Original Study

Allogeneic Transplantation for Patients With Advanced Myelofibrosis: Splenomegaly and High Serum LDH are Adverse Risk Factors for Successful Engraftment

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Abstract

Delayed neutrophil and platelet engraftment increases the early morbidity and mortality after allogeneic stem cell transplantation for myelofibrosis. With a long follow-up of our patients, we analyzed disease and transplant variables that contributed to engraftment and outcomes. Splenomegaly and high levels of lactate dehydrogenase correlated with engraftment. Splenomegaly and performance status correlated with survival. Donor type and Janus-Associated Kinase 2 (*JAK2*) status did not correlate with outcomes.

Background: Thirty consecutive patients underwent hematopoietic stem cell transplantation for myelofibrosis (MF) at our institution. The median age at the time of transplant was 49 (range, 18-68) years, 74% of patients had advanced Dynamic International Prognostic Scoring System (DIPSS) scores, and 83% received reduced-intensity conditioning. **Patients and Methods:** With a long follow-up of our patients, we analyzed disease and transplant variables that contributed to engraftment and outcomes. **Results:** Neutrophil engraftment was achieved in 27 patients (90%) at a median time of 15 (range, 10-44) days, and 19 patients (63%) achieved platelet recovery at a median time of 18 (range, 8-100) days. Splenomegaly was associated with poor neutrophil engraftment (subdistributional hazard ratio [SHR], 0.42; 95% confidence interval [CI], 0.21-0.83; $P = .01$) and platelet engraftment (SHR, 0.18; 95% CI, 0.07-0.48; $P < .001$). Increased levels of lactate dehydrogenase (LDH) was associated with poor platelet engraftment (SHR, 0.39; 95% CI, 0.16-0.94; $P = .04$). The median follow-up for surviving patients was 49 (range, 3-155) months. The 1-year cumulative incidence of nonrelapse mortality (NRM) and relapse were respectively, 57% (95% CI, 29%-76%) and 25% (95% CI, 7%-48%). Increased levels of LDH was associated with high NRM (SHR, 2.82; 95% CI, 1.08-7.35; $P = .03$). The 4-year overall survival (OS) and relapse-free survival (RFS) were 44% (95% CI, 29%-67%) and 37% (95% CI, 23%-61%), respectively. In the multivariable model, splenomegaly and Eastern Cooperative Oncology Group (ECOG) performance status (PS) > 1 were associated with worse OS (hazard ratio [HR], 5.40; 95% CI, 1.19-24.56); $P = .03$) and RFS (HR, 3.78; 95% CI, 1.01-14.06; $P < .05$), respectively. ECOG PS > 1 was also associated with worse RFS (HR, 5.00; 95% CI, 1.31-19.14; $P = .02$). In this patient group with advanced disease, DIPPS score, Lille score, Janus-Associated Kinase V617F (*JAK2 V617F*) mutation status, and donor type did not predict transplant outcome. **Conclusion:** We confirm curative potential, but high NRM of allogeneic transplant for advanced MF.

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is potentially curative for patients with myelofibrosis (MF) with cure rates of 30% to 60%.[1-9] However, rates of primary graft failure (GF) are 10% to 20%.[1,5,6,9-12] and secondary GF evidenced by persistent cytopenias and/or declining donor chimerism affects an additional 10% of recipients.[2,6,9] Most reports estimate that the 100-day mortality is 10% to 30%[3,4,6,7,9] and nonrelapse mortality (NRM) is 30% to 50%.[1,6,9] The long-term survival is in the range of 30% to 70% (Table 1).[1-3,5-9,13] In this report we describe our transplant experience, re-examine the effect of splenomegaly on engraftment and survival, and identify other predictors for the outcome of MF patients.

Patients and Methods

The primary objective of the study was to examine the effect of pretransplant variables on engraftment and survival of patients who underwent HSCT for MF. The institutional review board in accordance with the Declaration of Helsinki approved this analysis. The pretransplant variables of interest included sex, age at time of transplant, time from diagnosis to transplant, the Dynamic International Prognostic Scoring System (DIPSS) score, Lille score, Janus-Associated Kinase V617F (*JAK2 V617F)* mutation status, spleen status at time of transplant, albumin level before transplantation, lactate dehydrogenase (LDH) level before transplantation, Eastern Cooperative Oncology Group (ECOG) performance status, donor type (human leukocyte antigen [HLA]-identical related donor [MRD] vs. HLA-identical unrelated donor [MUD]), major blood group (ABO) matching, and Cytomegalovirus (CMV) status. They were summarized in terms of median and range for continuous variables and counts and percentages for categorical variables. End points of interest include neutrophil and platelet recovery, relapse-free survival (RFS), overall survival (OS), NRM, and relapse rate (RR). Neutrophil recovery was defined as an absolute neutrophil count $\geq 5 \times 10^9$/L for 3 consecutive days and platelet recovery as a platelet count $\geq 20 \times 10^9$/L for 7 consecutive days without transfusion support. Relapse and NRM constituted competing risks for neutrophil and platelet recovery. Engraftment and NRM were summarized using cumulative incidence curves to accommodate competing risks. The Fine and Gray method was used to evaluate the association between covariates and the end points with competing risks. The subdistributional HRs (SHRs) with 95% CIs and *P* values were reported. OS and RFS were summarized using Kaplan–Meier curves. Univariate and multivariate Cox proportional hazards models were used to examine the association between covariates and OS and RFS. Covariates with

Table 1 Major Published Studies on Hematopoietic Stem Cell Transplantation for Myelofibrosis

Study	n	Follow-Up, Years	OS/RFS/NRM/RR, %	Day 100 Mortality, %	Primary GF, %	Independent Risk Factors for Worse RFS and/or OS
Ballen et al[1] CIBMTR	289	5	MRD 37/33/32/28 URD 30/27/48/23	MRD 18 URD 35	MRD 9 URD 20	RFS PS <90%circulating blasts
Kroger et al,[2,a] EBMT	103	5	67/51/16[b]/29	[c]	2	OS Age >55 years HLA-mismatched donors RFS Age >55 years and Advanced Lille score
Patriarca et al[3]	100	3	42/35/43/41	17	12	A trend toward better OS with the use of peripheral blood stem cells
Robin et al[5]	147	4	39/32/39/29	—	10	OS Donors other than MRD, High-risk disease, male sex, and no splenectomy
Scott et al[13]	170	5	57/57/34/10	—	3.5	OS DIPSS score All-cause mortality and NRM DIPSS
Abelsson et al[6]	92	5	RIC 59/—/23/8 MAC 49/—/45/10	RIC 5.8 MAC 17.5	14	OS MAC, Age >60 years High Lille score
Gupta et al[7] CIBMTR	233	5	47/27/24/48	—	3	RFS Donors other than MRD
Alchalby et al[8]	150	5	60/—/—/—	—	—	OS *JAK2 V617F* wild type Age ≥57 years Constitutional symptoms
Rondelli et al[9]	66	2[d]	MRD 75/—/22/9 MUD 32/—/59/9	MRD 9[e] MUD 50[e]	MRD 3 MUD 24	OS Donors other than MRD

Lille score was used except for in Scott et al[13] and Gupta et al,[7] who used the DIPSS score.
Abbreviations: CIBMTR = Center for International Blood and Marrow Research; DIPSS = Dynamic International Prognostic Scoring System; EBMT = European Society for Blood and Marrow Transplantation; GF = graft failure; HLA = human leukocyte antigen; MAC = myeloablative conditioning; MRD = HLA-identical related donor; MUD = HLA-identical unrelated donor; NRM = nonrelapse mortality; OS = overall survival; PS = performance status; RFS = relapse-free survival; RIC = reduced-intensity conditioning; RR = relapse rate; URD = unrelated donors.
[a]Prospective trials.
[b]NRM at 1 year.
[c]Data not available.
[d]Twenty–five-month actual follow-up.
[e]Six-month mortality.