Poor Outcome of Myeloablative Conditioned Allogeneic Bone Marrow Transplantation for Myelofibrosis

Masahide Yamamoto, Kazuteru Ohashi, Yuka Hirashima, Takeshi Kobayashi, Kazuhiko Kakihana, Hideki Akiyama and Hisashi Sakamaki

Abstract

Objective This study retrospectively analyzed clinical outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for myelofibrosis (MF) in a single institution.

Methods During the past 20 years, 6 patients with MF have undergone allo-HSCT in our institution. We investigated the clinical characteristics and follow-up course of these patients.

Patients Median age was 47 years (range, 40-52 years). The median interval between diagnosis and allo-HSCT was 12.5 months (range, 5-97 months).

Results Among these 6 patients, 4 patients were categorized in the high-risk group according to the International Prognostic Scoring System. All 6 patients received myeloablative conditioning regimens, but most of them eventually died of relapse.

Conclusion In this small series, allo-HSCT resulted in dismal outcomes. Our experience clearly indicates the need for studies with a larger series of patients to evaluate the efficacy of this modality.

Key words: myelofibrosis, allogeneic hematopoietic stem cell transplantation, myeloablative conditioning


Introduction

The myeloproliferative disorder primary myelofibrosis (PMF) and the therapeutically indistinguishable advanced forms of essential thrombocythemia (ET-MF) and polycythemia vera (PV-MF) are extremely challenging disorders (1). Median survival after diagnosis is approximately 5 years and several adverse prognostic factors for survival have been reported, including age, anemia, leukocytosis or leukocytopenia, abnormal karyotype, constitutional symptoms and the presence of peripheral blasts (2-5). According to the International Prognostic Scoring System (IPSS) for PMF (6), patients can be divided into 4 categories: low (median survival, 136 months); intermediate-1 (median survival, 95 months); intermediate-2 (median survival, 48 months); and high (median survival, 27 months). The prognosis thus drastically worsens as PMF progresses. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative option currently available for PMF (7), allowing more than 50% of patients to survive long term in remission (8). Regarding the conditioning regimen, use of reduced-intensity conditioning (RIC) regimens was first reported by Devine et al. (9), indicating that RIC is well tolerated and provides effective therapy. Subsequent clinical evaluations have supported these basic principles (10, 11). Accordingly, the majority of patients with intermediate risk now receive dose-reduced conditioning as the regimen of choice. Another important issue when pursuing allo-HSCT is how to determine the optimal timing. Recent reports suggest that allo-HSCT should be performed before severe marrow fibrosis, clonal cytogenetic abnormalities, or severe abnormalities of hematological parameters develop (12). Close monitoring of disease evolution, including declines in platelet counts or hemoglobin levels or changes in peripheral white blood cell counts and differential counts, is thus mandatory to make an appropriate decision (12). However, disease progression can still occur while searching for suitable

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Table 1. Individual Patient Characteristics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>Cytogenetics</th>
<th>Conditioning</th>
<th>Donor</th>
<th>Source of Cell</th>
<th>Conditioning regimen</th>
<th>Background</th>
<th>Treatment to GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46/F</td>
<td>PMF</td>
<td>No data</td>
<td>Intensive</td>
<td>Yes</td>
<td>No</td>
<td>BU-CY, 135</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>49/F</td>
<td>PMF</td>
<td>*1</td>
<td>Intensive</td>
<td>No</td>
<td>No</td>
<td>BU, 6,300</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>51/M</td>
<td>PMF</td>
<td>*2</td>
<td>Intensive</td>
<td>Yes</td>
<td>No</td>
<td>BU, 4,100</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>42/F</td>
<td>ET</td>
<td>47,XX, +8</td>
<td>Intensive</td>
<td>Yes</td>
<td>No</td>
<td>BU, 43,100</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>40/F</td>
<td>PMF</td>
<td>*1</td>
<td>Intensive</td>
<td>Yes</td>
<td>No</td>
<td>BU, 4,400</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>42/F</td>
<td>ET</td>
<td>47,XX, +12</td>
<td>Intensive</td>
<td>Yes</td>
<td>No</td>
<td>BU, 40,000</td>
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<td>No</td>
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</tbody>
</table>

Abbreviations: F=female; M=male; PMF=primary myelofibrosis; MF=myelofibrosis; ET=essential thrombocytosis; HSCT=hematopoietic stem cell transplantation; IPSS=International prognostic scoring system; IDA=idarubicine; CA=cytarabine; BU=busulfan; HU=hydroxyurea; WBC=white blood cell; Hb=hemoglobin; Plt=platelet; LDH=lactate dehydrogenase; MRD=matched related donor; MUD=matched unrelated donor; BM=bone marrow; CY=cyclophosphamide; LPAM=melphalan; TBI=total body irradiation; CyA=cyclosporine; MTX=methotrexate; GVHD=graft-versus-host disease.

*1: 46,XX,-20,+mar [5/10], 47,XX,+9,-20,+mar [2/10], 46XX [3/10] at the time of HSCT, *2: data at the time of HSCT, *3: 47,XX, +9 [5/10] in 1 patient, 47,XX, +1, der(1;12)(q10;q10) [20/20] in 1 patient (Table 1). Mutational analysis, such as JAK2 V617F, was not performed in our series.

All 6 patients received a myeloablative conditioning regimen mainly because all patients were relatively young and had no obvious comorbidities. Two patients were conditioned using a total body irradiation (TBI)-containing regimen (12 Gy), including cytarabine at 8 g/m² and cyclophosphamide (CY) at 120 mg/kg. The remaining patients were conditioned using a non-TBI-containing regimen that included intravenous busulfan (BU) at 12.8 mg/kg and CY at 120 mg/kg in 3 patients and melphalan at 160 mg/m² in 1 patient. Cyclosporine plus short-term methotrexate was used for acute graft-versus-host disease (GVHD) prophylaxis.

Acute and chronic GVHD were diagnosed and graded according to previously established criteria. Engraftment after HSCT was judged according to a conventional definition. Complete remission (CR) was defined as disappearance of all clinical signs of myelofibrosis, and peripheral blood and cytogenetic abnormalities attributable to the disease. Relapse was defined as the reappearance of morphologic abnormalities after initial clearing of the marrow or the detection of previously existing cytogenetic abnormalities. Chimerism analysis was not performed at the time of relapse.

Table 2. Laboratory Data Just Before Conditioning

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Interval between diagnosis and HSCT (Month)</th>
<th>IPSS</th>
<th>Donor</th>
<th>Source of Cell</th>
<th>Conditioning regimen</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>IPSS</td>
<td>No</td>
<td>No</td>
<td>BU-CY, 135</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>IPSS</td>
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<td>No</td>
<td>BU, 6,300</td>
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</tr>
<tr>
<td>3</td>
<td>10</td>
<td>IPSS</td>
<td>Yes</td>
<td>No</td>
<td>BU, 4,100</td>
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</tr>
<tr>
<td>4</td>
<td>15</td>
<td>IPSS</td>
<td>Yes</td>
<td>No</td>
<td>BU, 43,100</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>IPSS</td>
<td>Yes</td>
<td>No</td>
<td>BU, 4,400</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>IPSS</td>
<td>Yes</td>
<td>No</td>
<td>BU, 40,000</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Materials and Methods

During the past 20 years, 6 patients with MF have undergone allo-HSCT in our institution. Patient characteristics are shown in Table 1. Four were PMF and 2 patients were ET-MF. The median age was 49 years (range, 43-58). The interval between diagnosis and transplantation ranged from 5 to 97 months (median, 12.5 months). Based on the IPSS risk-assessment model, 4 patients were categorized in the high-risk group. With regard to cytogenetic abnormality, all patients for whom chromosomal data were available showed complex karyotype abnormalities, including 46,XX, -20, +mar [5/10] in 1 patient, 47,XX, +8 [5/10] in 1 patient and 47,XX, +1, der(1;12)(q10;q10) [20/20] in 1 patient (Table 1). Mutational analysis, such as JAK2 V617F, was not performed in our series.

In our series of 6 patients who received myeloablative conditioning, myeloid engraftment (neutrophils >500/μL) was documented in all patients at a median of 24 days (range, 19-34 days), as shown in Table 2. With the exception of 2 patients who died soon after allo-HSCT due to relapse without showing full recovery of platelets, platelet engraftment (>50×10⁹/L) was also observed at a median of 33 days (range, 24-45 days) in the remaining 4 patients. Overall, all 3 patients (50%) developed acute GVHD (grade I in 1 patient, grade II in 2 patients) at a median of 33 days
Acute GVHD manifested as skin lesions in all patients, while acute GVHD involving the gut was observed in 1 patient (Table 2). One patient (Case 3) with grade I acute GVHD received early intervention with steroids, and these decisions were made by attending physicians, mostly because of early onset of acute GVHD in the setting of unrelated transplant. Two patients developed chronic GVHD; 1 patient was classified as having extensive disease and the other patient had limited disease (Table 2). In our series, 5 of 6 patients eventually died. Causes of death were relapse (n=4) and bacterial pneumonia superimposed onto bronchiolitis obliterans (n=1). Only 1 patient has survived to the most recent follow-up, but that patient also faced hematological relapse at day 2,012 after allo-HSCT. Disease relapse was thus observed in up to 5 patients and the median time to relapse from transplantation was 347 days (range, 17-2,012 days).

### Discussion

The present study reviewed the clinical outcomes for 6 patients with MF who underwent allo-HSCT with myeloablative conditioning. In our series, most patients died and faced eventual hematological relapse. Our results seem inferior to those of previous larger studies showing a 5-year OS of 47-61% in MF patients who received allo-HSCT with myeloablative conditioning (8, 13). However, when looking at patients >45 years old or those with a higher risk in those studies, the clinical outcomes (5-year OS) were as low as 14%, comparable with our dismal outcomes. Our patient population included 4 patients with high-risk disease according to the IPSS score. In view of these disease conditions, all of our patients received myeloablative conditioning rather than RIC, albeit with fatal outcomes. As MF is frequently a disease of older patients who may experience more treatment-related toxicity, tolerability of the conditioning regimen is of central importance. RIC appears to contribute to that objective. Gupta et al. recently reported a relatively low relapse rate after allo-HSCT in MF (14), even after RIC transplants, and also suggested that immunological mechanisms such as graft-versus-MF were effective at eliminating malignant clones without myeloablative chemotherapy. However, the present results could not confirm these findings, as most patients experienced eventual relapse, even though some patients developed acute or chronic GVHD. Thus, despite the small number of patients, our experience suggests that allo-HSCT with myeloablative conditioning such as BU/CY or CY/TBI is still feasible, but less effective in alleviating disease activity with the high-risk MF.

### The authors state that they have no Conflict of Interest (COI).

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References


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