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Nonmyeloablative Unrelated Donor Hematopoietic Cell Transplantation to Treat Patients with Poor-Risk, Relapsed, or Refractory Multiple Myeloma

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ABSTRACT

The purpose of this study was to determine long-term outcome of unrelated donor nonmyeloablative hematopoietic cell transplantation (HCT) in patients with poor-risk multiple myeloma. A total of 24 patients were enrolled; 17 patients (71%) had chemotherapy-refractory disease, and 14 (58%) experienced disease relapse or progression after previous autologous transplantation. Thirteen patients underwent planned autologous transplantation followed 43–135 days later with unrelated transplantation, whereas 11 proceeded directly to unrelated transplantation. All 24 patients were treated with fludarabine (90 mg/m^2) and 2 Gy of total body irradiation before HLA-matched unrelated peripheral blood stem cell transplantation. Postgrafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. The median follow-up was 3 years after allografting. One patient experienced nonfatal graft rejection. The incidences of acute grades II and III and chronic graft-versus-host disease were 54%, 13%, and 75%, respectively. The 3-year nonrelapse mortality (NRM) was 21%. Complete responses were observed in 10 patients (42%); partial responses, in 4 (17%). At 3 years, overall survival (OS) and progression-free survival (PFS) rates were 61% and 33%, respectively. Patients receiving tandem autologous-unrelated transplantation had superior OS and PFS (77% and 51%) compared with patients proceeding directly to unrelated donor transplantation (44% and 11%) (PFS *P* value = .03). In summary, for patients with poor-risk, relapsed, or refractory multiple myeloma, cytoreductive autologous HCT followed by nonmyeloablative conditioning and unrelated HCT is an effective treatment approach, with low NRM, high complete remission rates, and prolonged disease-free survival.

KEY WORDS

Multiple myeloma • Nonmyeloablative conditioning • Allogeneic hematopoietic cell transplantation • Unrelated donor • Graft-versus-tumor effect • Chronic graft-versus-host disease • Peripheral blood stem cell transplantation

INTRODUCTION

High-dose conditioning and autologous hematopoietic cell transplantation (HCT) is effective in prolonging survival for patients with multiple myeloma; nonetheless, nearly all patients eventually relapse [1-6]. Long-term remissions and possibly cures have been described with allogeneic HCT after conventional high-dose conditioning regimens [7-9]. However, high-dose conditioning regimens for allogeneic HCT are associated with a 40%–50% risk of early nonrelapse mortality (NRM) [7-10]. Nonmyeloablative conditioning regimens for allogeneic HCT have dramatically reduced early transplantation-related mortality (TRM) and sparked interest in applying this treatment to multiple myeloma [11-21]. One particularly promising treatment has been to combine the cytoreductive benefit of high-dose melphalan and autologous "rescue," followed by the graft-versus-tumor (GVT) effects of nonmyeloablative allografts, initially from HLA-matched siblings [22,23]. For patients who lack HLA-matched siblings, unrelated donor HCT is an important alternative [12]. Several reports have described reduced-intensity conditioning with unrelated donor HCT; however, the number of patients with multiple myeloma studied and the duration of follow-up have been limited to date [12,20,23-31].

In an earlier study [12], we showed that a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day given on 3 consecutive days and 2 Gy of total body irradiation (TBI) combined with postgrafting immunosuppression with cyclosporine (CSP) and mycophenolate mofetil (MMF) allowed stable engraftment of unrelated hematopoietic cells in patients with various hematologic malignancies. In the present article, we describe the clinical outcomes of 24 patients with advanced multiple myeloma who received grafts from HLA-matched unrelated donors with a median follow-up of 3 years. Thirteen of the 24 patients had planned autologous HCT followed by unrelated HCT, whereas 11 proceeded directly to unrelated HCT.

PATIENTS AND METHODS

Eligibility Criteria

A total of 24 patients with multiple myeloma were enrolled in 3 sequential phase I/II multi-institutional Fred Hutchinson Cancer Research Centers for unrelated HCT protocols for hematologic malignancies between May 16, 2000, and November 23, 2004 [32]. The patients were treated at 9 centers. Each patient signed a consent form approved by the local institutional review board. Inclusion criteria were the diagnosis of multiple myeloma, high risk for NRM from failure of previous treatment with high-dose autologous HCT or preexisting comorbidities, and failure of 1 or more front-line therapies [12].

HLA Typing and Matching

A total of 23 patient–donor pairs had HLA-allele level typing performed for 10 HLA alleles (HLA-A, -B, -C, -DRB1, and -DQB1) [33]. Patient 5 did not have high-resolution typing for all 10 HLA alleles. Twenty patients were matched with their donors for 10 of 10 HLA alleles, and 3 patients (patients 4, 9, and 14) had single HLA-C allele-level mismatches.

Peripheral Blood Stem Cell Mobilization/ High-Dose Melphalan/Autologous HCT

Thirteen patients underwent planned high-dose autologous HCT before unrelated donor HCT. Unless previously cryopreserved, peripheral blood stem cells (PBSCs) were collected and cryopreserved after cyclophosphamide (4 g/m^2) and Mensa (4 gtm^2) given on day 1, etopside (200 mgtm^2/day), on days 1–3; dexamethasone 40 mg/day on days 1–4, and granulocyte colony-stimulating factor (G-CSF; 10 μg/kg/day) were given from day 4 until collection [34]. Melphalan (200 mg/m^2) was given $>$ 30 days after mobilization chemotherapy. Autologous PBSCs were infused 48 hours after melphalan [22]. The median CD34$^+$ cell number was 6.1 $\times$ 10^6/kg (range, 3.5–8.8 $\times$ 10^6/kg). Patients proceeded to allografting after recovery from autologous HCT.

Eleven patients proceeded directly to unrelated donor HCT because of lack of availability of cryopreserved PBSCs, physician preference, or inability to obtain medical insurance coverage for a planned tandem autologous unrelated HCT.

Nonmyeloablative Conditioning Regimen and Posttransplantation Immunosuppression

Conditioning included 3 doses of fludarabine 30 mg/m^2/day on days −4 to −2, followed by 2-Gy TBI at rates of 0.07–0.10 Gy/min from linear accelerators on day 0. Postgrafting immunosuppression included CSP and MMF, as described previously [12,32]. Patients 1–7 received MMF 15 mg/kg every 12 hours, and patients 8–24 received MMF 15 mg/kg every 8 hours. Grading and treatment of graft-versus-host disease (GVHD) was done as described previously [12,35].

Collection of Unrelated PBSCs and Supportive Care

All patients received fresh G-CSF–mobilized PBSCs from unrelated donors coordinated through unrelated donor registry protocols [12]. National Marrow Donor Program donors received G-CSF 10 μg/kg/day on days −5 through −1. The median number of CD34$^+$ cells infused was 8.87 $\times$ 10^6/kg (range,