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Haploidentical Allogeneic Hematopoietic Cell Transplantation for Multiple Myeloma Using Post-Transplantation Cyclophosphamide Graft-versus-Host Disease Prophylaxis

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A B S T R A C T

Allogeneic (allo) hematopoietic cell transplantation (HCT) currently represents the only potentially curative therapy for patients affected by multiple myeloma (MM). Up to 30% of patients in western countries do not have a matched donor. Haploidentical HCT (haplo-HCT) may be an option, but currently, there are little available data regarding this treatment. We analyzed survival outcomes of 30 heavily pretreated MM patients who received haplo-HCT with post-transplantation cyclophosphamide as graft-versus-host-disease (GVHD) prophylaxis. Median neutrophil and platelet engraftments at day +30 were 87% (95% confidence interval [CI], 66% to 95%) and 60% (95% CI, 40% to 75%), respectively. The cumulative incidences of relapse or progression of disease (PD) and nonrelapse mortality at 18 months were 42% (95% CI, 23% to 59%) and 10% (95% CI, 2% to 24%), respectively. The cumulative incidence of grade II to IV acute GVHD at day +100 was 29% (95% CI, 14% to 47%). The cumulative incidence of chronic GVHD at 18 months was 7% (95% CI, 1% to 21%). With a median follow-up in survivors of 25 months (range, 15 to 73 months), the 18-month progression-free survival (PFS) and overall survival (OS) were 33% (95% CI, 17% to 50%) and 63% (95% CI, 44% to 78%), respectively. No differences were observed between peripheral blood and bone marrow graft in terms of engraftment, GVHD, or PD incidence. Chemorefractory disease at transplantation was associated with a lower/reduced 18-month PFS (9% versus 47%, $P = .01$) and OS (45% versus 74%, $P = .03$). This was explained by a higher PD incidence (55% versus 33%, $P = .05$). In this multicenter study, we report encouraging results with haplo-HCT for patients with heavily pretreated MM.

INTRODUCTION

Multiple myeloma (MM) is an incurable disease for which several new treatments are now available. However, none of these therapies are able to eradicate the neoplastic clone. Therefore, it is reasonable to consider allogeneic (allo) hematopoietic cell transplantation (HCT) as the treatment strategy for younger patients with high-risk disease. Allo-HCT exerts its therapeutic efficacy mainly via the graft-versus-myeloma effect. This concept is supported by the observation that graft-versus-host disease (GVHD) is associated with enhanced disease control and that donor lymphocytes infusions are able to induce responses in a substantial proportion of patients [1]. Currently, allo-HCT studies in this setting use HLA-identical related or unrelated donors (MUD) [2].

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In recent years, allo-HCT from haploidentical donors (haplo-HCT) has been proven effective and feasible in the context of different hematological diseases [3].The major advance in this field has been the introduction by Luznik et al. of a nonmyeloablative conditioning regimen (NMAC) followed by high-dose post-transplantation cyclophosphamide (PT-Cy), with the support of T cell–replete marrow-derived stem cells [4]. Using this approach, stable engraftment was obtained in approximately 90% of patients with a low rate of acute GVHD (aGVHD) and chronic GVHD (cGVHD). Haplo-HCT allows virtually all patients to proceed to allo-HCT. Moreover, it is easy to perform, as it does not require any graft manipulation, such as $CD34^+$ cell selection or CD3/CD19 cell depletion [5].

So far, there are no data regarding the outcome of MM patients treated with haplo-HCT, in particular with PT-Cy. In our study, we report the feasibility of haplo-HCT with PT-Cy for MM and describe the related clinical outcomes.

METHODS

Patients

In this retrospective multicenter study, we analyzed data from 30 MM patients who received reduced-toxicity/myeloablative (reduced-toxicity MAC) or NMAC allo-HCT at 6 different oncological centers between February 2011 and March 2017. Written informed consent for treatment was obtained from all patients and donors. Approval for this retrospective analysis was obtained from institutional review and privacy boards of participating centers. All patients had biopsy-proven MM diagnosis, as defined by International Myeloma Working Group criteria [6].

Eligibility criteria for transplantation included availability of a HLA-mismatched donor (≤7/10 HLA compatibility). Additional criteria included absence of active infection and lack of cardiac, pulmonary, hepatic, or renal dysfunction, which would preclude administration of the cytoreductive therapy.

Conditioning and Transplantation Procedure

The reduced-toxicity MAC predominant regimen (n = 8) consisted of thiotepa 5 mg/kg on day –6 and –5, fludarabine 50 mg/m^2 from day –5 to –3, and melphalan 140 mg/m^2 on day –2. The NMAC regimen most commonly used (n = 13) consisted of fludarabine 30 mg/m^2 from day –6 to day –2 followed by cyclophosphamide 14.5 mg/kg on days –6 and –5, and total body irradiation 200 cGy at day –1 [4]. Donor stem cells were infused on day 0, after at least 24 to 48 hours after the completion of chemotherapy.

GVHD Prophylaxis and Supportive Care

For all patients, GVHD prophylaxis consisted of post-transplantation cyclophosphamide 50 mg/kg at day +3 and +4 or +5. Mycophenolate mofetil was used in all patients from days +5 to +35. Cyclosporine (n = 24), tacrolimus (n = 3), or rapamycin (n = 2) were added to PT-Cy and mycophenolate mofetil as a third anti-GVHD drug. Patients were managed clinically according to standard institutional guidelines, including antimicrobial prophylaxis.

Definitions

Durie and Salmon Staging System, International Staging System, and Hematopoietic Stem Cell Transplantation–Specific Comorbidity Index were calculated according to previously published methods [6,7]. Standard definitions were used to assess response to therapy. Acute and chronic GVHD were graded according to National Institutes of Health criteria [8].

Overall survival (OS), progression-free survival (PFS), GVHD-free/relapse-free survival (GRFS), nonrelapse mortality (NRM), relapse incidence or progression of disease (PD), and neutrophil and platelet recovery were defined as reported elsewhere [9,10].

Chemorefractory disease at transplantation was defined as the achievement of less than partial remission after the last treatment before allo-HCT.

Study Endpoints and Statistical Analysis

Analyses were performed as of March 2017. The following variables were assessed for their effects on OS, PFS, PD, and NRM: recipient gender male versus female; age at transplantation ≥ 56 versus <56 years; previous lines of therapy before transplantation ≥3 versus <3; history of plasmacytoma; comorbidity index ≥ 3 versus <3; chemorefractory disease at transplantation; sibling donor versus nonsibling; donor age ≥ 33 (median) versus <33 years; unfavorable cytomegalovirus (CMV) serostatus (recipient positive and donor negative); use of reduced-toxicity MAC versus NMAC; and use of bone marrow (BM) versus peripheral blood stem cells (PBSC) graft. International Staging System score and cytogenetics data were available in only a fraction of patients; thus, they were not considered in the analysis. OS, PFS, and GRFS were performed with Kaplan-Meier analysis. Neutrophil and platelet engraftment, aGVHD, cGVHD, NRM, and PD were obtained with competing risk analysis. Univariate analyses were performed using the log-rank test. Kaplan-Meier analysis was performed using STATA version 13 [11]. Competing risk analysis was performed with R statistical software [12].

RESULTS

Engraftment and GVHD

Graft source was PBSC for 12 patients (40%) and BM for 18 patients (60%). Complete pretransplantation characteristics of the 30 patients are described in Table 1. Neutrophil and platelet engraftment at day +30 were 87% (95% confidence interval [CI], 66% to 95%) and 60% (95% CI, 40% to 75%), respectively. At day +60, neutrophil and platelet engraftment were 90% (95% CI, 68% to 97%) and 77% (95% CI, 56% to 89%), respectively. Of the patients who survived after day +30, all but 2 had complete donor engraftment. The cumulative incidence of grades II to IV aGVHD for the entire cohort at day +100 was 29% (95% CI, 14% to 47%). Only 1 patient developed grade III aGVHD. No grade IV aGVHD was reported. Median time to aGVHD onset was 32 days (range, 11 to 147 days). Cumulative incidence of any grade cGVHD at 12 and 18 months was 20% (95% CI, 8% to 37%). The cumulative incidence of moderate or severe cGVHD at 12 months and 18 months was 7% (95% CI, 1% to 21%). Two patients experienced severe cGVHD. No differences were reported between BM and PBSC graft in terms of neutrophil and platelet engraftment or acute and chronic GVHD.

Viral Reactivations and Fungal Infections

CMV reactivation was documented in 10 patients. Three of these patients were CMV positive before allo-HCT, while their donors were negative. One patient developed gastrointestinal CMV disease. Two patients reactivated Epstein-Barr Virus (EBV). None of them had EBV disease. Three patients developed hemorrhagic cystitis after allo-HCT. In 2 cases it was related to BK virus reactivation. We observed also varicella zoster virus (2 cases) and Human herpesvirus 6 (3 cases) reactivations. Proven invasive fungal disease was diagnosed in 2 patients.

NRM

The 12-month and 18-month NRM of the entire cohort was 7% (95% CI,1% to 20%) and 10% (95% CI, 2% to 24%), respectively. The 4 deaths were attributed to acute respiratory failure, acute multiorgan failure, *Pseudomonas aeruginosa* sepsis, late respiratory failure.

PD and Survival

The cumulative incidence of PD at 12 and 18 months was 18% (95% CI, 6% to 35%) and 42% (95% CI, 23% to 59%), respectively. Of the 20 patients who progressed, 14 died of PD. The median time to PD was 6 months after allo-HCT (range, 1 to 48 months). With a median follow-up in survivors of 25 months (range, 15 to 73 months), the 12-month and 18-month PFS were 40% (95% CI, 23% to 57%) and 33% (95% CI, 17% to 50%) (Figure 1A), while 12-month and 18-month OS were 63% (95% CI, 44% to 78%) in both cases (Figure 1B). At last follow up, 13 patients were alive and 6 were in complete remission. The composite endpoint GRFS at 12-months and 18-month was 32% (95% CI, 16% to 49%) and 19% (95% CI, 7% to 36%), mostly related to PD (18 of 25 patients).

Analysis of pretransplantation factors revealed that chemorefractory disease (stable disease or PD at