Outcome of Second Allogeneic Hematopoietic Cell Transplantation after Relapse of Myeloid Malignancies following Allogeneic Hematopoietic Cell Transplantation: A Retrospective Cohort on Behalf of the Grupo Español de Trasplante Hematopoyetico

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A B S T R A C T

Allogeneic stem cell transplantation (allo-HCT) represents the most effective immunotherapy for acute myeloid leukemia (AML) and myeloid malignancies. However, disease relapse remains the most common cause of treatment failure. By performing a second allo-HCT, durable remission can be achieved in some patients. However, a second allo-HCT is of no benefit for the majority of patients, so this approach requires further understanding. We present a retrospective cohort of 116 patients diagnosed with AML, myelodysplastic syndromes, and myeloproliferative disorders who consecutively underwent a second allo-HCT for disease relapse. The median age was 38 years (range, 4 to 69 years). Sixty-three patients were alive at last follow-up. The median follow-up of the whole cohort was 193 days (range, 2 to 6724 days) and the median follow-up of survivors was 1628 days (range, 52 to 5518 days). Overall survival (OS) at 5 years was 32% (SE ± 4.7%). Multivariate analysis identified active disease status ($P < .001$) and second allo-HCT < 430 days (the median of the time to second transplantation) after the first transplantation ($P < .001$) as factors for poor prognosis, whereas the use of an HLA-identical sibling donor for the second allo-HCT was identified as a good prognostic factor ($P < .05$) for OS. The use of myeloablative conditioning ($P = .01$), active disease ($P = .02$), and a donor other than an HLA-identical sibling (others versus HLA-identical siblings) ($P = .009$) were factors statistically significant for nonrelapse mortality in multivariate analysis. Time to second transplantation was statistically significant ($P = .001$) in the relapse multivariate analysis, whereas multivariate analysis identified active disease status ($P < .001$) and time to second transplantation ($P < .001$) as poor prognosis factors for disease-free survival. This study confirms active disease and early relapse as dismal prognostic factors for a second allo-HCT. Using a different donor at second allo-HCT did not appear to change outcome, but using an HLA-identical sibling donor for a second transplantation appears to be associated with better survival. Further studies are warranted.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HCT) represents the most effective immunotherapy for acute myeloid leukemia (AML) and other myeloid malignancies. However, disease relapse is the most common cause of treatment failure after allo-HCT, which carries a poor prognosis [1,2]. Relapse rates in myeloid malignancies after allo-HCT have been reported up to 70% [3]. The therapeutic approach for this group of patients varies according to several factors [4,5] and the best treatment for these patients is yet to be determined.

At present, there are limited curative options for relapse of AML or myeloid malignancies occurring after an allo-HCT. Novel drugs tested in early phase clinical trials have been subsequently applied to patients relapsing after allo-HCT, and although responses have been reported [6], the majority of patients fail to achieve durable remission. On the other hand, enhancing the graft-versus-tumor (GVT) effect by means of donor lymphocyte infusions (DLI) has been accepted as a post–allo-HCT relapse approach [7-10] since its initial use [11]. However, DLI is only indicated in a limited number of patients. Its efficacy is variable and depends, among other causes, on the underlying disease or the tumor burden [12]. Thus, patients who relapse with high disease burden would not generally be considered for DLI. A second allo-HCT is an option for these patients.

A second allo-HCT allows the administration of further intensive chemotherapy and switching the donor immune system. It is assumed that by doing this, a different GVT may develop. However, despite improvements in transplantation-related mortality, performing a second allo-HCT still entails

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high rates of toxicity and relapse. Altogether, this is linked to poor outcome, with a 5-year overall survival (OS) of 25% [3,13]. Although randomized prospective trials have not been reported in this setting, retrospective data suggest that a second allo-HCT, albeit feasible, implies high nonrelapse mortality (NRM) rates. However, the donor to be chosen, the use of T cell depletion, or whether and which other prognostic factors apply remain open questions. The length of the remission after the first allo-HCT and the disease status at second allo-HCT appear to be 2 main independent prognostic factors for the outcome of a second allogeneic transplantation [13,14], as in the first allo-HCT.

To assist in the clinical decision of whether or not to perform a second allo-HCT in such high-risk patients, further understanding of the prognosis of this difficult scenario is required. We report a retrospective cohort of patients diagnosed with myeloid malignancies who relapsed after allo-HCT and underwent a second allogeneic transplantation.

PATIENTS AND METHODS

Patients who underwent a second allo-HCT for relapse of AML, high-risk myelodysplastic syndromes (MDS) and myeloproliferative disease (MPN) between 1979 and 2011 in 19 Spanish transplantation centers were included. Data were collected from center members of the Grupo Español de Trasplante Hematopoyetico that agreed to participate; this was followed by data query updates requested to the participating centers. Patients included in this study gave previous consent for their data to be used when they consented for an allo-HCT, and from 2003, for their data to be included in the European Bone Marrow Transplantation database (EBMT). The study was reviewed and approved by the Comite Etico de Investigacion Clinica of Bellvitge Hospital (Barcelona, Spain) and the Agencia Española de Medicamentos y Productos Sanitarios, Spain.

Patients who received a second allo-HCT after a relapse of AML, MDS, or MPN were included, and those who received a second allo-HCT for primary or secondary graft failure were not included. Response and relapse were assessed by morphology: molecular and cytogenetic tests were not used for response in this study. We used the World Health Organization and National Cancer Institute criteria to assess response in MDS and AML patients, respectively [15,16]. To assess the length of the remission, *time to relapse* was defined as the time from first allo-HCT to relapse. Because this variable had missing data, *time to second transplantation*, which measured the time between the first and second allo-HCT, was created to assess the outcome according to the length of remission. For statistical analysis, time to second transplantation was divided in 2 groups according to the median cut-off point. For the descriptive results analysis, acute and chronic graft-versus-host disease (GVHD) were graded according to the Keystone 1994 consensus criteria [17] and the historical criteria [18].

Endpoints

The primary endpoints were OS, NRM, and disease-free survival (DFS). The analysis included OS, DFS, relapse, and NRM. These variables were defined and codified following the Statistical Guidelines for EBMT.

Statistical Analysis

Patient and transplantation characteristics were described using frequency categorical variables and as mean (SD) or median (interquartile range) continuous variables. The estimate of NRM was calculated using cumulative incidence curves. *NRM* was defined as the date of transplantation to death from any cause other than relapse, with relapse being defined as a competitive risk in the estimate of NRM. NRM was a competitive risk in the estimation of relapse incidence and results were presented as subhazard ratios according to the model of Fine and Gray. The probabilities of OS and DFS were analyzed using Kaplan-Meier estimates. *DFS* was defined as time to relapse or death from any cause. Univariate and multivariate analysis used the Cox proportional hazards regression model. For multivariate analysis, we included all independent variables with a P value $< .10$ in the univariate analysis. The P value was set at $< .05$ for statistical significance. Statistical analyses were performed with the Statistical Package Stata ver.13 and SPSS ver.17.

RESULTS

A total of 116 consecutive patients with AML, MDS, and MPN were included. All 3 MPN patients had the second allo-HCT in active disease. The median follow-up of the whole cohort was 193 days (range, 2 to 6724 days) and the median follow-up of the surviving patients was 1628 days (range, 52 to 5518 days). Sixty-nine patients were male and 47 were female. Four patients were <14 years old. The median age at second transplantation was 38 years (range, 4 to 69 years).

Underlying diagnoses were as follows: 88 patients were diagnosed with AML (76%) and 28 (24%) patients were diagnosed with MDS/MPN, of which 3 patients were diagnosed with high-risk MPN. In terms of disease status, patients were divided in 2 main groups and distributed as follows: 80 (70%) patients had active disease and 34 (30%) were in complete remission (CR) (disease status was unknown in 2 patients). The source of cells for the second allo-HCT was peripheral blood in 99 patients, bone marrow in 11 patients, and cord blood (CB) in 5. Two patients had a previous autologous HCT before a first allo-HCT. Eighteen patients (25%) received total body irradiation–based conditioning, 42 (36%) received a myeloablative conditioning (MAC), and 67 (58%) received a nonmyeloablative allo-HCT. The donor who was used for the first transplantation was also used for the second allo-HCT in 93 patients, whereas 18 patients received their transplant from a different donor. Donor HLA matching was distributed as follows: HLA-identical siblings for 96 patients (82.7%) and other matching for 20 patients (17.3%), of which 13 (11.2%) were unrelated donor, 5 (4.3%) were a nonidentical relative, 2 (1.8%)were syngeneic. Of the patients who had a second allo-HCT from an HLA-identical sibling, 7 transplantations were done using a different donor. Further information of patient characteristics can be found in Table 1. The median interval between the first allo-HCT and the relapse (time to relapse) was 242 days (range, 37 to 3589 days) and median time to second transplantation was 430 days (range, 55 to 3791 days).

DFS

The 5-year DFS was 30% (SE ± 4.5%). Univariate analysis showed that that disease status at transplantation ($P < .001$) and length of the remission before the second allo-HCT (divided in 2 groups as time to second transplantation, setting the cut-off point in the median) ($P < .001$) were statistically significant variables. The multivariate analysis confirmed the statistically significant variables of the univariate: disease status (hazard ratio [HR], 2.83; 95% confidence interval [CI], 1.58 to 5.07; $P < .001$) and time to second transplantation (HR, 2.45; 95% CI, 1.55 to 3.86; $P < .001$).

Relapse

The 5-year cumulative incidence of relapse was 37.8% (95% CI, 28.7 to 46.7). Three variables were statistically significant in the relapse univariate analysis: CB as source of stem cells ($P < .001$), nonmyeloablative conditioning ($P = .021$), and time to second transplantation > 430 days ($P = .001$). Multivariate analysis confirmed time to second transplantation > 430 days as the only statistically significant variable (subhazard ratio [SHR], .37; 95% CI, .20 to .67; $P = .001$).

NRM

The 5-year NRM was 32% (95% CI, 23.4 to 40.9). Several factors were identified as statistically significant in univariate analysis: active disease ($P = .03$), CB ($P = .02$), conditioning regimen busulfan/cyclophosphamide ($P = .008$), MAC