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Improved Outcome for Peripheral Blood Stem Cell Transplantation for Advanced Primary Myelodysplastic Syndrome

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ABSTRACT

Stem cell transplantation for myelodysplastic syndrome (MDS) is characterized by high transplant-related mortality (TRM), especially in older patients and those with more advanced disease. Outcome after peripheral blood stem cell transplantation (PBSCT) may be superior to earlier results with bone marrow transplantation. Forty-three patients (aged 12-73 years; median, 49 years) received an HLA-identical sibling donor PBSCT. Twenty three patients aged ≤55 years without prohibitive comorbidity received myeloablative total body irradiation–based conditioning, followed by a T cell–depleted PBSCT and delayed add-back of donor lymphocytes. Older patients or those with comorbidities (n = 20) received reduced-intensity conditioning and an unmanipulated PBSCT. Thirty-seven (86%) had advanced disease (refractory anemia with excess blasts [n = 9], refractory anemia with excess blasts in transformation [n = 6], acute myelogenous leukemia [n = 13], or treatment-related MDS [n = 9]); 6 had low-risk MDS (refractory anemia or refractory anemia with ringed sideroblasts). The median follow-up was 18 months (range, 5-89 months). Actuarial probabilities of 3-year overall survival (OS), disease-free survival, relapse, and TRM were 64%, 59%, 26%, and 23%, respectively, for 34 primary MDS patients. The best results were in 19 patients younger than 50 years of age undergoing myeloablative PBSCT (actuarial probabilities of OS, disease-free survival, relapse, and TRM were 81%, 72%, 22%, and 7%, respectively). Although outcomes for all stages of primary MDS were improved, that for therapy-related MDS remained dismal, with 11% OS, because of a high relapse rate (89%).

KEY WORDS

Peripheral blood stem cell transplantation • Myelodysplastic syndrome • Transplant-related mortality

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal hematopoietic disorder characterized by bone marrow dysplasia, cytopenias, and frequent evolution to acute myelogenous leukemia. The natural history is extremely variable; some patients survive many years, whereas others die within months after diagnosis. Factors associated with poor survival include an advanced French-American-British (FAB) subtype (a high percentage of bone marrow blasts), multiple cytopenias, an abnormal karyotype, prior cytotoxic therapy, and advanced age. A combination of marrow blast percentage, number of cytopenias, and karyotypic abnormalities has been used to define an international prognostic scoring system (IPSS) for MDS that can segregate patients into 4 subgroups with survival ranging from several months to several years [1]. Survival according to risk group is inferior in older patients (>60 years) [1]. Patients with therapy-related MDS are not included in this scoring system, but experience sug-

gests that such individuals often have rapidly progressive, refractory disease.

Treatment approaches for MDS have generally been unsatisfactory, and allogeneic stem cell transplantation (SCT) remains the only established curative treatment option. Historically, long-term disease-free survival (DFS) has been achieved in 30% to 50% of patients by using marrow from HLA-identical sibling donors. Success has been limited largely by a high rate (approximately 40%) of nonrelapse mortality [2-4]. Furthermore, approximately one third of transplant recipients relapse. The risk of recurrence depends on the stage of the disease before transplantation and the presence of high-risk karyotypic abnormalities [3,5]. Because they relapse less frequently, patients with refractory anemia (RA) or RA with ringed sideroblasts (RARS) have better outcomes than patients with increased blasts (RA with excess blasts; RAEB) or those in leukemic transformation [6,7].

Results of SCT for MDS have improved over the last decade as a result of better supportive care and the use of mobilized peripheral blood SCT (PBSCT) in lieu of bone marrow allografts [8,9]. PBSCT is associated with faster hematopoietic engraftment, an increased risk of chronic graft-versus-host disease (GVHD), and, perhaps, a more potent graft-versus-leukemia (GVL) effect. Despite improvements in transplantation strategies, older age is consistently a high-risk feature for nonrelapse mortality after myeloablative SCT (MST). Because the median age at diagnosis of MDS is 70 years, most patients are not candidates for standard myeloablative conditioning, and reduced-intensity conditioning (RIC) regimens have been introduced to minimize toxicity and harness a potential GVL effect. Although RIC transplantation strategies have curative potential, they carry a higher risk of relapse; this suggests that the conditioning regimen dose intensity may be important in disease control [10]. To better define the risk factors that affect outcome, we report our results of a retrospective study of MDS patients who received peripheral blood stem cell (PBSC) allografts from HLA-identical sibling donors.

PATIENTS AND METHODS

Study Population

Between May 1997 and June 2004, 43 consecutive patients (27 male and 16 female) aged 12 to 73 years (median, 49 years) with MDS and an HLA-identical sibling donor were treated under National Heart, Lung and Blood Institute Institutional Review Board–approved protocols. Patients aged ≤55 years without prohibitive comorbidity were enrolled into 4 successive MST protocols (97-H-0099, 99-H-0046, 02-H-0111, and 03-H0192) consisting of total body irradiation (TBI)–based conditioning, followed by a T cell–depleted allograft and scheduled posttransplantation donor lymphocyte infusions (n = 23). Patients ineligible for an ablative transplantation because of age or poor health were enrolled into 3 successive RIC protocols (97-H-0042, 99-H-0050, and 01-H-0162) that consisted of a fludarabine-based conditioning regimen followed by a T cell–replete allograft (n = 20).

Table 1 outlines patient characteristics and transplantation procedures. All diagnoses were classified according to FAB criteria [11]. There were no patients with chronic myelomonocytic leukemia. All patients were cytopenic in at least 2 cell lineages. Overall, 7 (16%) patients fulfilled the criteria for RA/RARS, 14 (33%) had RAEB, 9 (21%) had RAEB in transformation, and 13 (30%) had evidence of transformation to acute myelogenous leukemia before transplantation. In 34 (79%) patients, MDS arose de novo, whereas 9 (21%) patients had previously received chemotherapy, radiation, or both. By IPSS cytogenetic criteria, 14 patients (32%) had a high-risk karyotype (chromosome 7 or complex abnormalities), 20 patients (47%) had a low-risk karyotype (normal, -Y, 5q-, or 20q-), and 9 (21%) patients had a intermediate-risk karyotype (all other abnormalities). By overall IPSS score, no patients were considered low risk, 8 (19%) patients were intermediate 1, 7 (16%) patients were intermediate 2, and 28 (65%) patients were high risk. Six (14%) had received cytoreductive chemotherapy before transplantation without achieving a remission.

Preparative Regimen

The myeloablative preparative regimen consisted of either fractionated TBI (13.6 Gy) and cyclophosphamide (120 mg/kg) or fractionated TBI (12.0 Gy), cyclophosphamide (120 mg/kg), and fludarabine (125 mg/m^2). The RIC regimens used fludarabine (125-180 mg/m^2) and 1 of the following alkylating agents: cyclophosphamide (120 mg/kg), melphalan (140 mg/m^2), or infusional busulfan (6.4 mg/kg).

PBSC Collection and Processing

Donors received granulocyte colony-stimulating factor 10 μg/kg/d subcutaneously. Mobilized PBSCs were collected by leukapheresis on day 5 and again on days 6 and 7 if necessary to obtain a target dose of more than 5×10^6 CD34 cells per kilogram of the recipient's weight. T-cell depletion was performed on all MSTs by using 1 of 2 CD34 selection methods. The Ceprate T-cell depletion system (CellPro, Bothell, WA), which used combined CD34-positive and CD2-negative selection by immunoabsorption, was used in the first cohort of patients (protocol 97-H-0099). Subsequent protocols used the Isolex 300i immunomagnetic cell separation system, version 2.5