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Reduced-Intensity Hematopoietic Cell Transplantation for Patients with Primary Myelofibrosis: A Cohort Analysis from the Center for International Blood and Marrow Transplant Research

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A B S T R A C T

We evaluated outcomes and associated prognostic factors in 233 patients undergoing allogeneic hematopoietic cell transplantation (HCT) for primary myelofibrosis (MF) using reduced-intensity conditioning (RIC). The median age at RIC HCT was 55 yr. Donors were a matched sibling donor (MSD) in 34% of RIC HCTs, an HLA well-matched unrelated donor (URD) in 45%, and a partially matched/mismatched URD in 21%. Risk stratification according to the Dynamic International Prognostic Scoring System (DIPSS) was 12% low, 49% intermediate-1, 37% intermediate-2, and 1% high. The probability of survival at 5 yr was 47% (95% confidence interval [CI], 40% to 53%). In a multivariate analysis, donor type was the sole independent factor associated with survival. Adjusted probabilities of survival at 5-yr were 56% (95% CI, 44% to 67%) for MSD, 48% (95% CI, 37% to 58%) for well-matched URD, and 34% (95% CI, 21% to 47%) for partially matched/mismatched URD ($P = .002$). The relative risk (RR) for NRM was 3.92 ($P = .006$) for well-matched URD and 9.37 ($P < .0001$) for partially matched/mismatched URD. Trends toward increased NRM (RR, 1.7; $P = .07$) and inferior survival (RR,

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1.37; $P = .10$) were observed in DIPSS intermediate-2/high-risk patients compared with DIPSS low/intermediate-1 risk patients. Our data indicate that RIC HCT is a potentially curative option for patients with MF, and that donor type is the most important factor influencing survival in these patients.

INTRODUCTION

Primary myelofibrosis (MF) is a clonal stem cell disorder characterized by cytopenias, splenomegaly, marrow fibrosis, and systemic symptoms resulting from elevated inflammatory cytokine levels. Allogeneic hematopoietic cell transplantation (HCT) is the only known curative treatment option for MF. Full-intensity conditioning (FIC) in older patients with MF is associated with high rates of nonrelapse mortality (NRM), restricting the use of this option to younger and fitter patients [1]. Reduced-intensity conditioning (RIC) is increasingly used in patients with MF, as demonstrated by the trends reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) [1].

The outcome of HCT is usually determined by complex interactions among various patient-, disease-, and transplantation-related variables. Although potentially curative, HCT in patients with MF is associated with significant risks of morbidity and mortality. Thus, it is important to understand the factors associated with outcomes to determine which patients are likely to benefit from this approach. Previous studies evaluating the prognostic factors in patients with MF undergoing HCT have reported conflicting results [2-6], likely related to heterogeneity of the disease and patient populations, as well as small sample sizes lacking statistical power, and thus the inability to analyze these factors in multivariate analysis.

Our understanding of the natural history of primary MF has improved significantly with the evolution of new prognostic systems. These prognostic systems are important tools for assessing the risk of mortality associated with the disease, and thus can be useful in determining the candidacy for HCT. Lille score, the conventional prognostic scoring system, divides patients into low-, intermediate-, and high-risk categories [7]. The International Prognostic Scoring System (IPSS) was recently developed by the International Working Group of Myelofibrosis Research and Treatment [8]. Five independent risk factors at diagnosis—age >65 yr, hemoglobin <100 g/L, WBC count $>25 \times 10^9$/L, circulating blasts >1%, and presence of constitutional symptoms—were predictive of shorter survival in patients with primary MF. The presence of 0, 1, 2, and ≥3 factors are categorized as low-, intermediate-1-, intermediate 2-, and high-risk disease, respectively, with corresponding median survival of 135, 95, 48, and 27 mo. The risk factors for IPSS were also validated in a time-dependent fashion known as dynamic IPSS (DIPSS) [9]. DIPSS is used to assess the risk of mortality at any time during the course of disease. Further refinement of DIPSS was proposed by incorporating cytogenetics, transfusion dependence, and thrombocytopenia to create the DIPSS-plus scoring system [10]. DIPSS has largely replaced the Lille score for assessing the risk of mortality in primary MF.

The utility of new scoring systems in predicting the outcomes of patients undergoing RIC HCT is not well understood. Two recent studies have reported that post-HCT success was dependent on pre-HCT DIPSS scores [6,11]. A large proportion of patients received FIC in those studies. Another study from the European Group for Blood and Marrow Transplantation reported that DIPSS, although predictive, did not sufficiently differentiate between intermediate-1 and intermediate-2 risk populations in patients undergoing RIC HCT for MF [2].

In addition, various RIC regimens of varying intensities have been used in patients with MF [4,12-16]. The superiority of one regimen over other has not been established. The impact of other transplant-related factors such as conditioning regimen, donor type, and graft-versus-host disease (GVHD) prophylaxis has not been well studied in the RIC setting. Thus, the Chronic Leukemia Working Committee of the CIBMTR sought to determine the outcomes of patients with primary MF undergoing HCT using RIC, and analyzed the impact of patient-, disease-, and transplantation-related factors on outcomes.

METHODS

Data Source

The 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 HCTs 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 HIPAA privacy rule. Additional details on the data source are described elsewhere [17].

Patient Populations

We identified adult patients age >18 yr undergoing a first allogeneic HCT for primary MF from a related or unrelated donor between 1997 and 2010 using an RIC regimen. The intensity of the conditioning regimen was defined according to CIBMTR consensus criteria [16]. Patients whose disease had progressed to acute myelogenous leukemia before HCT were excluded. Additional exclusion criteria included syngeneic transplants, cord blood transplants, haploidentical transplants, and in vitro T cell–depleted grafts. Unrelated donor (URD) transplant recipients were classified based on available HLA typing as described previously [18].

Prognostic Scoring Systems

Risk stratification according to DIPSS score was calculated at the time of HCT [9]. DIPSS risk categorization could not be determined in 3 patients (<1%) because of missing data. Because of missing cytogenetics in 36% of the patients, we were not able to evaluate DIPSS-plus in this study.

Cytogenetics

Results of cytogenetics testing provided by the transplantation center were reviewed and classified as normal karyotype or abnormal karyotype. Abnormal karyotype was further subdivided into unfavorable and other abnormalities. Unfavorable cytogenetics was defined as described previously and included complex abnormalities (≥3) or 1 or 2 abnormalities, including +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), and 11q23 rearrangements [10].

Endpoints

The primary endpoint of the study was overall survival (OS). Other endpoints of interest were hematopoietic recovery, acute GVHD (aGVHD), chronic GVHD (cGVHD), relapse/progression, nonrelapse mortality (NRM), and progression-free survival (PFS). OS was defined as time from HCT to death from any cause, and patients were censored at the last follow-up. Relapse/progression was reported by the transplantation centers, with NRM considered a competing event. NRM was defined as death within the first 28 days of transplantation from any cause or death without evidence of disease progression/recurrence; relapse/progression was considered a competing event. PFS was defined as time to treatment failure (death or relapse/progression). For relapse/progression, NRM, and PFS, patients alive in continuous complete remission were censored at last follow-up. Hematopoietic recovery was defined as time to an absolute neutrophil count