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CD34-Selected Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Relapsed, High-Risk Multiple Myeloma

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A B S T R A C T

We report results of a retrospective analysis of 44 patients with relapsed and high-risk multiple myeloma (MM) undergoing allogeneic CD34-selected hematopoietic stem cell transplantation (HSCT) from HLA-compatible donors. Patients had multiply relapsed disease including relapse at <15 months after autologous transplantation and most patients (28 of 44; 65%) also had high-risk cytogenetics. Before transplantation, patients received busulfan (.8 mg/kg × 10 doses), melphalan (70 mg/m^2 × 2 days), fludarabine (25 mg/m^2 × 5 days), and rabbit antithymocyte globulin (2.5 mg/kg × 2 days). Patients with 10/10 HLA– matched donors were treated prophylactically with low doses of donor lymphocyte infusions (.5 to 1 × 10^6 CD3$^+$/kg) starting 4 to 6 months after CD34-selected HSCT. Acute (grade II to IV) graft-versus-host disease (GVHD) and transplantation-related mortality at 12 months were 2% and 18%, respectively. Chronic GVHD was not observed in any patient. Overall and progression-free survival at 2 years were 54% and 31%, respectively. By multivariate analyses, the outcomes of CD34-selected HSCT were influenced by presence of extramedullary disease, disease status before CD34-selected HSCT, and age. This study demonstrates notable safety and efficacy of CD34-selected HSCT in patients with multiply relapsed MM, including those with high-risk cytogenetics.

INTRODUCTION

Multiple myeloma (MM) is a malignant disease of plasma cells, with an estimated 25,000 new MM diagnoses annually, and about 11,000 patients are projected to die of the disease every year [1-3]. Approximately 25% of MM patients are considered "high-risk" as defined by routine cytogenetics. Despite the introduction of immunomodulatory agents and proteasome inhibitors, patients with high-risk myeloma continue to do poorly, even with tandem autologous stem cell transplantation (auto-SCT), with a median survival of approximately 3 years [3,4].

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative treatment available for patients with MM. Despite the potential advantages of graft-versus-tumor immune responses and a tumor-free source of stem cells, the success rate of patients undergoing conventional high-dose conditioning with allogeneic bone marrow or peripheral blood stem cell transplantation has been historically compromised by high incidences of acute and/or chronic graft-versus-host disease (GVHD) and transplantation-related mortality (TRM), exceeding 40% at

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day 100 after transplantation [5-7]. The introduction of nonmyeloablative conditioning regimens in the treatment of myeloma has reduced associated toxicities and TRM, but high rates of acute and chronic GVHD persist [8-10]. In addition, results from transplantations with nonmyeloablative regimens have been poor in patients with multiply relapsed disease [11,12]. $CD34^+$ selection has been effectively used in other hematologic malignancies as a strategy that allows intensification of the conditioning regimen while reducing the risks of acute and chronic GVHD. We have extensively studied CD34 selection in a variety of hematologic malignancies and have shown in retrospective analysis that long-term results of disease-free survival and overall survival (OS) are comparable to those after unmanipulated grafts, with significantly lower rates of acute and chronic GVHD [13,14]. In 2007, we began performing CD34-selected allogeneic HSCT in patients with relapsed MM. To determine the long-term disease-specific outcomes as well as determinants of prognosis, we performed a retrospective analysis of transplantation outcomes on the initial 44 patients treated that are summarized herein.

PATIENTS AND METHODS

Patients

We assessed the safety, toxicity, and efficacy of allogeneic CD34-selected HSCT in patients with high-risk, multiply relapsed MM at Memorial Sloan Kettering Cancer Center (MSKCC). The study was approved by the Institutional Review/Privacy Board at MSKCC and by the Food and Drug Administration.

Patients included in this study had relapsed MM after auto-SCT. Relapse had to occur either with normal cytogenetics within 15 months after the autologous transplantation or with high-risk cytogenetics. Patients had to have achieved at least a partial response (PR) after additional chemotherapy or second salvage auto-SCT. Patients with an HLA-matched related or unrelated donor (genotypically matched at all A, B, C, DRB1, and DQB1 loci, as tested by DNA analysis) and patients who had an unrelated donor with only 1 antigen or 1 allele mismatch at the HLA A, B, C, DRB1, or DQB1 loci were eligible for entry on this protocol. All patients on study with at least 1 year of follow-up after CD34-selected HSCT at the time of analysis are presented in this report, encompassing patients who underwent allogeneic HSCT between November 28, 2007 and October 9, 2013. T cell depletion was performed by positive CD34 selection using the Isolex 300i (Nexell Therapeutics, Irvine, CA) followed by rosetting with sheep erythrocytes for the initial 13 patients (2008 to 2009) and by $CD34^+$ enrichment by the CliniMACS CD34 Reagent System (Miltenyi Biotech, Bergisch Gladbach, Germany) in 31 patients thereafter. Patients did not receive immunosuppressive therapy after transplantation. All patients signed written informed consent for their treatment trials.

Conditioning Regimen

The preparative regimen began with busulfan at .8 mg/kg/dose every 6 hours for 10 doses i.v. and was administered on days −9 to −7. Busulfan doses were adjusted based on the pharmacokinetics of the first dose. Melphalan 70 mg/m^2/day i.v. was given on days −7 to −6, and fludarabine 25 mg/m^2/day i.v. was administered on days −6 to −2. Busulfan and melphalan doses were adjusted if the patient was >125% of ideal body weight, as calculated on an adjusted ideal body. Rabbit antithymocyte globulin was administered at 2.5 mg/kg/day on days −3 and −2. Methylprednisolone was given at 2 mg/kg/day for 2 days with the antithymocyte globulin administration and was discontinued thereafter.

Donor Lymphocyte Infusions

Recipients of 10/10 HLA-matched allografts were treated prophylactically with 5×10^5 $CD3^+$/kg from matched donors at 4 to 6 months after transplantation. A second infusion of 5×10^5 $CD3^+$/kg was administered 3 to 4 months after the first infusion. A third dose of 1×10^6 $CD3^+$/kg was administered 2 to 4 months after the second infusion. Recipients of HLA-mismatched allografts were only treated preemptively with 1×10^5 $CD3^+$/kg at diagnosis of relapse or progression, but no sooner than 4 to 6 months after transplantation. A second infusion of 5×10^5 $CD3^+$/kg was administered 1 to 3 months after the first infusion. A third infusion of 1×10^6 $CD3^+$/kg could be administered 3 to 4 months after the second infusion. All patients were eligible for second and third doses of donor lymphocyte infusion (DLI) only in the absence of GVHD.

Response Criteria

Responses to CD34-selected HSCT and DLI were assessed 3 monthly intervals according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma [15]. Patients were deemed to have progressed if they had an increase from their lowest response value by >25% of any of the following: (1) M-spike (absolute increase must be >.5 g/dL), (2) in patients who do not produce a measurable M-spike, the difference in the involved-uninvolved free light chains (absolute increase must be >10 mg/dL), (3) bone marrow involvement by MM cells, or (4) the development of new, or increase in size of old, bone lesions or soft tissue plasmacytomas.

Cytogenetics and Fluorescein In Situ Hybridization Analyses

Bone marrow samples were collected before HSCT and at 30 days, 100 days, 6 months, 12 months, and 24 months after HSCT. Analysis by MSKCC clinical laboratories was performed for immunohistochemistry of CD138 and light chains. Cytogenetics and fluorescence in situ hybridization were performed on magnetic bead–selected CD138-positive cells isolated from bone marrow aspirates. For the purpose of this study, patients were considered to have high-risk cytogenetics if they had at least 1 of the following: gain 1q, deletion 17p, complex cytogenetics, t(4;14), or t(14;16) by fluorescence in situ hybridization analyses or deletion 13 by karyotyping.

Biostatistics

OS and progression-free survival (PFS) from the time of HSCT were evaluated using Kaplan-Meier methodology. The log-rank test and Cox proportional hazard regression were used to compare the effect of disease and transplantation characteristics on the time-to-event endpoints. Cumulative incidence functions were used to estimate the incidences of grades II to IV acute GVHD and nonrelapse mortality (NRM). Competing risks for NRM were relapse, and for acute GVHD were relapse and death in the absence of GVHD. All analyses were conducted using the R statistical package [16].

RESULTS

Patient Characteristics

The pretransplantation characteristics of these patients, cytogenetics, and lines of treatment are detailed in Table 1. Median follow-up among survivors was 24.8 months (range, 11.2 to 81.2 months). The median age at the time of the study transplantation was 55.5 years (range, 32 to 68 years). All patients had prior auto-SCT followed by a relapse within 15 months. Eighteen of the 44 patients (40%) had 2 prior auto-SCTs. Additionally, 29 of 44 patients (65%) had high-risk cytogenetics and 13 of 44 patients (29%) were diagnosed with extramedullary disease manifestations before CD34-selected HSCT. All patients had 3 to 10 prior lines of treatment; 16 patients (36%) had >6 prior lines of treatment, 16 (36%) had 5 or 6 prior lines, and 12 (27%) had 3 or 4 lines. Median time from diagnosis to CD34-selected HSCT was 41 months. For 32 patients (72%), 10 of 10 HLA-matched donors were available (14 sibling donors, 18 matched unrelated donors), whereas the remaining 12 patients (28%) had 9 of 10 HLA-mismatched unrelated donors.

Graft Composition and Engraftment

T cell depletion performed by both methods achieved a median of 2.4×10^3 $CD3^+$/kg (range, 4.72×10^2 to 1.29×10^4 $CD3^+$/kg) for all patients. See Table 2 for complete graft composition of all 44 patients. No significant differences in the graft composition were observed when T cell depletion was performed for the initial 13 patients by positive CD34 selection followed by rosetting with sheep erythrocytes compared with the subsequent $CD34^+$ enrichment in the other patients (data not shown). All patients engrafted promptly at a median of 10 days after CD34-selected HSCT (range, 9 to 12 days). None of the patients developed graft failure or graft rejection.

OS and PFS

The clinical outcomes of all 44 patients are shown in Figure 1. The median PFS of 13.5 months translates into a PFS