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CD34+ Cell Selection versus Reduced-Intensity Conditioning and Unmodified Grafts for Allogeneic Hematopoietic Cell Transplantation in Patients Age >50 Years with Acute Myelogenous Leukemia and Myelodysplastic Syndrome

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Reduced-intensity conditioning (RIC) and T cell depletion (TCD) through CD34+ cell selection without the use of post-transplantation immunosuppression are 2 strategies used to reduce nonrelapse mortality (NRM) in older patients after allogeneic hematopoietic cell transplantation (allo-HCT). To compare the efficacy of the RIC and TCD approaches, we evaluated the outcomes of patients age >50 years with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) who underwent allo-HCT from an HLA-matched donor with one of these strategies. Baseline characteristics were comparable in the patients receiving TCD (n = 204) and those receiving RIC (n = 151), except for a higher proportion of unrelated donors (68% versus 40%; $P < .001$) and a higher comorbidity burden (Hematopoietic Cell Transplantation Comorbidity Index [HCT-CI] ≥3: 51% versus 38%; $P < .001$) in the TCD cohort. Analysis of outcomes at 3 years showed a higher chronic graft-versus-host disease (GVHD)/relapse-free survival (CRFS) (51% versus 7%; $P < .001$), lower incidences of grade II-IV acute GVHD (18% versus 46% at day +180) and chronic GVHD (6% versus 55% at 3 years; $P < .001$), and a lower incidence of relapse (19% versus 33% at 3 years; $P = .001$) in the TCD group compared with the RIC group. Relapse-free survival (RFS), overall survival (OS), and NRM were similar in the 2 groups. Combining transplantation approach (RIC versus TCD) and comorbidity burden (HCT-CI 0-2 versus ≥3), patients with an HCT-CI score of 0-2 seemed to benefit from the TCD approach. In conclusion, in this retrospective study, the use of a CD34+ cell-selected graft and a myeloablative conditioning regimen was associated with higher CRFS and similar RFS and OS compared with unmodified allo-RIC in patients age >50 years with AML and MDS.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is the sole curative treatment available for high-risk acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). Patients with standard and high-risk AML and advanced MDS are usually considered candidates for allo-HCT owing to the high risk of disease progression and relapse; however, this procedure has significant treatment-related mortality (TRM) and morbidity, especially in patients age >50 years. Several approaches have been considered to reduce TRM in older patients and patients with comorbidities. The most widely used strategy is to lower the intensity of the preparative regimen to either a reduced-intensity conditioning (RIC) or a nonmyeloablative conditioning regimen. Although this approach can significantly reduce TRM, it also increases the risk of relapse [1-4]. Another approach is ex vivo T cell depletion of the allograft through $CD34^+$ cell selection before transplantation. This strategy has been shown to significantly decrease the incidence of acute and chronic graft-versus-host disease (GVHD) with acceptable long-term relapse-free survival (RFS) and overall survival (OS) in patients with various diseases, including AML and MDS [5-12]. Moreover, the absence of a requirement for post-transplantation immunosuppressive therapy makes this approach attractive for patients with comorbidities who could avoid drug-related toxicity, especially from calcineurin inhibitors (CNIs). To compare the efficacy of the RIC and TCD approaches in the setting of a homogeneous population of patients age >50 years, we evaluated the outcomes of patients with AML and MDS who underwent allo-HCT from an 8/8 HLA-matched donor with the TCD approach at Memorial Sloan Kettering Cancer Center (MSKCC) or with the RIC approach at a consortium of 4 university hospitals in Spain.

PATIENTS AND METHODS

Patients

Patients diagnosed with AML or MDS and undergoing allo-HCT between January 2005 and September 2014 at MSKCC and in the Spanish consortium of 4 large university centers were identified through institutional HCT registries. For inclusion in the study, patients had to meet all of the following criteria: (1) age ≥50 years, (2) receipt of a first allo-HCT, (3) in complete remission (CR) or CR with incomplete hematologic recovery for AML or with <5% blasts in pretransplantation bone marrow evaluation for MDS, and (4) receipt of granulocyte colony-stimulating factor-mobilized peripheral blood progenitors from an 8/8 HLA-matched related or unrelated donor. Patients who underwent allo-HCT at MSKCC received a myeloablative conditioning (MAC) regimen followed by infusion of the graft with in vivo $CD34^+$ cell selection (TCD approach). Patients who underwent allo-HCT in the Spanish consortium received RIC followed by unmodified graft infusion and immunosuppressive therapy (RIC approach). Written informed consent for treatment was obtained from all patients and donors. Approval for this retrospective review was obtained from the Institutional Review and Privacy Board of all participating institutions.

Transplantation Procedures and Supportive Care

The TCD approach consisted of MAC in all patients with either total body irradiation (TBI) or chemotherapy-based regimens. One of 2 TBI-based regimens were used: TBI 1375 cGy given in 11 fractions followed by 2 daily doses of thiotepa (5 mg/kg/day) and either 2 daily doses of cyclophosphamide (60 mg/kg/day) starting after thiotepa or 5 daily doses of fludarabine (25 mg/m^2/day) beginning on the first day of thiotepa therapy [8,9]. The chemotherapy-based preparative regimen consisted of i.v. busulfan (.80 mg/kg/dose) every 6 hours for 10 doses, melphalan (70 mg/m^2/day) for 2 doses and fludarabine (25 mg/m^2/day) for 5 doses [10]. The TBI-based regimen was preferred in younger and fit patients, whereas the chemotherapy-based regimen was designed for older patients and patients not eligible for TBI. T cell depletion of granulocyte colony-stimulating factor-mobilized peripheral blood stem cells was performed as described previously [8,9,13]. Positive selection of $CD34^+$ cells was performed using the Isolex 300i Magnetic Cell Separator (Baxter, Deerfield, IL) and subsequent sheep RBC rosette depletion [9], or using the CliniMACS CD34 Reagent System (Miltenyi Biotec, Gladbach, Germany) [14]. Equine or rabbit antithymocyte globulin (ATG; 2.5 mg/kg/day on days -3 and -2) was used to promote engraftment in the majority of cases. No other post-transplantation immunosuppressive therapy was used for any of the patients. Preventive donor lymphocyte infusion was not planned in either transplantation protocol.

The RIC approach consisted of fludarabine-based conditioning (150 mg/m^2) in combination with busulfan (8 to 10 mg/kg) or busulfan and thiotepa (5 to 10 mg/kg). A few patients included in a specific protocol received fludarabine-melphalan (70 to 140 mg/m^2) conditioning, as reported previously [2,15]. Unmodified grafts from peripheral blood mobilized progenitors were infused on day 0. GHVD prophylaxis consisted of CNIs (tacrolimus or cyclosporine) in combination with either short-course methotrexate (15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11, followed by folinic acid rescue), mycophenolate mofetil started on day 0 (at least 10 hours after infusion of progenitors) at a dose of 15 mg/kg 3 times daily, or sirolimus started on day -6 at a dose of 2 to 4 mg/day. In this protocol, ATG was used only for patients receiving a graft from an HLA-mismatched unrelated donors; thus, no patient included in this study received ATG.

HLA matching was established by DNA sequence-specific oligonucleotide typing for HLA-A, -B, C, -DR-B1, and -DQ-B1 loci. An HLA-matched patient-donor combination was defined if both alleles were matched at the -A, -B, -C, and -DRB1 locus (8/8). Patients undergoing allo-HCT from an HLA-mismatched donor or a haploidentical donor were excluded. All patients received supportive care and prophylaxis against opportunistic infections according to standard guidelines.

Cytogenetics, Disease Risk Index, and Comorbidity Assessment and Scoring

Cytogenetics and Disease Risk Index (DRI) were calculated and classified as recently refined by Armand et al. [16]. Because all patients had to be in remission for inclusion in the study, the stage risk category was low in all patients; thus, there were no patients in the very high-risk group. The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was calculated as originally defined and following standard recommendations [17,18]. Patients were classified in the same risk groups as in the original publications of both models.

Endpoints, Definitions, and Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Comparisons of patient characteristics between the TCD and RIC groups were evaluated using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

The primary endpoint of the study was chronic GVHD-free/RFS (CRFS). Secondary endpoints included OS, RFS, NRM, and relapse. All time-to-event outcomes started from the date of transplantation (HCT date). CRFS considered moderate to severe chronic GVHD according to National Institutes of Health consensus criteria global score [19], disease relapse, or any-cause death as events; OS considered any-cause death as an event; and RFS considered both disease relapse and any-cause death as events. The probabilities of OS, RFS, and CRFS at selected time points were estimated using Kaplan-Meier methods. Univariate comparisons of OS, RFS, and CRFS across patient and transplantation characteristics were evaluated using the log-rank test.

Competing-risk analyses were used for NRM and relapse outcomes. NRM was defined as any-cause death, treating relapse as a competing risk. Relapse was defined as disease relapse, with death in the absence of relapse as a competing risk. The cumulative incidence failure rates for NRM and relapse were estimated based on the method described by Gray [20]. Univariate comparisons for NRM and relapse were evaluated using the Gray test [21] .

Multivariate models were developed using the Cox proportional hazards model for OS, RFS, and CRFS, and using the Fine and Gray model for NRM and relapse. The primary comparison was transplantation type, and all models were adjusted for age (>60 years) and donor (related versus unrelated). Additional factors were considered based on having a univariate P value <.10. Prognostic factors evaluated in the univariate analysis included sex of the patient and donor, diagnosis (AML versus MDS), DRI (low and intermediate versus high), HCT-CI (low versus intermediate versus high), and allo-HCT approach (TCD versus RIC).

We also examined the association between a combination of transplantation approach (TCD versus RIC) and comorbidity burden (HCT-CI 0 to 2 versus ≥3) with transplantation outcomes. Another set of multivariate models was built using this combination variable.

The patients were analyzed according to their status as of September 2015. All statistical analyses were performed using R 3.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC).