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Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Chronic and Advanced Phase Myelofibrosis

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A B S T R A C T

Myelofibrosis (MF) is a chronic progressive hematologic malignancy with a median overall survival (OS) of approximately 6 years. Allogeneic hematopoietic stem cell transplantation (HSCT) is the sole treatment approach that offers curative potential. The use of reduced-intensity conditioning regimens has expanded the application of HSCT to patients with MF up to age 70 years. Recent retrospective and prospective reports have suggested worse HSCT outcomes for patients with MF receiving an unrelated donor graft compared with those receiving a related donor graft. To identify patient- and HSCT-specific variables influencing outcomes, we conducted a retrospective analysis of 42 patients with chronic and advanced-phase MF who underwent HSCT at our institution. For this cohort, at a median follow-up of 43 months, progression-free survival (PFS) was 15 months and OS was 25 months. In multivariable analysis, the sole clinical variable that negatively influenced outcome was the use of an unrelated donor, with a median PFS and OS both of 11 months versus not yet reached in patients receiving a related donor graft. At 2 years, OS was 38% (95% confidence interval [CI], 20%-56%) and nonrelapse mortality (NRM) was 53% (95% CI, 36%-78%) in the unrelated donor graft group, compared with 75% (95% CI, 46%-90%) and 21% (95% CI, 9%-47%) in the related donor graft group. There was no difference in the rates of grade III-IV acute graft-versus-host disease between the unrelated and related donor groups (38% versus 38%). Despite a more aggressive disease state, 2-year PFS and OS were both 42% (95% CI, 15%-67%) in patients with myeloproliferative neoplasm-blast phase undergoing HSCT. Graft failure rate was higher in patients receiving a mismatched donor graft compared with those receiving a matched donor graft (60% versus 13%; $P = .0398$). Retransplantation of patients with graft failure resulted in long-term survival. Baseline splenomegaly did not affect transplantation outcomes. Given the particularly poor outcomes seen in the unrelated donor cohort here and elsewhere, a formal exploration of alternative hematopoietic stem cell sources is warranted.

INTRODUCTION

Myelofibrosis (MF) is a Philadelphia chromosome–negative myeloproliferative neoplasm (MPN) with a median survival of approximately 6 to 7 years [1]. MF is characterized by bone marrow myeloproliferation and reticulin/collagen fibrosis, extramedullary hematopoiesis resulting in progressive cytopenias, constitutional symptoms, and risk of leukemic transformation [2]. Considerable heterogeneity in clinical presentation, course, and outcome pose management challenges highlighting the need for a risk-adapted treatment approach in which the inherent risks of the disease are balanced with those of the therapy in achieving a specific therapeutic goal. The Dynamic International Prognostic Scoring System (DIPSS) and DIPSS Plus are MF-specific risk stratification tools used to balance treatment decisions with the inherent risk of the disease [3,4]. Although a watchful waiting approach is appropriate for patients with low-risk MF, those with intermediate/high-risk disease require therapeutic intervention often with a goal of alleviating cytopenias (immunomodulatory agents, androgens, erythropoiesis-stimulating agents), reducing splenomegaly (hydroxyurea, ruxolitinib, splenectomy), ameliorating

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systemic symptoms (ruxolitinib), or modifying the disease course (hematopoietic stem cell transplantation) [5].

Irrespective of driver mutation (*JAK2V617F*, *MPL515L/K*, *CALR exon 9*) status, hyperactive JAK-STAT pathway signaling is the unifying theme underlying the pathophysiology of MPNs [6]. The oral selective JAK1/2 inhibitor ruxolitinib (Jakafi; Incyte, Wilmington, DE) is the sole Food and Drug Administration (FDA)-approved therapy for MF and is very effective in reducing both the symptom burden and splenomegaly [7,8]. However, ruxolitinib therapy does not result in elimination of the MPN hematopoietic stem cells (HSCs) and thus is incapable of producing molecular and cytogenetic remissions and resolution of bone marrow histomorphological abnormalities.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapeutic modality with curative potential for patients with MF, and has been documented to achieve resolution of bone marrow fibrosis and bone marrow morphological atypia [9,10]. The advent of reduced-intensity conditioning (RIC) has extended the use of this definitive therapy to older patients (age 55-70 years) and those previously deemed unfit for myeloablative therapy because of advanced age, comorbid conditions, and poor performance status [10-12].

HSCT is traditionally reserved for those patients with DIPSS intermediate/high-risk disease. Recent prospective RIC HSCT trials have suggested improved outcomes in patients with lower-risk MF [11,12]. Recent proposals incorporating mutational profiles in modern prognostication seek to better refine the current clinical risk stratification tools, thereby identifying patients categorized in lower prognostic risk groups that may in fact be upgraded in risk score and justify more aggressive therapy, including HSCT [13].

The use of an unrelated donor (URD) graft has been identified in recent reports from both prospective and retrospective MF HSCT studies as associated with poor outcomes relative to the use of a related donor graft [12,14,15]. Owing to a higher rate of primary/secondary graft failure and nonrelapse mortality (NRM), the survival of patients with MF undergoing matched URD RIC HSCT is poor, and the biological mechanisms underlying this finding are unexplained. We reviewed the outcomes of patients with chronic-phase (CP) MF and post-MPN acute myelogenous leukemia (blast-phase [BP] MF) who underwent HSCT at Mount Sinai Hospital over a 6-year period. The aims of the present study were to (1) determine overall outcomes of patients with CP and BP MF undergoing HSCT, (2) identify patient and transplantation variables that may adversely influence outcomes, and (3) compare transplantation outcomes between related donor and URD cohorts and identify transplantation-related variables that may explain potential differences in outcomes.

METHODS

We identified a total of 42 patients with MF in CP and BP who underwent HSCT at Mount Sinai Hospital between 2008 and 2014. Eleven of the 42 patients (26%) participated in the Myeloproliferative Disorder Research Consortium (MPD-RC) 101 trial [12]. This research was approved by the Program for Protection of Human Subjects at Mount Sinai Medical Center.

The primary endpoints of this analysis were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included NRM, time to progression (TTP), and time to neutrophil and platelet engraftment. OS was calculated from the date of transplant to the date of last follow-up or the date of death. Neutrophil engraftment was defined as the first of 3 consecutive days of an absolute neutrophil count (ANC) >500/mm^3, and platelet engraftment was defined as the first of 3 consecutive days of a platelet count $\geq 20 \times 10^9$/L without a transfusion in the previous 7 days. Both neutrophil and platelet engraftment required demonstration of donor chimerism [16]. Primary graft failure was defined as failure to achieve neutrophil engraftment by day +30. Secondary graft failure was defined as loss of donor chimerism after initial engraftment. International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria were used to define progressive and relapsed disease [17].

Continuous patient-related, disease-related, and transplantation-related variables are reported as median and range, and categorical variables are reported as number and percentage. Cumulative incidence functions were used to estimate NRM, TTP, and neutrophil and platelet engraftment in a competing-risks setting. In the analysis of NRM, death from any cause without previous relapse was the defining event, and relapse was the competing event. For TTP and engraftment, relapse and engraftment, respectively, were considered the defining events, and death without previous relapse and death without previous engraftment, respectively, were the competing events. Univariable and multivariable hazard ratios (HRs) for OS and PFS were estimated using Cox proportional hazards models, whereas HRs for NRM, TTP, and engraftment were estimated using Fine and Gray's (1999) extension of Cox regression, which models the hazards of the cumulative incidence function. Following intention-to-treat principles, the event of second transplantation was ignored in the analysis of OS as opposed to censored (at the time of the second transplantation), to avoid overestimating the survival probability [18]. A time-dependent Cox proportional hazards model served as a sensitivity analysis to assess the impact of ignoring the event of second transplantation on OS. Univariable and multivariable HRs are presented for each outcome considering the following covariates: donor source, DIPSS risk score, sex, age, spleen size, and bone marrow fibrosis grade.

All hypothesis testing was 2-sided with the type 1 error rate fixed at 5% for determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Transplantation Characteristics

A total of 42 patients were identified through a search of electronic medical records to have undergone HSCT at Mount Sinai Hospital between 2008 and 2014. The baseline characteristics of these patients are presented in Table 1. Sixteen patients (38%) received a related donor graft, and 26 (62%) received a URD graft. There were no statistically significant differences in baseline characteristics between the patients receiving related donor transplants and those receiving URD transplants. Although the difference did not reach statistical significance, the patients with a URD were more likely than those with a related donor to have received therapy before transplantation (38% versus 19%; $P = .3033$). All patients were at least MF intermediate-2 status based on DIPSS Plus score (calculated at the time of transplantation), with 12 (29%) patients classified as MPN-BP. Five patients (12%; 1 related donor and 4 URD) received a 9/10 HLA-matched donor graft. The median age at time of transplantation was 58 years (range, 40-68 years). RIC was provided either with fludarabine 30 to 40 mg/m^2/day for 5 days and busulfan 8 mg/kg total dose (11 patients; 26%) or with fludarabine 30 mg/m^2/day for 5 days and melphalan 70 mg/m^2/day for 2 days (31 patients; 74%). Thirty-eight patients (90%) received prograf and methotrexate as graft-versus-host disease (GVHD) prophylaxis. Thymoglobulin (rabbit antithymocyte globulin [ATG]) was administered to 14 of the 26 patients (54%) who received a URD graft and either type of conditioning regimen.

Engraftment

At 28 days, mean neutrophil and platelet engraftment were 91% (95% CI, 83%-99%) and 49% (95% CI, 38%-64%), respectively, with 63% (95% CI, 51%-79%) of patients achieving platelet engraftment by day +100. MF-3 bone marrow fibrosis was associated with delayed neutrophil and platelet engraftment in univariable analysis. In multivariable analysis, MF-3 remained statistically significant for delayed neutrophil engraftment only. DIPSS Plus score, donor type,