Role of Allogeneic Stem Cell Transplant in the Treatment of Primary Myelofibrosis

Nur Soyer,1 Ferit Celik,2 Murat Tombuloglu,1 Fahri Sahin,1 Guray Saydam,1 Filiz Vural1

Abstract

Objectives: The only known curative therapy for primary myelofibrosis is allogeneic hematopoietic stem cell transplant.

Materials and Methods: We retrospectively evaluated 11 transplant procedures involving 10 patients (5 men and 5 women) diagnosed with primary myelofibrosis between 2005 and 2014.

Results: The median age at the time of transplant was 60.5 years (range, 22-62 years). Stem cell sources were unrelated (n=1) and related (n=11) peripheral blood stem cells. Conditioning regimen was myeloablative for 8 and reduced intensity for 3 transplants. The median number of infused CD34+ cells was 6.8 × 10^6 cells/kg (range, 3.2-10.4 × 10^6 cells/kg). Neutrophil and platelet engraftment occurred at median of 22 days (range, 12-31 days) and 19.5 days (range, 13-56 days). Acute and chronic graft-versus-host disease was seen in 4 of 11 allografts. Relapse and nonrelapse mortality rates were 20%. Six patients (60%) were still alive without disease after median follow-up of 68.5 months (range, 17-120 months). Median progression-free survival and overall survival were 61 months (range, 2-120 months) and 65 months (range, 2-120 months).

Conclusions: Our results suggest that allogeneic hematopoietic stem cell transplant may provide a curative treatment for primary myelofibrosis patients. A myeloablative regimen seems to be effective and safe, especially for younger primary myelofibrosis patients.

Key words: Conditioning regimen, Graft-versus-host disease, Survival

Introduction

Primary myelofibrosis (PMF) is a clonal stem cell disorder that is characterized by cytopenias, splenomegaly, and bone marrow fibrosis and included in myeloproliferative neoplasms according to World Health Organization criteria.1,2 The International Prognostic Scoring System is an applicable prognostic system for PMF at time of initial diagnosis. According to the International Prognostic Scoring System, there are 5 independent predictors of poor survival: age > 65 years, hemoglobin level < 10 g/dL, leukocyte count > 25 × 10^9/L, circulating blasts > 1%, and presence of constitutional symptoms. Presence of 0 adverse factors denotes low-risk (median survival of 11.3 y), 1 denotes intermediate-1 risk (median survival of 7.9 y), 2 denotes intermediate-2 risk (median survival of 4 y), and ≥ 3 denotes high-risk (median survival of 2.3 y) disease.3

Currently, the only known curative therapy for PMF is allogeneic hematopoietic stem cell transplantation (allo-HSCT). In a large-scale study using the database of the Center for International Bone Marrow Transplant Research, 5-year disease-free survival and treatment-related mortality rates were 33% and 35% for matched related transplants and 27% and 50% for unrelated transplants.4 In a prospective multicenter phase II study to determine efficacy of a reduced-intensity conditioning (RIC) regimen followed by allogeneic stem cell transplant, 5-year disease-free survival was 51%, and overall survival (OS) was 67%.5 However, Janus kinase 2 inhibitors are promising options, mainly effective in alleviating symptoms of the disease.6,7 Because these drugs are not curative, allo-HSCT remains an important option for PMF patients who are considered candidates for HSCT.

In this study, we retrospectively evaluated the clinical characteristics and follow-up course of PMF patients at our transplant center who underwent allo-HSCT.
Materials and Methods

Our study included 10 patients (5 men and 5 women) with PMF who underwent 11 allo-HSCT procedures between 2005 and 2014. This study was approved by the Ege University Ethics Committee (March 30, 2015, No. 15-3/8). Clinical and laboratory data were retrospectively collected from patient files. All diagnoses were confirmed according to World Health Organization 2008 criteria and the International Working Group for Myelofibrosis Research and Treatment consensus criteria.2,8 The myeloablative regimen consisted of 12.8 mg/kg busulfan and 120 mg/kg intravenous cyclophosphamide. The RIC regimen consisted of 180 mg/m² fludarabine and 6.4 mg/kg intravenous busulfan, 180 mg/m² fludarabine and 140 mg/m² melphalan, or 150 mg/m² fludarabine, 100 mg/kg cyclophosphamide, and 5 g/m² cytosine arabinoside. Methotrexate (15 mg/m² on day 1 after HSCT and 10 mg/m² on days 3 and 6 after HSCT) and cyclosporine (3 mg/kg/d starting on 1 day before HSCT) were used for graft-versus-host disease (GVHD) prophylaxis. The cyclosporine dose was adjusted according to the serum level of 200 ng/mL. If no GVHD occurred, cyclosporine was tapered and discontinued after day 180. Oral cotrimoxazole was given for prophylaxis against Pneumocystis jiroveci. Acyclovir and fluconazole were used for antiviral and antifungal prophylaxis. Platelet engraftment and neutrophil engraftment were defined as the first of 3 consecutive days of unsupported platelet count > 20 x 10⁹/L and absolute neutrophil count of more than 0.5 x 10⁹/L.

Donor chimerism was evaluated on days 30, 60, and 120 and subsequently according to clinical needs. Donor cells ≥ 90% were considered as predominantly donor chimerism and < 90% as mixed chimerism. Acute and chronic GVHD were graded according to modified Gluckberg and US National Institutes of Health consensus criteria.9,10 Disease response was assessed at 6 and 12 months and annually thereafter, according to International Working Group for Myelofibrosis Research and Treatment and European Leukemia Net criteria.11 Statistical analyses were performed with SPSS software (SPSS: An IBM Company, IBM Corporation, Armonk, NY, USA). Continuous variables are shown as medians with ranges and categorical variables as numbers with percentages. Overall survival was defined as time from HSCT to death from any cause, and patients were censored at the last follow-up. Progression-free survival was defined as time to treatment failure (death or relapse/progression) after transplant. Nonrelapse mortality was defined as death related to transplant.

Results

We retrospectively evaluated 11 allo-HSCT procedures from 10 patients. All patients were in chronic phase of PMF at the time of the transplant. The median age at diagnosis was 58.5 years (range, 22-59 y). Seven patients were treated before transplant; 4 of them received hydroxyurea, whereas the others were treated with interferon (2 patients) and azacytidine (1 patient). Splenomegaly was found in 9 patients. Before transplant, median leukocyte count was 22.9 x 10⁹/L (range, 1.4-42.8 x 10⁹/L) and platelet count was 160 x 10⁹/L (range, 63-554 x 10⁹/L). Median hemoglobin level was 8.6 g/dL (6.3-9.5 g/dL). The Dynamic International Prognostic Scoring System (DIPSS) category of all patients was intermediate-2 at the time of transplant.

Medi an time from diagnosis to HSCT was 31 months (range, 4-53 mo). Of 11 transplanted allografts, 10 (91%) were HLA-matched sibling donors and 1 (9%) was HLA-matched unrelated donor. Myeloablative regimens were used for 8 of the 11 transplant procedures (72.7%), and RIC regimens were used in 3 of the 11 transplant procedures (27.3%). Of 11 transplant procedures, 7 were ABO matched and 4 ABO mismatched (Figure 1). Median age at the time of HSCT was 60.5 years (range, 22-62 y). Median number of infused CD34+ cells was 6.8 x 10⁶ cells/kg (range, 3.2-10.4 x 10⁶ cells/kg). All patients experienced engraftment of neutrophil and platelet; neutrophil engraftment and platelet engraftment occurred at median of 22 days (range, 12-31 d) and 19.5 days (range, 13-56 d). Acute GVHD occurred with 4 of 11 transplanted allografts, with 2 of these being grade 3/4 acute GVHD. Chronic GVHD occurred with 4 of the 11 transplanted allografts, with 2 of these being limited and 2 being extensive (Figure 1).

Two patients died of relapsed disease. Relapse rate was 20%. Two patients died because of grade 4 acute GVHD and infection. Nonrelapse mortality rate was 20%. Six patients (60%) were still alive without disease after median follow-up of 68.5 months (range, 17-120 mo) (Figure 2). Median progression-free survival was 61 months (range,
patients were alive without disease, with 5 of these patients receiving myeloablative conditioning regimen. Therefore, a myeloablative regimen seems to be effective and safe for patients with PMF.

There are several studies in the literature that have evaluated transplant outcomes of PMF. In a prospective multicenter study, Kröger and associates evaluated 103 myelofibrosis patients treated with RIC allo-HSCT. The 5-year OS and disease-free survival was 67% and 51%. In another prospective study that enrolled 66 myelofibrosis patients treated with RIC allo-HSCT, the authors reported OS as 75% in the sibling group (median not reached) and 32% in the unrelated group (median OS of 6 mo). In a prospective pilot study, the 3-year estimated OS and disease-free survival was 84% with RIC allo-HSCT. In a large retrospective study (289 patients) from the Center for International Bone Marrow Transplant Research database, 5-year disease-free survival and treatment-related mortality were 33% and 35% for matched related and 27% and 50% for unrelated transplants. Patients received different types of conditioning regimens in that study. Gupta and associates evaluated 233 myelofibrosis patients undergoing allo-HSCT with RIC regimens. The 5-year OS was 47%. The 5-year OS rates were 56%, 48%, and 34% ($P = .002$) for match related, well-matched unrelated, and mismatched unrelated donors. In a large retrospective cohort (250 patients), 3-year OS was 55%, relapse incidence was 32%, and nonrelapse mortality was 28%. These prospective and retrospective studies lend support to our data regarding the efficacy of allo-HSCT.

Some studies have reported that survival is associated with performance status, older age, HLA mismatched donor status, absence of peripheral blood

### Table 1. Clinical Characteristics and Follow-Up Course of Patients With Primary Myelofibrosis Who Underwent Allogeneic Hematopoietic Stem Cell Transplant

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Tx, y.</th>
<th>Donor Type</th>
<th>Conditioning Regimen</th>
<th>Onset</th>
<th>Grade</th>
<th>Localization</th>
<th>Chronic GVHD Type</th>
<th>Donor Chimerism (%)</th>
<th>Relapse (day)</th>
<th>Current Status</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>MRD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Live</td>
<td>Limited</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>MRD</td>
<td>Flu-Mel</td>
<td>70</td>
<td>2</td>
<td>Liver</td>
<td>Limited</td>
<td>100</td>
<td>13</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>MRD</td>
<td>Cy-Bu</td>
<td>12</td>
<td>2</td>
<td>Liver</td>
<td>Limited</td>
<td>100</td>
<td>0</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>MRD</td>
<td>Flu-Bu</td>
<td>10</td>
<td>0</td>
<td>Skin</td>
<td>Limited</td>
<td>100</td>
<td>116</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>MRD</td>
<td>Flu-Ara-Cy</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>MRD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>MRD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>MRD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>MUD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>MUD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>MUD</td>
<td>Cy-Bu</td>
<td>10</td>
<td>0</td>
<td>Extensive</td>
<td>100</td>
<td>100</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Ara-C, cytosine arabinoside; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; Mel, melphalan; MRD, match-related donor; MUD, match-unrelated donor; Tx, transplant

*Same patient.
blasts, and type of donor. In many studies, survival was significantly higher, with allo-HSCT from sibling donors than from unrelated donors. In one of these studies, survival was affected positively by absence of peripheral blood blasts and good performance status. In other studies, older age (> 55 y) was associated with worse survival. In our study, patients numbers were too small to analyze these influencing factors on survival.

Scott and associates reported a retrospective analysis of allo-HSCT results in myelofibrosis patients. They evaluated the prognostic usefulness of the DIPSS in myelofibrosis patients treated with allo-HSCT. Five-year relapse rate was 10%, relapse-free survival rate was 57%, OS rate was 57%, and nonrelapse mortality rate was 34%. Among patients with DIPSS high-risk disease, post-HSCT mortality and nonrelapse mortality were significantly higher than in patients with low-risk disease. Although median OS was 2.5 years in the high-risk patients, median OS rates were 6.3 years and 7 years in patients with intermediate-1 and intermediate-2 risk. The authors concluded that patients with intermediate-2 or high-risk disease by DIPSS should be considered for HSCT. In our series, all patients had intermediate-2 risk disease according to DIPSS. On the other hand, Yamamoto and associates reported worse outcomes with allo-HSCT in high-risk myelofibrosis patients according to the International Prognostic Scoring System. The authors reported that a myeloablative regimen was feasible but less effective in high-risk myelofibrosis patients, even though the number of their patients was low. These studies showed that prognostic evaluation in myelofibrosis is a useful marker to decide on the time of transplant and in regard to patient selection.

Patient and donor selection is important for transplant success. The DIPSS score at the time of transplant, comorbidities, biological age, disease status, and donor type need to be considered in HSCT decisions. In conclusion, despite the small number of patients, our results suggest that allo-HSCT may provide a curative treatment for patients with PMF. A myeloablative regimen seems to be feasible and effective for patients.

References