various translocations in five, and other

structural or numeric abnormalities in seven patients. Twenty patients had undergone splenectomy at various intervals before HCT, generally because of symptoms related to massive splenomegaly. Twenty patients had been transfused with red blood cells, platelets or both, 14 had received hydroxyurea, 8 interferon, 5 anagrelide, 4 corticosteroids, 4 erythropoietin, 2 chemotherapy other than hydroxyurea, 11 had been given a variety of other therapies, and 19 patients had not received prior therapy.

The indications for transplantation included single or multilineage peripheral blood cytopenias (platelets $<100 \times 10^9/L$; Hgb $<10 \text{ g/dL}$; neutrophils $<1.5 \times 10^9/L$) (n=35), leukemic transformation (n=5) or “spent phase” of P. vera or ET (n=15). One patient presented originally with a myeloproliferative disorder consistent with IMF (normal karyotype on two determinations), and received supportive therapy only. Prolonged follow-up showed a rise in leukocytes, and eventually cytogenetic analysis revealed a t(2; 9; 22), a picture consistent with the development of chronic myeloid leukemia on the background of IMF. In two patients, the pre-transplant work-up revealed evidence for non-Hodgkin lymphoma on cervical lymph node biopsies. The possibility of lymphoma-associated myelofibrosis could not be categorically excluded. However, the extent of lymphoma was minimal, and the patients were considered to have two synchronous malignancies and remained in the study. All patients had given informed consent according to the requirements of the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Data on 13 of these patients were included in a previous report.¹¹

Disease classification

For the purpose of risk analysis, the disease was classified based on pre-transplant findings, using the criteria proposed by Dupriez et al. for IMF:⁷ Hgb values (≥ 10 [favorable] vs. < 10 g/dL) and WBC (> 4 and $< 30 \times 10^9/L$ [favorable] vs. either < 4 or $> 30 \times 10^9/L$). Patients with both parameters in the favorable range were classified as good risk (score 1), those with one favorable parameter as intermediate risk (score 2), and those without favorable parameters, as high risk (score 3). In addition, we considered platelet counts ($\geq 100 \times 10^9/L$ vs. $< 100 \times 10^9/L$), cytogenetic abnormalities, and degree of marrow fibrosis (graded as 1, 2 or 3, with 3 including patients who showed evidence of osteosclerosis) using a grading scheme as reported recently.¹³

Donor selection

HLA-typing was carried out as described.¹⁸ Thirty-six patients had suitable related donors (genotypically HLA-identical siblings in 31, and family members who were HLA genotypically identical for one haplotype but differed for one or two HLA antigens on the second haplotype in 5 patients). Unrelated donors were identified for 20 patients; 14 were HLA-matched with the patient, and six were HLA-mismatched as determined by intermediate or high resolution typing.^{19,20}

Transplantation

Donor and transplant characteristics are summarized in Table 2. Forty-four patients were conditioned with a combination of BU, 1 mg/kg given orally every 6 hours over 4 days (16 mg total), followed by CY, 60 mg/kg i.v. for 2 consecutive days. In 39 of these patients, BU doses were adjusted to achieve steady state plasma levels of 800-900 ng/mL (targeted BU) as

described.^{21,22} The remaining patients, enrolled in the initial phase of this trial, were conditioned with total body irradiation (TBI) in combination with either BU or CY as described.^{23,24} The source of stem cells was bone marrow in 33, and G-CSF–mobilized cells from peripheral blood in 23 patients. In all but three patients, GVHD prophylaxis consisted of a combination of cyclosporine (CSP) and methotrexate (MTX) or CSP and mycophenolate mofetil (MMF). Acute and chronic GVHD were evaluated according to established criteria.^{25,26}

Criteria for engraftment and response

The day of engraftment was defined as the first of 3 consecutive days on which blood granulocytes rose to $0.5 \times 10^9/L$.²⁷ Donor cell engraftment was documented by sex chromosome analysis (in patients with opposite sex donor) or by analysis of variable number tandem repeats for which patient and donor differed.

In patients with marrow fibrosis, transplant-mediated complete remission was defined as 100% donor cell engraftment and evidence of regression of fibrosis as determined by sequential bone marrow biopsies (the tempo of regression of fibrosis varied considerably). In patients with myelodysplastic features or with frank leukemia, regression of marrow fibrosis, absence of leukemic blasts and disappearance of dysplastic changes were required for complete remission.¹³

Statistical analysis

Proportional hazards regression models were used to assess the association of various factors with the hazard of failure for time-to-event endpoints such as overall mortality and relapse. Time to engraftment was compared between groups with the two-sample t-test among patients who

engrafted. Proportions of patients who engrafted were compared with the chi-square test. Survival estimates were obtained using the method of Kaplan and Meier. Cumulative incidence estimates were used to summarize the probability of GVHD and relapse, where deaths without GVHD and deaths without relapse were regarded as competing events for the respective endpoints.²⁸ Reported p-values associated with regression models were derived from the Wald test, and all p-values are two-sided. No adjustments were made for multiple comparisons. Results were analyzed as of June 1, 2002.

RESULTS

Engraftment and Relapse

Granulocyte engraftment as defined under *Methods* was achieved in 53 of 56 patients (95%), and platelet engraftment in 40 patients by the time they left the transplant center. Eventually all surviving patients except one recovered normal platelet counts. The median time to granulocyte engraftment was 17 days among splenectomized patients, and 24 days among patients without splenectomy ($p=0.01$). The corresponding figures for platelet engraftment were 16 and 24 days, respectively ($p=0.06$).

All patients transplanted from HLA-identical related donors had sustained engraftment. One of five patients transplanted from HLA-nonidentical related donors, and 2 of 20 patients transplanted from unrelated donors experienced primary graft failure; all three had been conditioned with targeted BUCY and received marrow as a source of stem cells. Three additional

patients, one transplanted from an HLA-nonidentical family member and two from HLA-identical unrelated donors, showed initial complete donor cell engraftment. However, chimerism studies on marrow cells obtained 26, 48 and 86 months after transplantation, respectively, showed 'mixed chimerism' with 80% to 98% host cells. In two of these patients the underlying diagnosis was IMF, and in one P. vera. The patient with P. vera also showed a rising hematocrit. The donor component among marrow CD33⁺ cells increased again from a low of 15% to 80%, and among CD3⁺ cells from 50% to 99% over the ensuing 9 months and the hematocrit normalized without therapeutic interventions. The two patients with IMF have remained mixed chimeras without morphologic or cytogenetic evidence of disease.

Thus, failure of sustained engraftment occurred in 6 of 25 patients (26%) transplanted from alternative donors (p=0.04; HR 0.1, CI 0.01-0.9). All relapses and failures of sustained engraftment occurred among the 33 patients transplanted with marrow cells, leading to a difference in the proportion of failures as compared to patients transplanted with peripheral blood progenitors (p=0.04). Among 20 patients with prior splenectomy, four failed to achieve sustained engraftment, compared to 2 of 36 without splenectomy (p=0.17). Also, none of 21 CMV negative patients transplanted from CMV negative donors failed to engraft, compared to 5 of 26 transplants where either the patient or the donor (or both) were CMV positive, and 1 of 9 in whom CMV information was incomplete.

GVHD

Thirty-eight patients developed acute GVHD grades II-IV for a cumulative incidence of 68% (12 patients [21%] had grades III-IV). Incidence rates were similar for HLA-identical related (21 of

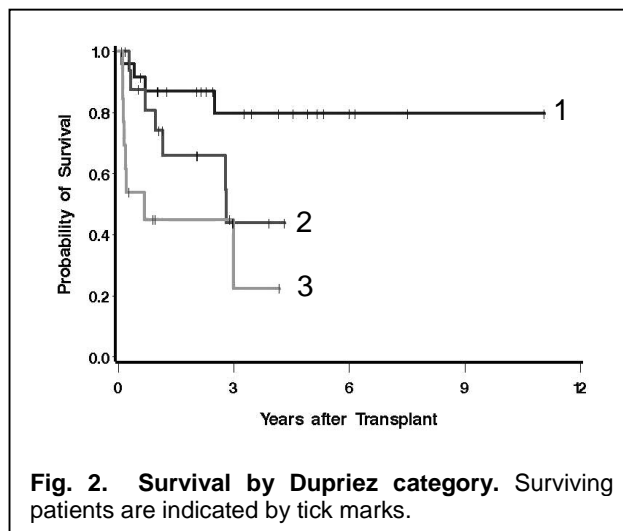
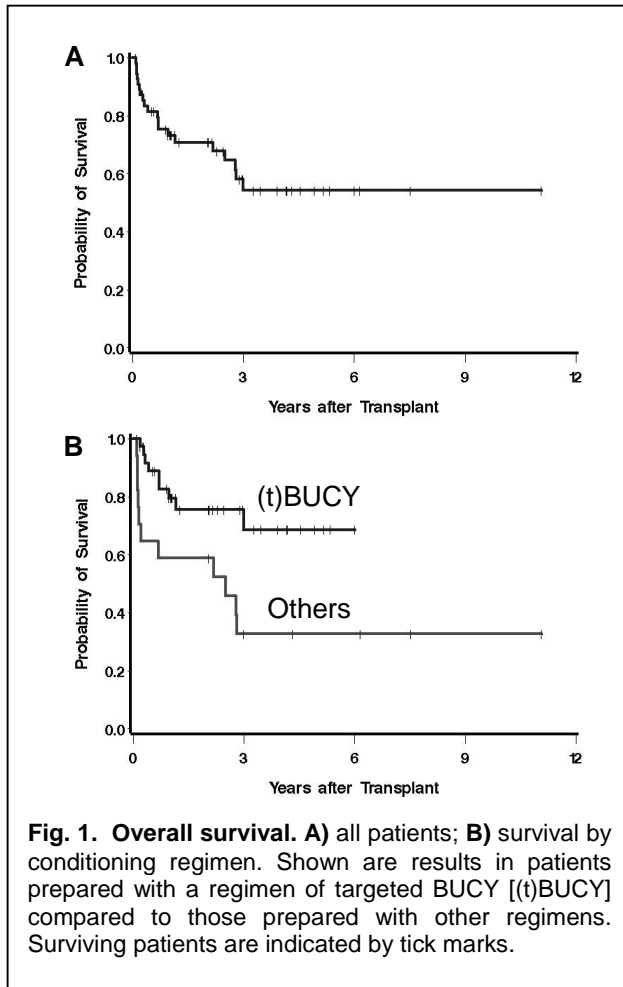
31) and alternative donor transplants (17 of 25). Chronic GVHD occurred in 31 among 54 evaluable patients for a cumulative incidence of 59% at 2 years; it was limited in 3, and extensive in 28 patients. Sixteen patients still require immunosuppressive therapy at 6 months to 3 years after transplantation.

Toxicity and causes of death

Twenty patients have died (Table 3), eight within 100 days of transplantation, and 12 between 4 months and 3 years after transplantation. The most frequent causes of death were pneumonia and disseminated infections, often caused by viral or fungal organisms (seven patients dying within 100 days, and six patients dying later). Two patients died of progressive disease. GVHD was the primary cause of death in two patients, and one patient developed a lymphoma (in host cells) 1 year after transplantation. Nine of 12 patients prepared with TBI-containing regimens died, compared to 2 of 5 prepared with BUCY without dose adjustment, and 9 of 39 given BUCY with BU dose adjustment. Steady state BU levels, determined in 37 patients, ranged from 682 to 1154, mean 845 (SD±97) ng/mL. Among eight of these patients who died from transplant-related causes, BU_{SS} levels were 830±80 ng/mL compared to 849±101 ng/mL among 29 patients who survived.

Survival and responses

Currently, 36 patients are surviving 0.5 to 11.6 (median 2.8) years after transplantation (Figure 1A) including two patients with initial graft failure. One received a successful second transplant using G-CSF–mobilized peripheral blood cells (rather than marrow) from the original donor after conditioning with tBUCY. The second patient is in remission on interferon therapy.



Three additional patients are “mixed chimeras.” Survival was superior in patients conditioned with a targeted BUCY regimen (Figure 1B). Table 4 summarizes univariate regression models for the outcome “overall mortality.” Neither type of donor, source of stem cells, presence of excess blasts, duration of disease prior to HCT, nor splenectomy were statistically significantly associated with the hazard of mortality. Because of the small numbers of patients and events in some of the resulting groups, the possibility that clinically relevant differences exist but failed to reach statistical significance must be considered.

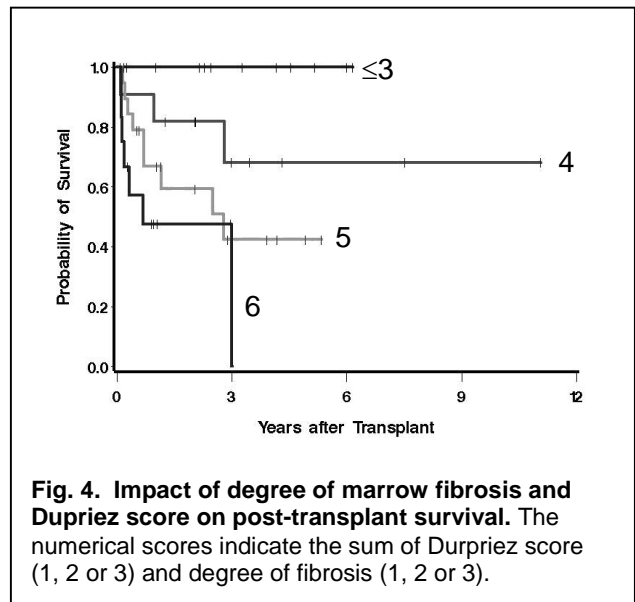
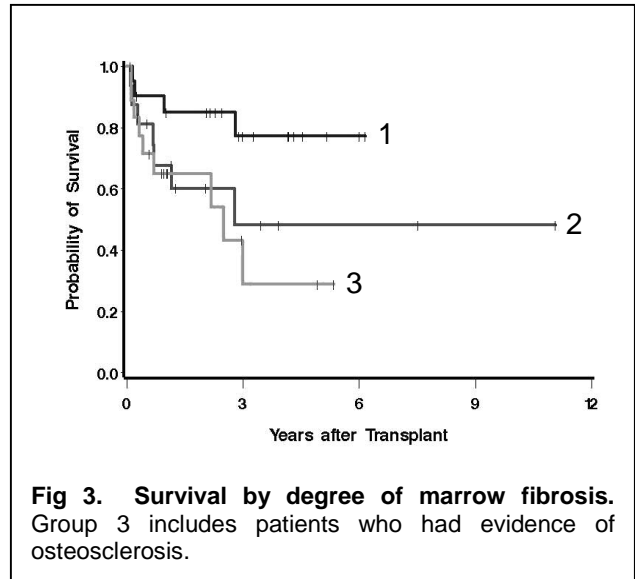
Increasing severity by Dupriez classification (Figure 2) and clonal cytogenetic abnormalities were significantly associated with post-transplant mortality. The degree of marrow fibrosis was suggestively associated with the hazard of mortality, with increasing fibrosis leading to worse outcome (Figure 3; Table 4). There was also a suggestion of

increasing hazard of death with increasing age in univariate analysis ($p=0.07$) and in several

multivariable models. Higher platelet counts at transplant were associated with improved outcome (Table 4).

Several of the variables associated with outcome were also correlated with each other. Due to the small number of events (20 deaths), the ability to fit multivariable regression models was limited. Nonetheless, several models were fit, some of which are summarized in Table 5. In general, the qualitative conclusions resulting from the univariate models remained after examining each of the multivariable models (data not shown). This finding indicates that each of the factors that yielded a suggestive or statistically significant association with the hazard of mortality in the univariate models actually was associated with mortality, and not simply through an association with other factors. Two models in particular were of

note. One considered Dupriez classification and degree of myelofibrosis, and the second, Dupriez classification and peripheral blood platelet counts. Both models suggest that factors



added to the Dupriez classification improved prognostic accuracy for post-transplant outcome (Figure 4).

At the most recent follow-up, 6 months to 10 years after transplantation, patients had WBCs of 2.5-13.6 x 10⁹/L (median 6.8), ANC 1.68-5.9 (median 2.9) x 10⁹/L, platelets 49-313 (median 190) x 10⁹/L, and hematocrit 25-42.3 (median 39). Follow-up marrow biopsies were available in 49 patients, 6 months to 8 years after transplantation. Among these, 30 showed no fibrosis or only traces of marrow fibrosis (some as early as 12 months after transplantation), 13 were staged as showing grade 2, and 6 as grade 3 even 2 years after transplantation. Among 27 survivors without splenectomy, 18 had spleens of normal size, in 7 the spleen was “palpable” at the costal margin, in two patients the spleen reached to 14 cm (at 6 months) and 21 cm (at 10 months), respectively, below the costal margin, and in 2 no information was available.

DISCUSSION

This study of HCT in patients with myelofibrosis of various etiologies extends previous reports which suggest that HCT offers curative therapy for these disorders.¹³ Most patients enrolled in this trial had received conventional management, frequently over extended periods of time, and came to transplantation only when other therapeutic measures were not or no longer effective. Other patients had not been treated, and by the Dupriez criteria, would be considered good-risk patients. However, as outlined above, other factors such as the degree of marrow fibrosis and clonal cytogenetic abnormalities also affected outcome. The results show that in these patients

with advanced disease successful HCT is possible not only with related but also with unrelated donors. Patients with lower Dupriez scores, higher platelet counts, less severe marrow fibrosis, and normal karyotype fared better than patients with more advanced disease. Multivariable analyses showed that incorporation of the degree of marrow fibrosis and peripheral blood platelet counts, in addition to the Dupriez severity score (which considers hemoglobin and leukocyte count only), into a grading scheme allowed for refinement of prognostic accuracy. Peripheral blood CD34+ cell counts, identified by Barosi et al. as a measure of disease progression,²⁹ were not available consistently and, thus, were not included in the analysis. All 12 patients who had low-risk Dupriez scores along with grade I (mild) fibrosis, and platelet counts $\geq 100 \times 10^9/L$ are surviving in remission. The probability of survival decreased in parallel to an increase in the cumulative scores of all these parameters. The Dupriez score correlated with platelet counts: two of 23 patients (9%) with a score of 1 had platelet counts of less than $100 \times 10^9/L$, compared to 3 of 14 (21%) with a score of 2, and 8 of 11 (73%) with a score of 3.

It is not clear why the degree of marrow fibrosis had an effect on outcome. In the non-transplant context, the degree of marrow fibrosis has not been found to correlate with prognosis. Conceivably the expansion of extramedullary hemopoiesis with more severe myelofibrosis results in tissue damage, for example in the form of fibrosis, in organs such as the lungs or liver. As a consequence, these organs may be more susceptible to transplant-related complications, while in the absence of conditioning, therapy (i.e. in patients who are not transplanted), such an effect would not become manifest.

Second only to the Dupriez score, an abnormal karyotype had the strongest negative effect on survival. While only 6 of 31 patients with normal karyotypes died, 11 of 19 with clonal cytogenetic abnormalities succumbed to various complications. The significance of clonal cytogenetic abnormalities for prognosis in patients with myelofibrosis is not clear. Tefferi et al. observed abnormal karyotypes in 57% of 165 patients, in particular 20q-, 13q-, +8, +9, 12p- and abnormalities of chromosomes 1 and 7.³⁰ The presence of +8, found in five patients in the current series, or 12p- was associated with inferior survival. While additional work is needed, the data presented here support the concept that an abnormal karyotype represents a high risk feature, certainly with HCT.

Among factors other than disease characteristics, the transplant conditioning regimen had a significant effect on outcome. It is of note, however, that there was some correlation between Dupriez score and conditioning regimen: While 18 of 23 patients (78%) with a score of 1 were conditioned with targeted BUCY, 10 of 14 (71%) with a score of 2, and 5 of 11 (45%) with a score of 3 received that regimen. Since all patients with myelofibrosis, regardless of severity, were enrolled into the same protocol, and the targeted BUCY regimen was used consistently in the more recently transplanted patients, the observed association of conditioning regimen and disease score apparently reflects a recent trend towards earlier referral of patients for transplantation. Nevertheless, the beneficial effect of a targeted BUCY regimen remained even after adjusting for the Dupriez score. Furthermore, patients prepared with targeted BUCY tended to be older than patients conditioned with other regimens (median 45.7 vs. 40.4 years; $p=0.07$). These results with a targeted BUCY regimen are in agreement with observations in patients with chronic myelogenous leukemia (CML)²¹ and with myelodysplastic syndrome,²⁴ which suggest

that maintenance of BU plasma levels within a narrow range contributes to improved regimen tolerance. There was a suggestion that transplant outcome was inferior in patients more than 50 years of age (see Tables 4 and 5). As myelofibrosis is frequently a disease of older patients who may experience more treatment-related toxicity, tolerability of the conditioning regimen is of central importance. BU targeting appears to contribute to that objective. Devine et al. recently reported on four patients with myelofibrosis transplanted after “reduced intensity” conditioning with fludarabine and melphalan.³¹ All four patients achieved engraftment and were surviving 11-19 months after transplantation. Whether these results can be confirmed in larger series or with other nonmyeloablative regimens that have been used for various indications³² remains to be determined.

Primary graft failure occurred in three patients in the present study who were transplanted with marrow cells from alternative donors. Delayed mixed chimerism was observed in another three patients, for an overall incidence of failure of complete and sustained donor cell engraftment of 10%. One of the patients with mixed chimerism with a primary diagnosis of P. vera showed a rising hematocrit about 7 years after transplantation and underwent several phlebotomies. Subsequently, without further intervention, blood cell counts normalized, and the proportion of host cells, both lymphoid and myeloid, progressively declined. The mechanism for such a phenomenon is unclear; the kinetics suggest a transient activity of a host clone surviving for years after transplantation. No disease marker was present in the other two mixed hemopoietic chimeras.

Concern about graft failure was a reason for the initial reluctance to carry out transplants in patients with myelofibrosis. The present study and other publications show, however, that graft failure is a problem only in a minority of patients, particularly those transplanted from “alternative” donors and given marrow as a source of stem cells. Despite this complication, overall outcome among patients transplanted from unrelated donors was comparable to that with HLA-identical sibling donors. This result is in keeping with reports which show that selection of unrelated donors on the basis of high resolution HLA typing can yield transplant results comparable to those achieved with HLA-genotypically identical sibling donors.²⁴

In conclusion, allogeneic hemopoietic cell transplantation offers curative therapy for patients with myelofibrosis, generally with structural normalization of the marrow. Results with HLA-identical unrelated donors are comparable to those with related donors, and HCT can be carried out successfully in patients in their 50s and 60s. The data suggest that, in patients who are interested in pursuing transplantation, HCT should be carried out before severe marrow fibrosis, clonal cytogenetic abnormalities, and severe abnormalities of hematologic parameters develop.

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Table 1. Patient and disease characteristics

Datum	Number of patients
Number of patients studied	56
Patient – age (yrs), range (median)	10–66 (43)
– Patient gender, M / F	28 / 28
Disease duration (ms), range (median)	3–312 (33)
Primary diagnosis	
– IMF	33
– ET with myelofibrosis	10
– P. vera with myelofibrosis	5
– Myelofibrosis with increased blasts*	5
– Other [†]	3
Degree of marrow fibrosis [‡]	
– 1 (mild)	21
– 2 (moderate)	17
– 3 (severe)	18
Dupriez classification at transplant [§]	
– Good	25
– Intermediate	17
– Poor	13
Platelet count at transplant [¶]	
≥ 100,000	40
< 100,000	15
Prior splenectomy	
– Yes / No	20 / 36

* All 5 had IMF.

[†] One patient had IMF that evolved to CML. Two patients had evidence of NHL in lymph nodes, suggesting the synchronous occurrence of two malignancies.

[‡] According to Guardiola et al.¹³

[§] Data incomplete in 1 patient.

[¶] Counts not available in 1 patient.

Abbreviations: IMF = idiopathic myelofibrosis; ET = essential thrombocythemia; P. vera = polycythemia vera.

Table 2. Donor and transplant characteristics

Datum		Number of patients
Donor age (yrs), range (median)	6–65 (39)	
Donor gender, M / F		31 / 25
Relationship		
– Related		36
– HLA-identical sibling	31	
– HLA-nonidentical relative*	5	
– Unrelated		20
– HLA-identical	14	
– HLA-nonidentical [†]	6	
Source of stem cells		
– Marrow		33
– Peripheral blood		23
Conditioning regimen		
– BUCY (targeted)		44 (39)
– BUTBI (1200)		7
– CYTBI (1200)		5
GVHD prophylaxis		
– MTX + CSP		50
– MMF + CSP		3
– MTX + FK506		2
– MTX		1
CMV status (patient/donor) [‡]		
+/+		10
+/-		10
-/+		6
-/-		21

* One donor was HLA phenotypically matched; two were mismatched for HLA-B, one for DR, and one for DR and DQ.

[†] Two were mismatched for DQB1, one each for HLA-A or HLA-B, and two for DR and DQ.

[‡] In nine patient/donor pairs, the information on CMV was incomplete.

Abbreviations: BU = busulfan; TBI = total body irradiation (cGy); MTX = methotrexate; CSP = cyclosporine; MMF = mycophenolate mofetil; FK506 = tacrolimus.

Table 3. Causes of death

Causes	Number of patients
Progressive disease/Relapse	2
Non-relapse causes	18
– Pneumonia / IPS	5*
– Other infections	8
– Invasive aspergillosis	3
– Aspergillosis + GVHD	2
– Encephalitis ± TTP	2
– VZV + HUS	1
– Intracranial hemorrhage	1
– GVHD	3
– NHL	1

*Cytomegalovirus was isolated in one patient.

Abbreviations: IPS = idiopathic pneumonia syndrome; GVHD = graft-vs.-host disease;

TTP = thrombotic thrombocytopenic purpura; VZV = varicella zoster virus;

HUS = hemolytic uremic syndrome; NHL = non-Hodgkin lymphoma.

Table 4. Univariate regression models for overall mortality.

Factor		Hazard Ratio	95% CI	p-value
(No. of pts. dying/all pts.)				
Conditioning Regimen				
Other Regimens (11/17)		1	---	---
Targeted BUCY (9/39)		0.3	0.1 to 0.8	.01
Platelet Count				
$\geq 10^9/L$ (10/40)		1	---	---
$< 10^9/L$ (9/15)		3.6	1.4 to 8.9	.006
Dupriez Classification				
1 (4/25)		1	---	---
2 (7/17)		2.9	0.9 to 10.1	.09
3 (8/13)		6.5	2.0 to 22.0	.002
Degree of Fibrosis				
1 (4/21)		1	---	---
2 (7/17)		2.9	0.8 to 9.9	.09
3 (9/18)		3.7	1.1 to 12.1	.03
Karyotype				
Normal	(6/29)	1	---	---
Clonal	(11/21)	5	1.5–18.2	.009
Age (years)		Increasing age,	---	.07
Modeled as a continuous linear variable		Increasing hazard		
Age (years)				
< 40 (5/19)		1	---	---
40-50 (7/20)		1.3	0.4 to 4.2	.61
> 50 (8/17)		2.5	0.8 to 7.6	.12
Splenectomy				
No	(14/36)	1	---	---
Yes	(6/20)	0.8	0.3 to 2.0	.58

Factor (No. of pts. dying/all pts.)	Hazard Ratio	95% CI	p-value
Excess Blasts			
No (17/51)	1	---	---
Yes (3/5)	1.8	0.5 to 6.2	.34
Source of Stem Cells			
BM (13/33)	1	---	---
PBSC (7/23)	1.1	0.4 to 2.8	.88
Donor			
Unrelated or Mismatched Related (10/25)	1	---	---
HLA-identical Sibling (10/31)	0.7	0.3 to 1.7	.42
Disease Duration			
(modeled as a continuous linear variable)	---	---	.85

Abbreviations: BM = bone marrow; PBSC = peripheral blood stem cells

Table 5. Multivariable regression models for overall mortality.

	Hazard Ratio	95% CI	p-value
Conditioning Regimen			
Other Regimens	1	---	---
Targeted BUCY	0.3	0.1 to 0.8	.01
Dupriez Classification			
1	1	---	---
2	2.3	0.7 to 8.1	.19
3	7.2	2.1 to 25.0	.002
Platelet Count			
$\geq 10^9/L$	1	---	---
$< 10^9/L$	2.2	0.8 to 6.0	.13
Dupriez Classification			
1	1	---	---
2	2.6	0.8 to 9.1	.13
3	4.5	1.2 to 16.9	.03
Degree of Fibrosis			
1	1	---	---
2	3.2	0.9 to 11.4	.08
3	2.8	0.8 to 9.4	.11
Dupriez Classification			
1	1	---	---
2	2.6	0.8 to 9.3	.13
3	6.5	1.8 to 22.9	.004

	Hazard Ratio	95% CI	p-value
Karyotype			
normal	1	---	---
clonal	5.3	1.5–18.2	.009
Dupriez			
1	1	---	---
2	0.8	0.2–3.6	.82
3	3.4	0.9–12.3	.06

Additional models considered were: conditioning regimen and fibrosis; conditioning regimen and platelet count; platelet count and fibrosis; conditioning regimen and age; Dupriez classification and age; fibrosis and age; platelet count and age. Those models did not appear to contribute substantially to the data shown above.

FIGURE LEGEND

Figure 1. Overall survival. A) all patients; B) survival by conditioning regimen. Shown are results in patients prepared with a regimen of targeted BUCY [(t)BUCY] compared to those prepared with other regimens. Surviving patients are indicated by tick marks.

Figure 2. Survival by Dupriez category. Surviving patients are indicated by tick marks.

Figure 3. Survival by degree of marrow fibrosis. Group 3 includes patients who had evidence of osteosclerosis.

Figure 4. Impact of degree of marrow fibrosis and Dupriez score on post-transplant survival. The numerical scores indicate the sum of Dupriez score (1, 2 or 3) and degree of fibrosis (1, 2 or 3).