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Allogeneic haematopoietic cell transplantation for myelofibrosis in 30 patients 60–78 years of age

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SUMMARY

We analysed the results of haematopoietic cell transplantation (HCT) in 30 patients aged 60–78 (median 65) years, with primary myelofibrosis or myelofibrosis evolving from antecedent polycythaemia vera or essential thrombocythemia. Donors were human leucocyte antigen (HLA)-identical siblings ($N = 15$) or unrelated individuals ($N = 15$). Various conditioning regimens were used, ranging from very low intensity (fludarabine plus 2 Gy total body irradiation) to high dose (busulfan plus cyclophosphamide). Stem cell sources were granulocyte colony-stimulating factor mobilized peripheral blood progenitor cells in 29 patients and marrow in one patient. Sustained engraftment was documented in 27 of 30 patients. Day -100 mortality was 13%. With a median follow-up of 22 (range 0.5–69) months, 3-year overall survival and progression-free survival were 45% and 40%, respectively. Currently, 13 patients are surviving. Seven patients died with disease progression at 0.5–22 months, and 10 patients died from other causes at 1.5–37.5 months after HCT. While the selection of older patients for transplantation was probably biased, the present results are encouraging. Motivated older patients with myelofibrosis without substantial comorbid conditions should be offered the option of allogeneic HCT.

Keywords

myelofibrosis, older patients; haematopoietic cell transplantation

INTRODUCTION

The clinical course of primary myelofibrosis (PMF) is variable, but always progressive. Dependent upon patient age and disease features at presentation, the median life expectancy may range from a few years to more than a decade (Cervantes *et al*, 2009). As the disease advances, patients generally become symptomatic due to varying degrees of anaemia or

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splenomegaly or both, and present with fatigue and other constitutional symptoms. Patients with polycythaemia vera (PV) or essential thrombocythaemia (ET) may have a rather benign course over many years or even decades. However, when they develop myelofibrosis and reach the advanced phase of their disease, splenomegaly and anaemia may lead to considerable morbidity, similar to that observed with PMF, and treatment options are limited (Tefferi *et al*, 2007). Eventually the disease may transform into acute leukaemia in a proportion of patients.

The recent identification of mutations in the *JAK2* gene in almost all patients with PV and 50%–60% of patients with PMF or ET has generated considerable enthusiasm about the possibility of developing compounds that might inhibit JAK2 autophosphorylation. Several such compounds are currently being tested in clinical trials (Mesa *et al*, 2008; Verstovsek *et al*, 2010). Data so far suggest that the major benefit is regression of splenomegaly and improvement in subjective well-being (Cervantes *et al*, 2009; Verstovsek *et al*, 2010; Mesa *et al*, 2008). While the follow-up of patients enrolled in clinical trials with JAK2 inhibitors is still short, inhibition of JAK2 is not expected to be curative for these diseases. Allogeneic haematopoietic cell transplantation (HCT) is currently the only treatment modality with proven curative potential (Cervantes *et al*, 2009; Kerbaux *et al*, 2007; Kröger *et al*, 2009; Rondelli *et al*, 2005; Ballen *et al*, 2010). Typically, HCT has been offered to patients with progressive peripheral blood cytopenias or evidence of transformation to leukaemia.

As most patients with PMF and many patients with myelofibrosis after PV or ET are 60 years of age or older, they have frequently been excluded from HCT because of concern about regimen-related toxicity. Stepwise modification of high dose regimens and the development of reduced intensity conditioning (RIC) regimens has enabled transplants to be performed successfully in older patients (Cervantes *et al*, 2009; Deeg *et al*, 2003; Kerbaux *et al*, 2007; Devine *et al*, 2002; Hessling *et al*, 2002; Snyder *et al*, 2006; Snyder *et al*, 2010). Both strategies have been shown to result in rapid regression of bone marrow fibrosis and to induce molecular remissions in *JAK2* V617F positive patients (Kroger *et al*, 2007a).

To evaluate the outcome of transplantation in older patients with myelofibrosis, we performed a retrospective analysis of results in 30 patients, aged 60 years or older, who were transplanted after conditioning with various intensity conditioning regimens.

PATIENTS AND METHODS

Patients

A retrospective analysis was performed of the transplant course of 30 patients with PMF or myelofibrosis following PV or ET who had undergone allogeneic HCT at one of four academic centres in the U.S.A between December 1999 and December 2007. All patients had given informed consent according to the requirements at the respective institutions. Pertinent patient, disease and transplant characteristics are summarized in Table I. Patients were 60–78 (median 65.0) years old. Seven patients had shown leukemic transformation and five of these were refractory to chemotherapy. Two patients had failed a prior autologous transplant. Co-morbidity scores as determined by the Haematopoietic Cell Transplantation Co-morbidity Index (HCT-CI) ranged from 0 to 6 (Sorrer *et al*, 2005).

Donor and transplant characteristics

Donors were human leucocyte antigen (HLA)-identical siblings in 15 and HLA-matched unrelated volunteers in 15 patients. Thirteen patients were conditioned with fludarabine (Flu) plus 2 Gy total body irradiation (TBI) (Laport *et al*, 2008), two with Flu plus melphalan (Mel) plus anti-thymocyte globulin (ATG) (Popat *et al*, 2006; Oran *et al*, 2007), four with anti-CD52 monoclonal antibody alemtuzumab (campath [camp]) combined with

Flu (Popat *et al*, 2005), anti-CD45 antibody and 4.5 Gy TBI (Popat *et al*, 2005), two with Flu plus busulfan (Bu) (de Lima *et al*, 2004), two with Flu plus Bu and ATG, three with Bu plus cyclophosphamide (Cy), two with Bu plus Cy with ATG (Kerbaux *et al*, 2007), and one with Bu plus Mel and camp (Popat *et al*, 2005).

The source of stem cells was granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood progenitor cells (PBPC) in 29 patients who received $8.5 \pm 4.2 \times 10^6$ CD34⁺ cells/kg, and bone marrow in one patient (Patient 8; 4.1×10^8 mononuclear cells/kg). Graft-versus-host disease (GVHD) prophylaxis consisted of previously described regimens, including cyclosporine (CSP) plus mycophenolate mofetil (MMF) in 11 patients (Giaccone *et al*, 2005), tacrolimus (Tac) plus methotrexate (MTX) in 6, Tac in 5, CSP plus MTX in 6, and Tac plus MMF in one patient (Eissa *et al*, 2010).

Evaluation

Time of engraftment was defined as the first of three consecutive days with an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/l$, and platelet engraftment as the first of three days with platelet counts $> 20 \times 10^9/l$, without transfusion support (Petersdorf *et al*, 1998). Patients were subsequently followed for complete recovery of (donor-derived) haematopoiesis. Patients were also evaluated for regression of splenomegaly and marrow fibrosis. Acute and chronic GVHD severity were assessed and treated as described previously (Martin *et al*, 1998; Benesch & Deeg, 2008). We did not reclassify chronic GVHD according to the more recently developed National Institutes of Health consensus criteria (Filipovich *et al*, 2005; Flowers *et al*, 2009).

Relapse/disease progression was defined as re-appearance or persistence of host cells with the morphological, cytogenetic, molecular or immunophenotypic markers of the disease pretransplant. The presence of residual marrow fibrosis in the absence of those markers was not considered as disease persistence as in some patients fibrosis resolves only slowly (Sale *et al*, 2006).

Statistical analysis

Kaplan-Meier estimates were used to plot overall survival. All statistical analyses were performed using R 2.8.0 statistical software. Results were analysed as of April 2010.

RESULTS

Engraftment and Haematopoietic Recovery

Primary engraftment of donor cells with recovery of normal haematopoietic parameters was documented in 27 of 30 patients. One patient died on day 17, too early to assess for engraftment. The remaining two patients, conditioned with Flu/Mel/ATG and Flu/Camp/CD45/TBI, respectively, both showed disease progression. One surviving patient (Patient 3) was found to be a mixed chimera at the last chimerism determination (day 100). While chimerism has not been tested since, the patient has shown normal haematopoietic recovery. Except for the nine patients with disease progression or relapse, splenomegaly regressed and marrow examination showed improvement or complete resolution of marrow fibrosis in all those who were followed for at least 6 months.

GVHD

Acute GVHD grades II–IV/III–IV developed in 11/4 of 27 evaluable patients (40%/ 15%), and chronic GVHD occurred in 10 of 22 evaluable patients (45%) (Table I).

Relapse

Four patients died before day 100, two with disease progression (days 17 and 37, respectively), one with respiratory failure (day 49), and one with GVHD (day 79). Overall, disease progression or relapse occurred in 9 patients, for an incidence of 30% at 3 years. Three of these patients lacked evidence of donor cell engraftment (see above). Among the remaining six patients, three had been conditioned with Flu/2Gy TBI (one transplanted from a sibling and two from unrelated donors), two with Bu/Cy $\pm$ ATG (both transplanted from unrelated donors), and one with Flu/Camp/CD45/TBI (transplanted from a sibling donor).

It was of note that none of the eight patients with antecedent ET or PV showed disease progression or relapse, although two died with infections and one from complications related to GVHD.

Survival

With a follow-up of 0.5–69 (median 22) months, 13 patients have survived for an overall survival (OS) of 45% and progression-free survival of 40% at 3 years (Fig 1). There was no significant difference in survival between patients aged 60–65 years and those 66–78 years of age.

Causes of Death

At last follow-up 17 patients had died (Table I). Seven patients died with disease progression (6 of these had been transplanted from unrelated donors) and 10 patients (6 transplanted from HLA-identical siblings and 4 recipients of unrelated donor transplants) died from non-relapse causes, for a 3-year incidence of non-relapse mortality of 30%. Major causes of death were infections and organ failure.

DISCUSSION

While the early disease course of patients with PMF and other myeloproliferative neoplasms that may progress to myelofibrosis generally is indolent, management becomes increasingly challenging at more advanced disease stages. The only treatment modality with proven curative potential, generally reserved for advanced disease, is HCT. There has been reluctance to offer HCT to older patients with myelofibrosis, because of concerns about treatment-related toxicity. However, some reports have shown very encouraging results, particularly in patients conditioned with RIC regimens (Snyder *et al*, 2006; Kröger *et al*, 2009; Rondelli *et al*, 2005; Snyder *et al*, 2010). In the present analysis we combined data on 30 patients, 60 years or older, who were transplanted for myelofibrosis at one of four centres in the USA. The focus was on age rather than a particular conditioning regimen. The results showed that patients in their 60s and even 70s can be transplanted successfully and achieve complete haematological recovery following conditioning with regimens of various intensities, which was remarkable given the age and co-morbid illnesses present in this cohort.

Sequential marrow or blood samples to assess donor cell engraftment were available only in a proportion of patients. However, among patients with haematological reconstitution and without other evidence of disease progression, only one patient was found to be a mixed chimera (as determined by CD33⁺ cells) at the latest chimerism determination. Persistent mixed donor/patient chimerism in patients with myelofibrosis has been reported previously even in patients conditioned with high intensity regimens (Kerbaux *et al*, 2007). Currently 13 of 30 patients are surviving, 11 in unmaintained remission. These include 7 of 14 conditioned with Flu/2Gy TBI, and 6 of 16 conditioned with other regimens, including 3 of 4 patients conditioned with a Flu/Bu combination at “conventional” doses as used in

younger patients (Kerbaux *et al*, 2007) Among seven patients with evidence of leukaemia transformation at the time of HCT, two died from disease progression, and three with infectious complications, while two are alive. One of these is in complete remission at 73 months after receiving a second transplant. The second patient is alive at 43.2 months, showing mixed chimerism at the latest determination. A recent report by Ciurea *et al* (2010) indicates that superior long-term survival may be obtained in patients who responded to pre-HCT chemotherapy and were conditioned with a melphalan-based regimen.

Several previous reports have included transplant results in older patients with myelofibrosis (Kerbaux *et al*, 2007; Devine *et al*, 2002; Hessling *et al*, 2002; Snyder *et al*, 2006; Kröger *et al*, 2009; Rondelli *et al*, 2005; Snyder *et al*, 2010). Nine patients, median age 54 years, were transplanted using a reduced intensity regimen of fludarabine and TBI (Snyder *et al*, 2006). Seven of 9 patients engrafted, and the probability of survival at one year was 55%. A more recent report from the same center group suggests that superior results are achieved with a regimen that includes tacrolimus plus sirolimus for GVHD prophylaxis (Snyder *et al*, 2010). Kroger, *et al* (2007b) treated 21 patients, 32–63 (median 53) years old, with a busulfan (10 mg/kg), fludarabine (180 mg/m²) plus ATG regimen. Engraftment was achieved in all but one patient, and the 3-year progression-free survival was reported to be 84%. Thus, survival was higher than in the present study, but patients were also younger by more than a decade. The relevance of age is underscored by a more recent report on results in 103 patients by the same investigators (Kröger *et al*, 2009) showing overall survival of 48% among patients who were older than 55 years at the time of HCT. Rondelli, *et al* (2005) reported results in 21 patients, 27–68 (median 54) years of age, treated with five different RIC regimens at several centres. Fifteen patients achieved initial engraftment. At a median follow-up of 31 months, 17 patients were alive in remission. Another report on 104 patients, 18–70 years of age, with PMF or myelofibrosis after PV or ET showed a 7-year survival of 61% (Kerbaux *et al*, 2007). That report included 9 patients older than 60 years who were conditioned with a regimen of fludarabine plus 2 Gy TBI, of whom 4 (44%) were surviving in remission. Ballen *et al* (2010) recently presented results on 289 patients with PMF reported to the Center for International Blood and Marrow Transplant Research (Ballen *et al*, 2010). Patients were 18–73 (median 47) years old and were transplanted from related ($N = 188$) or unrelated donors ($N = 101$). The day-100 non-relapse mortality was 18% and 35% for related and unrelated transplant recipients, respectively. The corresponding 5-year relapse-free survival probabilities were 33% and 27%, respectively. For patients conditioned with RIC regimens, 3-year relapse-free survival was 39% and 17% for related and unrelated HCT, respectively.

Thus, considering the age range of patients included in the present report, results compare favourably with other data in the literature. Overall these studies suggest that patients with advanced myelofibrosis, either PMF or myelofibrosis following PV or ET, even in the 7th or 8th decade of life can be treated successfully and be cured by HCT. While all consecutive patients from the four centres were included, it must be acknowledged that the selection of older patients for HCT and the choice of conditioning regimens used in preparation for HCT was likely to have been biased. Presumably, decisions were not based on chronological, but rather “biological” age, no matter how difficult this may be to define.

As pharmacological inhibitors of JAK2 are becoming available, it is likely that in some patients HCT will be delayed as long as symptomatic responses to JAK2 inhibition are observed. It is possible, therefore, that patients will be referred for HCT at an even more advanced disease stage, and it remains to be seen whether results as encouraging as the present ones are achievable in those patients. Further trials are needed.

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Fig 1. Overall survival, progression-free survival, relapse, and non-relapse mortality in 30 patients with myelofibrosis aged 60–78 years.

Patient and disease characteristics, transplant regimen, and outcome

Table 1

Patient	Diagnosis	Age (year s)	Disease Duration (months)	Co- Morbidity Score ²	Donor	Conditioning Regimen ¹	GVHD Prophylaxis	Engraft	GVHD Acute (grade)- chronic	Chimerism ⁴	Disease Progression	PFS (months)	OS (month s)	Cause of Death
19	PMF	60	5.6	2	MSIB	Bu/Cy	CSP, MTX	Y	3-n/a	n/a	N	3.6	3.6	Multi-Organ Failure
20	PMF	60	7	1	URD	Bu/Cy	CSP, MTX	Y	3-Y	n/a	Y	4.8	6.2	Disease Progression
21	PMF	60	56	1	MSIB	Bu/Cy	CSP, MTX	Y	2-N	Donor	N	6.5	6.5	Infection
9	PMF	64	25	0	URD	Bu/Cy/ATG	CSP, MTX	Y	0-N	Donor CD3 CD33	Y	13.2	18.0	Disease Progression
18	PMF	60	12	3	MSIB	Bu/Cy/ATG	CSP, MTX	Y	0-N	Donor CD3 CD33	N	>68.6	>68.6	n/a
3	PMF	70	4.3	6	URD	camp/Flu/ CD45/4.5 Gy TBI	Tacrolimus	Y	0-N	Donor	N	13.2	13.2	Respiratory Failure
11	PMF	63	7.6	4	MSIB	camp/Flu/ CD45/4.5 Gy TBI	Tacrolimus	Y	0-N	Donor ³	Y	>24.4	>73.0	n/a
15	PMF	62	65	8	URD	Flu/camp/4.5 Gy TBI	Tacrolimus	N	0-n/a	Host	Y	0.0	1.2	Disease Progression
17	PMF	61	18	3	URD	Flu/camp/4.5 Gy TBI	Tacrolimus	Y	4- n/a	Donor	N	2.6	2.6	GVHD
25	MF post ET	65	122	6	MSIB	Flu/Bu	Tac, MTX	Y	0-Y	Donor	N	37.6	37.6	Infection
29	MF post PV	66	165	1	MSIB	Flu/Bu	Tac, MTX	Y	0-Y	Donor CD3, CD33	N	>42.4	>42.4	n/a
30	MF post ET.	66	42	1	MSIB	Flu/Bu	Tac, MTX	Y	2-N	Mixed chimerism	N	4.0	4.0	Acute GVHD
2	PMF	75	69	0	MSIB	Flu/Bu/ATG	Tac, MTX	Y	1-N	Mixed chimerism	N	>43.2	>43.2	n/a
27	MF post ET	61	108	3	MSIB	Bu/Flu/ATG	Tac, MTX	Y	0-N	Donor CD3 CD33	N	>3.3	>32.4	n/a
1	PMF	78	35	4	URD	Flu/2 Gy TBI	CSP, MMF	Y	2-N	Donor CD3 CD33	N	>26.3	>26.3	n/a
4	PMF	69	5.6	6	MSIB	Flu/2 Gy TBI	CSP, MMF	N	n/a	n/a	Y	0.0	0.6	Disease Progression
5	PMF	68	67	5	MSIB	Flu/2 Gy TBI	Tacro, MMF	Y	1-N	Donor CD3 CD33	N	>50.2	>50.2	n/a
7	PMF	66	5	1	MSIB	Flu/2 Gy TBI	CSP, MTX	Y	0-Y	n/a	N	14.2	14.2	Infection
8	PMF	65	3	2	URD	Flu/2 Gy TBI	CSP, MMF	Y	2-Y	n/a	Y	6.1	11.3	Disease Progression
10	PMF	64	101	3	URD	Flu/2 Gy TBI	CSP, MMF	Y	2-Y	Donor CD3 CD33	Y	11.7	11.7	Disease Progression
12	PMF	63	39	6	URD	Flu/2 Gy TBI	CSP, MMF	N	2-N	Donor CD3 CD33	N	>25.9	>25.9	n/a
13	PMF	63	29	3	URD	Flu/2 Gy TBI	CSP, MMF	Y	0-n/a	n/a	N	1.6	1.6	Respiratory Failure
14	PMF	62	10.5	1	MSIB	Flu/2 Gy TBI	Tac, MTX	Y	2-N	Donor CD3 CD33	N	>8.4	>42.5	n/a
23	MF post ET	73	130	0	URD	Flu/2 Gy TBI	CSP, MMF	Y	1-Y	Donor CD3 CD33	N	>56.4	>56.4	n/a
24	MF post ET	67	4	2	URD	Flu/2 Gy TBI	CSP, MMF	Y	2-Y	Donor CD3 CD33	N	>18.4	>18.4	n/a

Patient	Diagnosis	Age (years)	Disease Duration (months)	Co-Morbidity Score ²	Donor	Conditioning Regimen	GVHD Prophylaxis	Engraft	GVHD (grade)-chronic	Chimerism ⁴	Disease Progression	PFS (months)	OS (months)	Cause of Death
26	MF post ET	64	4.1	0	MSIB	Flu/2 Gy TBI	CSP, MMF	Y	0-N	Host	Y	>1.0	>4.7	n/a
28	MF post PV	66	27	4	URD	Flu/2 Gy TBI	CSP, MMF	Y	3- n/a	Donor CD3 CD33	N	6.6	6.6	Infection
6	PMF	67	7.3	4	URD	Flu/Mel/ATG	Tac/MTX/Pentostatin	N	1-Y	Not done	Y	0.0	22.1	Disease Progression, Autologous Recovery
22	PMF	60	93	n/a	MSIB	Flu/Mel/ATG	CSP, MMF	Y	0-n/a	n/a	N	3.4	3.4	Dissecting Aneurysm
16	PMF	62	8.2	2	URD	Flu/Mel/camp	Tacrolimus	Y	1-limited	Donor	N	>48.7	>48.7	n/a

Patients 8 and 13 had failed a preceding autologous transplant.

Patients 2, 6, 15, 25, 28, 29 and 30 had shown leukaemic transformation before transplantation

Patients ordered by conditioning regimen.

Abbreviations: CSP = cyclosporine; MF post-ET or PV = myelofibrosis after preceding diagnosis of Essential Thrombocythaemia or Polycythaemia vera; MMF = mycophenolate mofetil; MTX = methotrexate; N = no; n/a = not applicable; PMF = primary myelofibrosis; Tac = tacrolimus; Y= yes.

¹ Flu/2 Gy TBI = Fludarabine 3 × 30 mg/m² i.v. plus 2 Gy total body irradiation (TBI).
Flu/Bu + ATG = Fludarabine 4 × 30 mg/m² i.v. plus busulfan 9.6 mg/kg to 16 mg/kg given over 3 to 4 days (adjusted to achieve steady state plasma levels of 800–900 ng/ml) or fludarabine 4 × 40 mg/m² plus busulfan 2 × 130 mg/m² with or without thymoglobulin (ATG) 6 mg/kg i.v. over 3 days.

camp/Flu/CD45/4.5 Gy TBI = Alemtuzumab (campath) 4 × 10 mg/kg, fludarabine 30 mg/m² × 4, anti-CD45 antibody, 4 × 0.4 mg/kg, plus 4.5 Gy of TBI.
Flu/Mel/ATG (or camp) = Fludarabine 5 × 15 mg/m² plus melphalan (Mel) 70 mg/m² × 2, plus Alemtuzumab (campath) 3 × 10 mg or ATG (Atgam) 4 × 10 mg/kg.
Bu/Cy ± ATG = Busulfan 16 mg/kg per 4 days with dose adjustments to achieve plasma steady state concentrations of 800–900 ng/ml plus cyclophosphamide (Cy) 2 × 60 mg/kg i.v., with or without ATG 4.5 mg/kg given over 30 days.

Flu/camp/4.5 Gy TBI = Fludarabine 30 mg/m² × 4, Alemtuzumab (campath) 4 × 10 mg/kg plus 4.5 Gy of TBI.

² According to HCT-CI

³ After a second transplant

⁴ In patients indicated by “Donor” chimerism was determined in total marrow mononuclear cells. Other patients had separate determination in CD3⁺ and CD33⁺ cells.