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Reduced-Intensity Conditioning before Allogeneic Hematopoietic Stem Cell Transplantation in Patients Over 60 Years: A Report from the SFGM-TC

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This retrospective multicenter report assessed the outcome of 600 patients with hematologic diseases older than 60 years who received reduced-intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation (allo-HSCT), with the specific aim to compare outcomes of patients between 60 and 65 years old (N = 493) with those older than 65 years (N = 107). Except for donor age, there were no significant differences between the groups regarding patients, diseases, and allo-HSCT characteristics. At time of RIC allo-HSCT, 276 patients (46%) were in complete remission. With a median follow-up of 22.8 and 23.7 months in the younger and the older groups, respectively, 2-year relapse, nonrelapse mortality, disease-free survival, and overall survival rates were similar in both groups (29.6% vs. 20.4%; 29.9% vs. 34.6%; 40.6% vs. 46.7%; 49.2% vs. 50.2%, respectively; P = NS for all comparisons). In a Cox multivariate analysis, after adjustment for disease and transplant factors, age per se was not an adverse factor for survival (relative risk = 1.08; 95% confidence interval, 0.81-1.44, P = .62). We conclude that in selected patients, RIC allo-HSCT could be offered to patients over 65 years old.

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INTRODUCTION

The use of the so-called reduced-intensity conditioning (RIC) regimens before allogeneic hematopoietic stem cell transplantation (allo-HSCT) has widely expanded over the last decade, allowing patients with hematologic diseases and comorbidities or older age to benefit from a potential immune graft-versus-tumor effect [1]. Indeed, RIC regimens represent a compromise between maximum myeloablation and immunosuppression required for successful engraftment. Initial seminal reports of RIC allo-HSCT demonstrated successful engraftment with a marked reduction in nonrelapse mortality (NRM), contributing to the continued increase in allo-HSCT activity worldwide. Despite a trend toward increased

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incidence of relapse compared with standard myeloablative conditioning regimens, RIC regimens have allowed for decreasing the incidence of overall NRM. Thus, several retrospective comparisons of outcomes between myeloablative and RIC regimens have shown similar overall survival (OS) rates of efficacy with RIC allo-HSCT [2-7].

At present, assessment of eligibility for RIC or standard myeloablative conditioning based on age and comorbidities [8,9] remains a challenging issue in many patients and different disease settings. Age above 50 years is usually considered a contraindication to the use of standard myeloablative conditioning, whereas RIC regimens are offered up to the age of 65 in many centers (especially in Europe) [3,10-21]. Of note, very few large studies have reported the outcome of patients above age 65 who received RIC allo-HSCT [19,20].

This multicenter report assessed the outcome of 600 patients with hematologic diseases older than age 60 who received RIC allo-HSCT, with the specific aim to compare outcomes of patients between 60 and 65 years old to patients older than 65.

PATIENTS AND METHODS

Study Design

This was a retrospective multicenter study assessing the results of all consecutive RIC allo-HSCTs for patients ≥60 years old with various hematologic diseases, and reported to the Société Française de Greffe de Moelle-Thérapie Cellulaire (SFGM-TC) registry between 1998 and 2008. Twenty-six transplant centers participated in the study, with a median of 13 (range: 6-64) patients per center. The study was approved by the scientific committee of the SFGM-TC and performed according to the SFGM-TC guidelines and to the declaration of Helsinki.

Patients and Characteristics

Patients' disease and transplant characteristics are summarized in Table 1. The median time between diagnosis and allo-HSCT was 17 (range: 2-485) months. The median age for the entire cohort was 62.2 (range: 60.0-70.7) years. Diagnoses were as follows: acute leukemia (n = 211; 35%), myelodysplastic/myelopoliferative syndromes (n = 151; 25%), plasma cell disorders (n = 88; 15%), lymphomas (n = 78, 13%), chronic leukemias (n = 67; 11%), and aplastic anemia (n = 5, 1%). The majority of patients were transplanted after 2005 (n = 366, 61%). Overall, 276 patients were in complete remission (CR) at time of RIC allo-HSCT, and 453 patients (75%) had high-risk (relapse/refractory or active disease or status beyond CR1 at transplantation) disease features, whereas 147 (25%) had a standard-risk disease. Regarding donor type, 368 patients (61%) received allo-HSCT from an HLA-matched related donor, whereas 191 patients (32%) received the graft from an HLA-matched unrelated donor, and 38 (7%) from a mismatched donor. HLA characteristics of the donor were missing in 3 cases. Granulocyte-colony stimulating factor–mobilized peripheral blood stem cells were used in 82% of cases (n = 492). The combination of fludarabine and busulfan was the most commonly used RIC regimen (n = 273, 46%). In the majority of cases, graft versus-host-disease (GVHD) prophylaxis consisted of cyclosporine-A alone (n = 182, 30%) or cyclosporine and mycophenolate mofetil (n = 253, 42%). Supportive care was performed according to each center's guidelines and was expected to be the same in both age groups.

Statistical Methods

The baseline characteristics of the 2 patient groups were compared using a chi-square test for categoric data and the Mann-Whitney *U* test for continuous data. Probabilities of OS and disease-free survival (DFS) were calculated using the Kaplan-Meier method. The probability of NRM and relapse incidence were calculated using the cumulative incidence procedure, in a competing risks setting, with death in remission treated as a competing event to relapse. Dates of onset of acute and chronic GVHD (aGVHD, cGVHD) were not available, and therefore proportions of GVHD were compared between the groups using the chi-square test for trend. The prognostic impact of patient, disease, and transplant variables on survival for the entire study group was examined using the log-rank test. The variables included in the univariate analysis were: disease type (lymphoid vs myeloid vs others), disease risk (standard vs high risk), patient age at transplantation, patient's sex, patient and donor cytomegalovirus (CMV) status, interval between diagnosis of disease and transplantation (<12 months, between 12 and 24 months, or 24-48 months, and beyond 48 months), year of transplantation, donor type, source of stem cells, conditioning regimen (fludarabine/busulfan vs fludarabine/melphalan vs fludarabine/total body irridation vs others, and fludarabine/total body irridiation vs others), and GVHD prophylaxis (ciclosporin alone vs ciclosporin/mycophenolate mofetyl vs ciclosporin/methotrexate vs others). Variables found to be significant at the $P < .20$ level were then entered into a multivariate proportional hazards analysis together with patient age group. Data were analyzed using the SPSS (SPSS, Inc., Chicago, IL) software package.

RESULTS

To assess the applicability of RIC allo-HSCT to the older age group, we compared the characteristics