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Sequential Intensified Conditioning Regimen Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Intermediate- or High-Risk Acute Myeloid Leukemia in Complete Remission: A Study from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

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A B S T R A C T

Post-transplant relapse is the leading cause of treatment failure in acute myeloid leukemia (AML) patients after reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation (allo-HSCT). To improve their outcome, we evaluated the outcome of a sequential intermediate-intensity conditioning regimen combining fludarabine, cytosine arabinoside, amsacrine, cyclophosphamide, and either total body irradiation or busulfan (FLAMSA) in patients with intermediate or high-risk AML in first or second complete remission (CR). A total of 265 patients (median age, 55 years; range, 19 to 76) with AML who underwent allo-HSCT using a FLAMSA regimen were included. At the time of transplant, 216 (81.5%) were in CR1 and 49 (18.5%) in CR2. Cytogenetic was intermediate in 114 (43%) and poor in 42 (15.8%) patients, whereas 109 patients (41.1%) had a secondary AML. With a median follow-up of 46 months (range, 1 to 145), the Kaplan-Meier estimate of overall and leukemia-free survival at 2 years were 56.1% (95% CI, 49.7% to 62.6%) and 52.8% (95% CI, 46.4% to 59.2%), respectively. At 2 years, the cumulative incidences of relapse and nonrelapse mortality were 22.8% (95% CI, 17.6% to 28.4%) and 24.0% (95% CI, 18.8% to 29.5%), respectively. In multivariate analysis, patient age and cytogenetics were the only parameters with a significant impact on overall survival. These data suggest that the FLAMSA sequential intermediate conditioning regimen provides an efficient disease control in intermediate- and high-risk AML patients, including those in CR2 and with secondary AML.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective postremission consolidation treatment, potentially curative, in acute myeloid leukemia (AML) patients [1,2]. Reduced-intensity conditioning (RIC) regimens

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have been developed to control or overcome toxicity and nonrelapse mortality (NRM) associated with allo-HSCT [2]. RIC regimens rely on the graft-versus-leukemia effect mediated by the graft's immune cells [3]. RIC allo-HSCT is now widely used for AML patients with intermediate- or high-risk cytogenetics, particularly in older or heavily pretreated patients and in those with medical comorbidities [2].

Although a significant proportion of patients are cured after RIC allo-HSCT, relapse after transplant is still the leading cause of treatment failure in the RIC setting. In patients transplanted in complete remission (CR), AML cytogenetic status and prior myelodysplastic syndrome or cytotoxic therapy are strong predictors of relapse. Therefore, the effectiveness of different intermediate-intensity conditioning regimens to enhance graft-versus-leukemia while safely minimizing NRM has been evaluated [2,4,5]. One such strategy is the so-called sequential conditioning regimen that combines a short course of intensive chemotherapy followed by a RIC allograft. Thus, the Munich group developed the FLAMSA sequential strategy combining a short course of intensive chemotherapy to improve disease control using fludarabine 30 mg/m^2/day, intermediate-dose cytosine arabinoside 2 g/m^2/day, and amsacrine 100 mg/m^2/day from day −12 to −9, followed, after a 3-day rest, by RIC using 4 Gy total body irradiation (TBI) on day −5, cyclophosphamide 40 to 60 mg/kg/day on days −4 and −3, and antithymocyte globulin (ATG) from days −4 to −2. This strategy has shown encouraging results in relapsed or refractory AML patients [6,7]. In addition, Schmid et al. [8] reported an effective disease control and a low NRM with this strategy in 23 patients with high-risk AML in CR. Thereafter, 4 Gy TBI has been replaced by i.v. busulfan (Bu) 6.4 mg/kg total dose (or equivalent oral dose) to decrease the toxicity associated with TBI in elderly patients or in patients with severe comorbidities [9,10].

Larger studies are needed to evaluate the role of TBI or Bu-based FLAMSA sequential regimen in patients with AML in CR. We report here on 265 patients with AML in first (CR1) or second CR (CR2) in which a FLAMSA sequential allo-HSCT, TBI, and Bu-based FLAMSA are compared. In addition, the contribution of prophylactic donor lymphocyte infusion (DLI) was assessed in the subgroup of patients who were alive and free of disease at 6 months.

METHODS

Study Design and Data Collection

This retrospective multicenter analysis was performed and approved by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation registry. The European Group for Blood and Marrow Transplantation is a voluntary working group of more than 500 transplant centers; all centers are required to report annually all stem cell transplantations and follow-up. Use of patients' personal information for research purposes is authorized through the signature of an informed consent by the patients. This study included all adult patients (age > 18 years) with AML in first or second morphologic CR who underwent a bone marrow or granulocyte colony-stimulating factor–mobilized peripheral blood stem cell allo-HSCT from an HLA matched related donor or unrelated donor between 2002 and 2014. In addition, to be eligible patients must have had available cytogenetics data or secondary AML and to have received a so-called sequential conditioning regimen. The latter was defined by the use of a short intensive course of chemotherapy combining fludarabine, intermediate-dose cytosine arabinoside, and amsacrine followed after a 3-day rest by a RIC regimen combining cyclophosphamide and either TBI 4 Gy or i.v. Bu 6.4 mg/kg total dose (or equivalent oral dose of Bu).

Cytogenetics was classified according to the European Leukemia Net [11]. All allogeneic grafts were obtained from HLA-A, -B, -C, -DR, and -DQ matched donors. A single HLA mismatch of 10 was allowed at the antigen or allele level. A list of the participating centers is available online (see supplementary data online).

Statistical Analysis

Endpoints included overall survival (OS), leukemia-free survival (LFS), cumulative incidence of relapse, NRM, and acute and chronic graft-versus-host disease (aGVHD and cGVHD, respectively). All outcomes were measured from the time of allo-HSCT. OS was based on death, regardless of the cause. LFS was defined as survival with no evidence of relapse. NRM was defined as death in CR. Patients alive without relapse were censored at the time of last contact.

OS and LFS rates were calculated by the Kaplan-Meier estimator. Cumulative incidence functions were used to estimate the probabilities of aGVHD and cGVHD, NRM, and relapse to accommodate competing risks. NRM and relapse were the competing risks. For aGVHD and cGVHD, the competing risk was death without the event. For all prognostic analyses, median patient age and median year of transplant were used as a cut-off point.

Univariate analyses were performed using the log-rank test for OS and LFS and Gray's test for cumulative incidences. cGVHD was analyzed as a time-dependent variable. For multivariate regression a Cox proportional hazards model was build. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). All tests were 2-sided, and the Type I error rate was fixed at .05. A landmark analysis was conducted 6 months after allo-HSCT on patients alive and free of disease to evaluate the impact of pre-emptive DLIs within the first 6 months on outcome. Patients developing grades II to IV aGVHD or cGVHD before DLI (group DLI) or within the first 6 months (group no DLI) were excluded from the landmark analysis. Statistical analyses were performed with SPSS version 19 (SPSS Inc./IBM, Armonk, NY) and R 3.0.1 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patient and Donor Characteristics

A total of 265 patients were included in this study. Patient and donor characteristics are summarized in Table 1. The median age of recipients was 55 years (range, 19 to 76). At transplantation, 216 patients (81.5%) were in CR1 and 49 (18.5%) in CR2. The median time between AML diagnosis and transplantation was 135 days (range, 43 to 225) in patients with AML in CR1 and 627 days (range, 135 to 1701) for those in CR2.

One hundred nine patients (41.1%) had a secondary AML and 156 (58.9%) had a de novo AML, including 114 (43.0%) with intermediate-risk and 42 (15.8%) with high-risk cytogenetics. Of note, no patient had low-risk cytogenetic among de novo AML. Seventy-four donors (27.9%) were matched related and 191 (72.1%) were unrelated . The stem cell source was bone marrow in 14 cases (5.3%) and granulocyte colony-stimulating factor–mobilized peripheral blood stem cells in the remaining 251 (94.7%). All patients except for 7 received in vivo T cell depletion using ATG. The ATG used was Thymoglobulin (Genzyme, Lyon, France) in 102 patients (median total dose, 6 mg/kg; interquartile range, 5 to 7) and ATG Fresenius (Fresenius Biotech GmbH, Munich, Germany) in 129 patients (median total dose, 60 mg/kg; interquartile range, 30 to 60); ATG administered was unknown in 2 patients.

One hundred fifty-nine patients (60%) were treated with a TBI-based (TBI group) and 106 (40%) with a modified Bu-based FLAMSA regimen (Bu group, 96 i.v. Bu and 10 oral Bu). The comparison between the TBI and Bu groups is shown on Table 1. Compared with the TBI group, patients in the Bu group were significantly older (61 years [range, 25 to 74] versus 52 years [range, 19 to 76]; $P < .0001$), were transplanted more recently (2011 [range, 2005 to 2014] versus 2009 [range, 2002 to 2014]; $P < .0001$), and included more secondary AML (59.4% versus 28.9%; $P < .0001$). The median follow-up among surviving patients was 46 months (range, 1 to 145) and was significantly longer in the TBI group (50 months; range, 1 to 145) compared with that in the Bu group (27 months; range, 3 to 106) ($P = .006$).

Engraftment and GVHD

Engraftment was successful in 153 patients (96.2%) in the TBI and 101 (95.3%) in the Bu group, respectively ($P = .56$).