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Allogeneic Hematopoietic Cell Transplantation for Advanced Polycythemia Vera and Essential Thrombocythemia

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Allogeneic hematopoietic cell transplantation (HCT) is curative for selected patients with advanced essential thrombocythemia (ET) or polycythemia vera (PV). From 1990 to 2007, 75 patients with ET (median age 49 years) and 42 patients with PV (median age 53 years) underwent transplantations at the Fred Hutchinson Cancer Research Center (FHCRC; n = 43) or at other Center for International Blood and Marrow Transplant Research (CIBMTR) centers (n = 74). Thirty-eight percent of the patients had splenomegaly and 28% had a prior splen ectomy. Most patients (69% for ET and 67% for PV) received a myeloablative (MA) conditioning regimen. Cumulative incidence of neutrophil engraftment at 28 days was 88% for ET patients and 90% for PV patients. Acute graft-versus-host disease (aGVHD) grades II to IV occurred in 57% and 50% of ET and PV patients, respectively. The 1-year treatment-related mortality (TRM) was 27% for ET and 22% for PV. The 5-year cumulative incidence of relapse was 13% for ET and 30% for PV. Five-year survival/progression-free survival (PFS) was 55%/47% and 71%/48% for ET and PV, respectively. Patients without splenomegaly had faster neutrophil and platelet engraftment, but there were no differences in TRM, survival, or PFS. Presence of myelofibrosis (MF) did not affect engraftment or TRM. Over 45% of the patients who undergo transplantations for ET and PV experience long-term PFS.

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INTRODUCTION

Polycythemia vera (PV) and essential thrombocythemia (ET) are Philadelphia chromosome-negative myeloproliferative neoplasms with long natural histories. PV is characterized by elevated red blood cell mass, often accompanied by high platelet count and WBC counts and splenomegaly. ET is characterized almost exclusively by a high platelet count. Both diseases may evolve to myelofibrosis (MF), or can potentially transform to acute myeloid leukemia (AML). Both diseases have been linked to the acquired mutation V617F in the Janus kinase 2 (*JAK2*) gene [1,2]. Almost all patients with PV and one-half of those with ET have a *JAK2* mutation involving either exon 12 or 14 [3]. The diagnostic criterion for PV and ET have been revised to include these molecular findings, and clinical trials with oral inhibitors of the JAK2 kinase are under way [3]. Patients with ET are at increased risk of both thrombosis and bleeding. The incidence of thrombosis ranges from 6% to 10% per patient-year and the incidence of bleeding from 1% to 3% per patient-year [4]. The risk of evolution to MF or AML is approximately 2% and 4%, respectively [5-7]. Most patients with low-risk ET do well on low-dose aspirin alone, whereas hydroxyurea, anagrelide, and interferon are used for cytoreduction in some high-risk patients [8,9]. However, the rate of thrombotic events remains at 1.7% per patient year, which can contribute to significant morbidity [10].

Patients with PV are at higher risk of thrombosis, often in large vessels [11]. The risk of progression to MF is estimated at 5% to 15% [11]. An analysis of 1638 patients with PV revealed 22 cases of myelodysplastic syndrome (MDS)/AML, occurring at a median of 8 years from diagnosis [12]. All cases were fatal within 6 months. Advanced age, higher WBC at diagnosis, and prior treatment with alkylating agents increased the risk of MDS/AML. Other studies of patients with PV have reported an incidence of AML approaching 15% [13]. A recent report indicated that 25% of patients with myeloproliferative neoplasms who developed MDS/AML were never exposed to alkylating agents, highlighting the fact that this complication is part of the natural history of the disease [14]. Allogeneic hematopoietic cell transplantation (HCT) is not typically considered until late in the course of these disorders or when the disease cannot be controlled with conventional therapies.

Although PV and ET are usually indolent diseases, HCT may be a therapeutic option particularly for patients with high-risk features such as recurrent thrombosis or rapid or difficult to control disease progression [13]. If HCT is to be performed, ideal timing would be before transformation to AML.

There is a paucity of data describing post-HCT outcomes in these diseases, and only small studies were previously reported [15,16]. In this study, the largest report dedicated to PV and ET, we analyze the long-term outcomes of 117 patients with PV and ET undergoing allogeneic HCT, generally at advanced stages of their disease, and describe the effect of prognostic factors, such as spleen status and MF, on transplantation outcomes.

MATERIALS AND METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a centralized Statistical Center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source have been described elsewhere [17].

Patients treated at the Fred Hutchinson Cancer Research Center (FHCRC), a CIBMTR-affiliated center, gave informed consent for the transplantations and for the use of medical information for research. This retrospective study was approved by the Institutional Review Board of the FHCRC.

Patients

The study included all consecutive patients who received related or unrelated allogeneic HCT with bone marrow or peripheral blood cells for PV or ET between 1990 and 2007 and were treated at the FHCRC or reported to the CIBMTR research database. Patients receiving high-intensity myeloablative (MA), low- or reduced-intensity conditioning (RIC), or nonmyeloablative (NMA) transplantations were included. Patients whose disease had transformed to MF or MDS were included. Patients who received syngeneic or umbilical cord blood transplants or whose disease had progressed to AML were excluded.

The final study cohort consisted of 117 patients. The follow-up completeness index from time of HCT, which is the ratio of total observed person-time to the potential person-time of follow-up in a study, was 95% at 1 year after HCT, 91% at 2 years, and 84% at 3 years [18].

Outcomes and Study Definitions

The primary endpoint of this study was to determine the survival in patients with PV and ET who underwent HCT. Patients were considered to have an event at time of death from any cause; survivors were censored at last contact. Secondary endpoints included progression-free survival (PFS), recurrent/progressive disease, treatment-related mortality (TRM), engraftment, and graft-versus-host disease (GVHD). TRM was defined as death occurring in remission, or with stable disease; recurrence/progression was considered a competing event. Recurrent disease/disease progression was defined as time to first evidence of recurrence or progression of disease as reported to the CIBMTR by the transplantation centers, and TRM was considered a competing event. PFS was defined as survival without progressive or recurrent disease. Recurrent disease/disease progression and death in remission were considered events. For recurrence/progression, TRM, and PFS, patients alive in continuous remission or had a stable disease (as reported to the CIBMTR by the transplantation centers) were censored at last follow-up. Transplantation centers were asked to provide data on disease recurrence/progression on standard follow-up forms. Transplantation centers defined relapsed/progressive disease according to their own criteria, as there were no established criteria for relapsed disease at this time.

Secondary endpoints included neutrophil recovery, defined as time to an absolute neutrophil count $>0.5 \times 10^9$/L sustained for 3 consecutive days, and platelet recovery, defined as time to achieve a platelet count of $>20 \times 10^9$/L without platelet transfusions for 3 consecutive days. The diagnosis of acute GVHD (aGVHD) was based on the occurrence of grades II, III, or IV skin, gastrointestinal, or liver abnormalities according to the Glucksberg-Seattle criteria of aGVHD [19]; and chronic GVHD (cGVHD) was based on the occurrence of symptoms in any organ system fulfilling the criteria for cGVHD [20]. For engraftment and GVHD, death without the event was considered a competing event. All outcomes were assessed from the date of HCT. Preparative regimens were classified as high or lower intensity. High-intensity regimens included those fulfilling the CIBMTR Regimen-Related Toxicity Working Committee's published criteria for MA regimens; lower-intensity regimens included those fulfilling the criteria for reduced-intensity or NMA conditioning [21].

Statistical Analysis

Patient, disease, and treatment-related factors were analyzed using chi-square test for categorical and Kruskal-Wallis test for continuous variables. TRM, recurrence/progression, engraftment, aGVHD, and cGVHD were estimated as cumulative incidents, taking into account competing risks. Survival and PFS were calculated using the Kaplan-Meier product limit estimate [22].

Due to small patient numbers, multivariate analysis was not performed. Univariate analysis of the association between survival and the following a priori proposed prognostic factors was conducted: disease (ET versus PV), age, presence of MF, spleen status (splenectomy versus splenomegaly versus normal spleen), time from diagnosis to transplantation, blood counts at HCT, presence of circulating blasts in peripheral blood at HCT, donor–recipient HLA matching, center, and conditioning regimen. For continuous variables (age, time from diagnosis to HCT, and blood counts at HCT), the median value was identified and the cohort divided into those with values greater or smaller than the median. Survival curves were compared using the log-rank test. Probabilities of survival were also compared at 1, 3, and 5 years using a pointwise test.

Univariate analysis of the association between conditioning regimen intensity and TRM was also conducted. The association between GVHD (cGVHD/aGVHD) and relapse/progression was examined in a proportional hazards model by adding GVHD as a time dependent covariate. SAS software, version 9.1 (SAS Institute, Cary, NC) was used in all analyses.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. Our cohort included 75 patients with ET and 42 patients with PV. The median age at transplantation was 50 years. Over 90% of patients were white. The median interval from diagnosis to HCT was 94 months. Patients treated at the FHCRC were younger and had longer time from diagnosis to HCT (140 months for the FHCRC patients versus 81 months for the non-FHCRC patients; $P = .002$). MA conditioning regimens were given to 68% of patients. Peripheral blood stem cells were used as the stem cell source in 68% of patients. About one-third of the patients received organs that were transplanted from an HLA-identical sibling. The remaining two-thirds received the transplant from unrelated donors; among these patients, 70% received the transplant from a well-matched unrelated donor. Median follow-up of surviving patients was 51 months. Data on JAK2 mutation status, thromboembolic events, or the development of MDS before HCT were not available in this cohort that dates back to 1990. Cytogenetic data were available on 43% of the patients, and most had a normal karyotype. Patients received a variety of treatments before HCT including steroids, interferon, and low-dose chemotherapy. The reasons for

Table 1. Characteristics of Patients Receiving Allogeneic Transplants for ET and PV, Reported to the CIBMTR between 1990 and 2007

Characteristics of Patients	ET	PV
Patient related		
Number of patients	75	42
Number of centers	32	23
Patient age, median (range), years	49 (20-64)	53 (30-66)
21-40	18 (24)	3 (7)
41-50	22 (29)	16 (38)
51-60	29 (39)	16 (38)
>60	6 (8)	7 (17)
Sex		
Male	29 (39)	23 (55)
Race group		
White	72 (96)	38 (90)
Black	0	1 (2)
Asian/Pacific Islander	1 (1)	1 (2)
Other	1 (1)	2 (5)
Missing	1 (1)	0
Karnofsky score before transplantation		
<90%	29 (39)	15 (36)
≥90%	41 (55)	25 (60)
Missing	5 (7)	2 (5)
Spleen status at transplantation		
Normal spleen	27 (36)	7 (17)
Splenomegaly	28 (37)	16 (38)
Splenectomy	16 (21)	17 (40)
Missing	4 (5)	2 (5)
WBC at time of transplantation, median (range), $\times 10^9$/L	8 (1-67)	15 (2-97)
Platelet count at time of transplantation, median (range), $\times 10^9$/L	322 (11-2000)	265 (32-2000)
Hemoglobin at time of transplantation, median (range), g/dL	11 (7-16)	12 (7-16)
Blast % in blood at time of transplantation, median (range)	0 (<1-11)	0 (<1-6)
Transformation to MF		
Absent	39 (52)	21 (50)
Present	29 (39)	17 (40)
Unknown	7 (9)	4 (10)
Transplant related		
Diagnosis to transplantation, median (range), months	91 (4-317)	120 (8-326)
TBI given as part of conditioning	20 (27)	10 (24)
Conditioning regimen intensity and regimen		
MA	52 (69)	28 (67)
Cyclophosphamide + TBI	14 (27)	5 (18)
Busulfan + cyclophosphamide	31 (60)	18 (64)
Busulfan +/− other	6 (12)	3 (11)
TBI +/− other	1 (2)	2 (7)
NMA	23 (31)	14 (33)
Busulfan + Cyclophosphamide	2 (9)	1 (7)
TBI +/− other	5 (22)	3 (21)
Busulfan +/− other	11 (48)	7 (50)
Fludara + melphalan +/− other	5 (22)	3 (21)
Donor type		
HLA-identical sibling	19 (25)	13 (31)
Well matched, unrelated*	41 (55)	21 (50)
Partially matched, unrelated†	15 (20)	8 (19)
Donor–recipient sex match		
M–M	20 (27)	13 (31)
F–F	25 (33)	9 (21)
M–F	17 (23)	8 (19)
F–M	13 (17)	12 (29)
Donor/recipient CMV status		
D(+)/R(+)	21 (28)	17 (40)
D(+)/R(−)	5 (7)	3 (7)
D(−)/R(+)	14 (19)	7 (17)
D(−)/R(−)	30 (40)	13 (31)
Missing	5 (7)	2 (5)
Graft type		
Bone marrow	23 (31)	14 (33)
Peripheral blood	52 (69)	28 (67)
Year of transplantation		
1990-1995	8 (11)	5 (12)
1996-2000	15 (20)	6 (14)
2001-2005	33 (44)	19 (45)
2006-2007	19 (25)	12 (29)
GVHD prophylaxis		
Tacrolimus + methotrexate	39 (52)	23 (55)
Cyclosporine + methotrexate	31 (41)	17 (40)
Others	5 (7)	2 (5)
Median follow-up of survivors (range) months	51 (11-169)	52 (3-154)

ET indicates essential thrombocythemia; PV, polycythemia vera; CIBMTR, Center for International Blood and Marrow Transplant Research; TBI, total body irradiation; MA, myeloablative; NMA, nonmyeloablative; CMV, cytomegalovirus; GVHD, graft-versus-host disease.
*Well-matched unrelated includes: 8/8 or 6/6 allele matched.
†Partially matched unrelated includes: (1) Single allele mismatch 7/8; (2) Single antigen mismatch 7/8; (3) 8/8 antigen matched at HLA-A, HLA-B, HLA-C, and HLA-DRB1 (allele level typing not available on all loci).

proceeding to transplantation were not captured consistently. Thirty-nine percent of patients had transformed to MF by the time of HCT.

Table 2 describes outcomes separately for patients with ET and PV. In the entire cohort (ET and PV patients as 1 group), the median time to neutrophil engraftment was 16 days (range, 1-398 days). The incidence of primary graft failure (no neutrophil engraftment by day 28) was 11%. One patient with graft failure showed autologous recovery and lived to day 1735. The median time to platelet engraftment was 20 days (range, 1-126 days). At 100 days, the incidence of aGVHD grades II to IV was 54%. The incidence of cGVHD at 5 years was 48%. The incidence of TRM was 16% at 100 days, 25% at 1 year, and 33% at 5 years.

Relapse and Survival

In the entire cohort, the 1-year and 5-year risk of relapse/progression was 16% and 19%, respectively (Table 2). The 1-year and 5-year survival for ET was 69% and 55%, respectively, and for PV it was 71% and 71%, respectively (Table 2 and Figure 1). The respective figures for PFS were 62% and 47% for ET and 54% and 48% for PV (Table 2 and Figure 2). For ET, the median follow-up of patients was 51

Table 2. Univariate Analysis of Post-HCT Outcomes for Advanced ET and PV

Characteristics	ET Probability (95% CI)	PV Probability (95% CI)
Neutrophil engraftment median (range)	16 (1-53)	17 (1-398)
Platelet engraftment median (range)	19 (1-126)	21 (1-79)
Outcomes		
Neutrophil engraftment	n = 74	n = 40
at 28 days	88 (80-94)	90 (79-97)
at 100 days	95 (89-98)	95 (87-99)
Platelet engraftment	n = 75	n = 40
at 28 days	59 (47-69)	65 (50-79)
at 100 days	80 (70-88)	80 (66-91)
aGVHD grade II-IV	n = 75	n = 42
at 100 days	57 (45-68)	50 (35-65)
aGVHD grade III-IV	n = 75	n = 42
at 100 days	21 (13-31)	24 (12-38)
cGVHD	n = 72	n = 39
at 1 year	40 (29-51)	52 (35-68)
at 5 years	47 (35-59)	52 (35-68)
Treatment-related mortality	n = 75	n = 42
at 100 days	16 (9-25)	17 (7-29)
at 1 year	27 (18-38)	22 (11-36)
at 5 years*	40 (28-53)	22 (11-36)
Progression/relapse	n = 75	n = 42
at 1 year	11 (5-19)	25 (13-39)
at 5 years*	13 (6-21)	30 (17-45)
Progression-free survival		
NEval	n = 75	n = 42
at 1 year	62 (51-73)	54 (38-69)
at 5 years	47 (35-60)	48 (33-63)
Survival		
NEval	n = 75	n = 42
at 1 year	69 (58-79)	71 (56-84)
at 5 years	55 (42-67)	71 (56-84)

HCT indicates hematopoietic cell transplantation; ET, essential thrombocythemia; PV, polycythemia vera; CI, confidence interval; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NEval, number evaluable.
*Pointwise $P < .05$.

months with a maximum of 169 months. At 5 years, 15 patients were at risk. At 169 months, 14 of the 15 at-risk patients were still alive, and of those, 13 were disease-free. For PV, the median follow-up was 52 months with a maximum of 154 months. At 5 years, 11 patients were at risk. At 154 months, 10 of the 11 at-risk patients were still alive, and of those, 7 were disease-free.

Causes of Death

Death occurred in 42% of patients with ET and 31% of patients with PV. The causes of death after HCT are listed in Table 3. The most common reported causes of death for patients with ET were organ toxicity (50%) and GVHD (22%). Organ toxicity included death from pneumonitis, adult respiratory distress syndrome, and organ failure. The most common

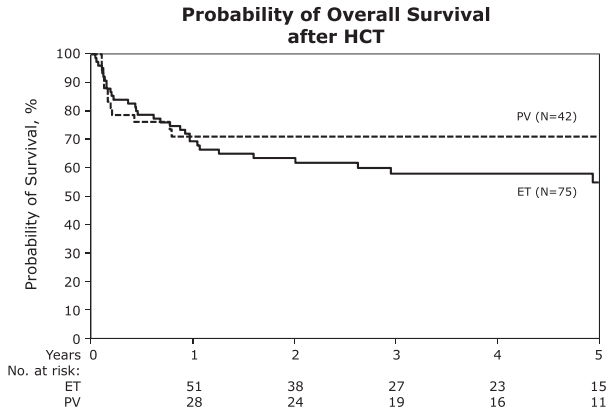

Figure 1. Overall survival of patients with essential thrombocythemia (ET) and polycythemia vera (PV) undergoing allogeneic hematopoietic cell transplantation (HCT).

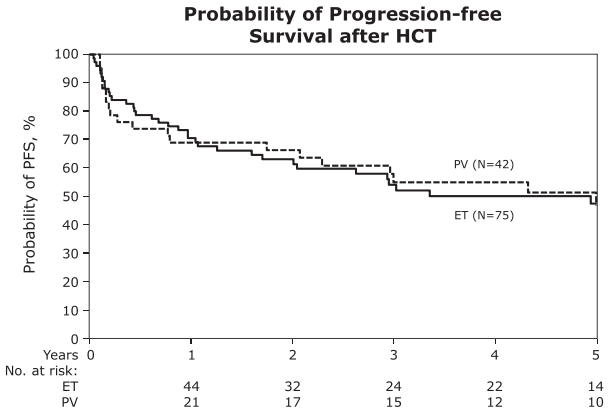

Figure 2. Progression-free survival of patients with essential thrombocythemia (ET) and polycythemia vera (PV) undergoing allogeneic hematopoietic cell transplantation (HCT).

Table 3. Primary Cause of Death

Cause of Death	ET	PV
Total number of deaths	32	13
Infection	6 (19)	2 (15)
GVHD	7 (22)	2 (15)
Primary disease	1 (3)	3 (23)
Organ toxicity	16 (50)	5 (38)
Secondary malignancy	2 (6)	1 (8)

ET indicates essential thrombocythemia; PV, polycythemia vera; GVHD, graft-versus-host disease.

reported causes of death for PV patients were organ toxicity (38%) and the primary disease (23%). One patient died of a vascular complication.

Predictors for Survival, TRM, and Recurrence/Progression

Table 4 summarizes univariate analysis results of potential predictors for survival. Age, time from diagnosis to HCT, WBC count, platelet count, hemoglobin at the time of HCT, presence of circulating blasts at HCT, spleen status, or graft source were not significantly associated with survival. Survival was poorer for patients receiving mismatched unrelated transplantations, although there were only 15 such patients in this cohort. A statistically significant center effect was associated with improved survival at 1 year, but not at 5 years after transplantation. FHCRC patients included all the patients who underwent transplantations at FHCRC, including those reported to the CIBMTR. Neither aGVHD nor cGVHD correlated with the risk of relapse (data not shown).

Eighty patients received an MA or high-intensity conditioning regimen, and 37 patients received a reduced-intensity or NMA conditioning regimen. In univariate analysis, 5-year TRM was higher for MA regimens (40% versus 18%; $P < .05$; Table 4). The 1-year and 5-year relapse rates were lower in patients receiving MA regimens, 8% versus 33% ($P = .003$) at 1 year and 9% versus 41% ($P < .001$) at 5 years, respectively. However, there was no difference in survival by regimen intensity; 5-year survival rates were 57% for patients receiving an MA regimen and 69% for patients receiving a reduced-intensity regimen ($P > .05$).

Splenomegaly and Splenectomy

Neutrophil and platelet engraftment were delayed in patients with splenomegaly. Median time to neutrophil engraftment was 17 days in patients with a normal spleen size compared to 23 days in patients with splenomegaly ($P < .001$). Median time to platelet engraftment was 20 days in patients with normal spleen size and 26 days for patients with splenomegaly ($P = .024$). Patients who had undergone a splenectomy before HCT had a median time to engraftment of 14 days for neutrophils and 19 days for platelets. There was no difference in aGVHD, cGVHD, relapse, or PFS among patients with normal spleen size, with splenomegaly, or those patients who had undergone a splenectomy. Similarly, there was no difference in survival (Table 4).

Table 4. Univariate Analysis of Risk Factors of Survival

Overall Survival	Probability (95% CI) at 1 Year	Probability (95% CI) at 5 Years
Patient age at transplantation		
<50 years (median, n = 55)	69 (56-80)	61 (47-74)
≥50 years (median, n = 62)	71 (59-82)	61 (48-73)
WBC at transplantation		
<9.7 × 10^9/L (median, n = 57)	68 (55-79)	59 (46-72)
≥9.7 × 10^9/L (median, n = 58)	72 (60-83)	62 (48-76)
Platelet count at transplantation		
<307×10^9/L (median, n = 55)	65 (52-77)	57 (42-71)
≥307×10^9/L (median, n = 56)	77 (65-87)	68 (54-80)
Hemoglobin at transplantation		
<11 g/dL (median, n = 42)	67 (52-80)	59 (42-75)
≥11 g/dL (median, n = 58)	76 (64-86)	67 (54-79)
Circulating blasts in peripheral blood at transplantation		
No blast (n = 60)	65 (52-76)	55 (41-68)
Blast (n = 27)	62 (43-79)	48 (26-71)
Graft source		
Bone marrow (n = 37)	62 (46-77)	59 (43-74)
Peripheral blood (n = 80)	73 (63-83)	60 (48-73)
Time from diagnosis to transplantation		
<95 months (median, n = 58)	64 (51-76)	58 (45-70)
≥95 months (median, n = 57)	75 (63-85)	63 (49-76)
Donor–recipient HLA match*		
HLA identical sibling probability (n = 32)	68 (51-83)	62 (43-79)
Well-matched URD probability (n = 62)	76 (64-86)	67 (55-78)
Partially matched URD probability (n = 15)	53 (29-77)	22 (1-61)
Transplant center†,‡		
FHCRC (n = 43)	86 (74-95)	72 (57-85)
Non-FHCRC (n = 74)	60 (49-71)	54 (42-66)
Conditioning regimen		
MA (n = 80)	69 (58-78)	57 (46-69)
NMA/RIC (n = 37)	72 (57-86)	69 (52-83)
Spleen status		
Normal spleen	76 (60-89)	76 (60-89)
Splenomegaly	70 (56-83)	58 (43-73)
Splenectomy	67 (50-81)	58 (40-75)
MF†,‡		
No MF	61 (49-73)	54 (41-67)
Transformed to MF	85 (73-93)	73 (58-86)
Treatment-related mortality*,‡		
MA (95% CI; n = 80)	31 (21-41)	40 (29-52)
NMA/RIC (95% CI; n = 37)	14 (5-27)	18 (7-32)

CI indicates confidence interval; URD, unrelated donor; FHCRC, Fred Hutchinson Cancer Research Center; MA, myeloablative; NMA, nonmyeloablative; RIC, reduced-intensity conditioning; MF, myelofibrosis.
*Pointwise $P < .05$ at 5 years.
†Log-rank $P < .05$.
‡Pointwise $P < .05$ at 1 year.

Myelofibrosis

In 46 patients (39%), the disease had transformed to MF before HCT (Table 4). The vast majority of these patients were reported from the FHCRC

(81%). Patients with MF were younger (median age 47 versus 53 years, respectively; $P = .011$) and had a longer interval from diagnosis to transplantation (125 months versus 75 months; $P = .005$) than those without MF. Time from diagnosis to HCT for patients with MF was similar for patients from the FHCRC and the non-FHCRC groups ($P = .22$), but the FHCRC patients were more likely to have received an MA conditioning regimen. Presence of MF did not affect 28-day engraftment rates or TRM. Grades II to IV aGVHD rates at 100 days ($P = .028$) and cGVHD rates at 1 year ($P = .004$) and 5 years ($P \leq .001$) were higher in patients with MF. Relapse rates at 1 year ($P = .018$) and 5 years ($P = .015$) were lower in patients with MF (data not shown). Splenectomy had no effect on survival of patients with MF (data not shown). Patients with MF had a higher 1-year but not 5-year survival post-HCT (Table 4).

DISCUSSION

In this retrospective analysis, we observed that HCT results in long-term PFS in over 45% of selected patients with ET and PV. In particular, we found that the probability for relapse within 1 year was low (11%) for patients with ET, and did not increase substantially by 5 years. Although the overall probability of relapse was higher (25%) for patients with PV, only a small proportion experienced relapse after the first year. There were no relapses after 3 years for either ET or PV. Thus, in selected patients with ET or PV, HCT seems to be curative, and the outcome tends to be dictated by transplantation-associated complications more commonly than by resistant disease. Although this study did not compare transplantation to conventional therapies, the low rate of relapse, particularly late after transplantation, is encouraging.

Splenomegaly is a feature typical of the myeloproliferative neoplasms, particularly MF; however, it has not been clear whether splenomegaly affects outcome of HCT. Preliminary data from the CIBMTR in a broader population suggests that splenectomy facilitates engraftment, without an effect on TRM [23]. Thirty percent of our patients had undergone a splenectomy at some point before transplantation, although the indication for splenectomy was not known. Our results indicate that splenomegaly is associated with delayed neutrophil and platelet engraftment, but does not seem to decrease survival and PFS. The current study does not support routine splenectomy before transplantation. Recently, posttransplantation splenectomy has been reported as a way to manage markedly delayed engraftment in 2 patients with MF and splenomegaly [24].

Transformation to MF did not affect engraftment or TRM, but 1-year survival was superior among patients whose disease had transformed to MF. In general, patients with MF were younger at the time of HCT, and had a significantly longer interval between diagnosis and HCT, which may indicate more indolent disease. Given the small sample size, it was not possible to determine whether MF itself was associated with superior 1-year survival or whether it was a marker for another factor, such as younger age, or a center effect. Nonetheless, in contrast to many instances in which disease progression is associated with inferior outcome of HCT, progression of ET and PV to MF does not seem to reduce the chances of survival.

The incidence of cGVHD was observed in 48% of our patients at 5 years post-HCT, likely reflecting the predominance of grafts that were either peripheral blood stem cells, from an unrelated donor, or both. There was no correlation between GVHD and relapse rate in our study. This finding suggests that the graft-versus-Myeloproliferatie Disease effect may not be essential for a successful transplantation outcome, although this conclusion may be limited by small numbers of patients. A report of a successful syngeneic graft for treatment of MF supports the concept that graft-versus-lymphoma, and therefore GVHD, are not required [25]. Nonetheless, donor lymphocyte infusion has been reported to induce clinical and molecular remissions in patients who relapse after allogeneic transplantation for PV. Therefore, at this time, the immunomodulatory benefit to allogeneic transplantation in patients with ET and PV remains unclear [26].

The Seattle group initially reported a small series of patients with ET and PV receiving allogeneic transplants, and showed a 3-year survival of 64% [27]. Patients with MF did better than patients who had progressed to MDS/AML. Patients who had undergone a prior splenectomy had faster neutrophil engraftment (15 versus 20 days; $P = .004$). An updated study from Seattle, which included 104 patients with MF, PV, or ET receiving allogeneic related or unrelated donor transplants, reported a 7-year actuarial survival of 61% [16]. Nonrelapse mortality was 34% at 5 years; patients who received a targeted busulfan and cyclophosphamide regimen experienced a better survival compared with patients treated with other conditioning regimens. In a multivariate analysis, conditioning regimen, younger age, high platelet count at transplantation, and lower comorbidity score predicted for better survival. Twenty-five patients previously reported by the FHCRC are included in the current analysis. In our study, neither age nor blood counts at transplantation predicted for survival. Appropriate indications for transplantation could not be confirmed in this study, but might include development of cytopenias, recurrent thrombosis, poor response to standard therapy, or transformation to MF or MDS. Strategies to reduce early toxicity (the most common cause of death was organ toxicity)

might include a reduced-intensity regimen, particularly for older patients, or a targeted busulfan-based regimen.

Robin et al. [28] analyzed the outcomes of 147 patients with MF undergoing allogeneic HCT. Sixty-nine patients (47%) had MF secondary to PV or ET. The 4-year overall survival was 39% (95% confidence interval [CI], 30%-45%) for the entire group, and results in patients with primary and secondary MF were not analyzed separately. Comparisons are difficult among the different studies with some studies including only patients with MF (primary or secondary) and other studies of patients with prior leukemic transformation.

Similar to these previous studies, our study was limited by its retrospective nature, with transplantations performed in a variety of centers over a prolonged time period with different conditioning regimens and GVHD prophylaxis regimens. Patients underwent transplantations in 32 centers, but 1 center, the FHCRC, contributed 43 patients. Furthermore, the reasons for selecting HCT could not be ascertained for all patients, although it is reasonable to assume that the patients had at least 1 risk factor for poor outcome with conventional therapy. At the FHCRC, peripheral blood cytopenias and evidence for transformation to MF were the 2 most common indications for transplantation; almost one-half the patients had transformed to MF at the time of transplantation. Selection bias also makes it difficult to use these results as guidance for treatment of patients with ET and PV in general. Even though our study has a long median follow-up of over 4 years, the population is highly selected with a lower median age (49 and 53 years, respectively) than the general population with ET and PV, which is in the 7th decade [29].

Many patients with ET and PV do well with standard therapies, such as hydroxyurea, interferon, and phlebotomy, and are not considered candidates for HCT [10,30,31]. In addition, it is not clear how the availability of JAK2 inhibitors, now approved by the Food & Drug Administration, will affect the long-term disease course and therefore modify the decision process for or against HCT. The impact of JAK2 allele burden on prognosis and response to therapy remains controversial [32,33]. As JAK2 data were not available on the majority of patients in the present study, many of whom underwent transplantation before 2005, the relevance of JAK2 mutation for HCT outcome could not be assessed. Patients who had transformed to AML were excluded from this study, but represent a high-risk group of patients. Response to treatment of the patients reported here was determined by the transplantation centers, and criteria for relapse/progression may have differed as many patients underwent transplantation before standard response criterions were established [34]. Furthermore, as cytogenetic data were often lacking, the impact of karyotype on outcome could not be analyzed [35].

This report provides encouraging long-term outcome results for selected patients with ET and PV receiving allogeneic HCT. Future studies will need to determine the optimum role and timing of HCT in the face of emerging molecular-targeted therapies for these diseases.

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