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Potent Graft-versus-Leukemia Effect after Reduced-Intensity Allogeneic SCT for Intermediate-Risk AML with *FLT3*-ITD or Wild-Type *NPM1* and *CEBPA* without *FLT3*-ITD

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To investigate the role of reduced-intensity allogeneic (RIC-allo) stem cell transplant (SCT) as postremission therapy in adult intermediate-risk patients with acute myelogenous leukemia (AML) with *FLT3*-ITD or wild-type *NPM1* and *CEBPA* without *FLT3*-ITD, we conducted a single-center retrospective study between January 2001 and December 2010. Sixty-six patients were included: 37 treated with RIC-alloSCT and 29 with nonallogeneic SCT therapies. Both groups were comparable concerning age, WBC count at diagnosis, gender, karyotype, genotype, and number of courses of chemotherapy to reach complete remission (CR1). Median follow-up after CR1 was 37 months (range, 11-112 months) and 48 months (range, 9-83 months) in the allo and no-allo groups, respectively. In the allo versus no-allo groups, the 3-year cumulative incidence of relapse (CIR) rates were 25% ± 8% versus 61% ± 9%; $P = .005$. The 3-year nonrelapse mortality (NRM), overall survival (OS), and relapse-free survival (RFS) were 22% ± 7% versus 4% ± 4% ($P = .005$), 52% ± 9% versus 44% ± 10% ($P = .75$), and 53% ± 9% versus 35% ± 9% ($P = .28$), respectively. Multivariate analysis indicated that CIR was reduced by allo (hazard ratio [HR], 0.32; $P = .01$). A landmark analysis performed at day 185 after CR1 confirmed a lower CIR after allo. RIC-allo reduces the risk of relapse, suggesting a potent graft-versus-leukemia (GVL) effect in these patients at a high risk of relapse.

Biol Blood Marrow Transplant 18: 1845-1850 (2012) © *2012 American Society for Blood and Marrow Transplantation*

KEY WORDS: Acute myeloid leukemia, FLT3-ITD, NPM1, CEBPA, Reduced conditioning, Allogeneic stem cell transplantation

INTRODUCTION

The role of allogeneic stem cell transplant (allo-SCT) in adults with intermediate-risk acute myeloid leukemia (IR-AML) in first complete remission (CR1) is controversial and remains a domain of intense investigation [1-4]. A recent meta-analysis of prospective clinical trials has reported a significant benefit of myeloablative allo for relapse-free survival (RFS) and overall survival (OS) [5]. The median age of patients in most of these trials was in the 30s, and an equivalent benefit in older patients remains uncertain. A German-Austrian retrospective study has demonstrated that genotypes defined by the mutational status of FMS-like tyrosine kinase 3 (*FLT3*), nucleophosmin1 (*NPM1*), and CCAAT/enhancer binding protein α (*CEBPA*) genes were associated with the outcome for cytogenetically normal AML [6]. The benefit of allo was limited to the subgroup of patients with the prognostically adverse genotype *FLT3* internal tandem duplication (*FLT3*-ITD) or the genotype consisting of wild-type *NPM1* and *CEBPA* without *FLT3*-ITD (triple-negative). In these patients, allo improved RFS. It must be emphasized that patients were under

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Financial disclosure: See Acknowledgments on page 1850.

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Received March 28, 2012; accepted June 18, 2012

1083-8791/$36.00
http://dx.doi.org/10.1016/j.bbmt.2012.06.012

60 years of age, and underwent transplantation with an HLA matched-related donor (MRD) after a myeloablative conditioning regimen. As a consequence, the benefit of reduced-intensity allo (RIC-allo) as postremission therapy in older patients with IR-AML and *FLT3*-ITD or a triple-negative genotype remains uncertain. In an effort to further explore the role of allo in this setting, we performed a retrospective study of patients treated with RIC-allo or nonallogeneic SCT therapies in the absence of a suitable donor. Our aim was to compare both postremission strategies.

MATERIALS AND METHODS

Selection of Patients

The selection criteria for inclusion in this study were set to select a population of patients between 18 and 65 years of age, diagnosed with de novo AML (except acute promyelocytic leukemia) between January 2001 and December 2010 at our center. All patient records were reviewed, and some patients were excluded from the analysis as detailed in Figure 1. AML with favorable or adverse karyotypes were excluded. Patients transplanted in CR1 after a myeloablative conditioning regimen were also excluded, as were patients who never reached complete remission (CR). Genetic-risk groups were defined according to the recommendations from an international expert panel [7]. Patients diagnosed before 2007 at our center were not genotypically defined at diagnosis, and those with available frozen leukemic cells were retrospectively analyzed. Thus, patients with a normal karyotype and either *FLT3*-ITD or triple-negative genotype (intermediate-I group) were included in the present study, as were patients with cytogenetic abnormalities not classified as favorable or adverse and either *FLT3*-ITD or triple-negative genotype (intermediate-II group). We have included patients with cytogenetic abnormalities not classified as favorable or adverse when associated with an adverse genotype because there is some evidence that *FLT3*-ITD and triple-negative genotype adversely affect the outcome of these patients [7-9] as they do for patients with a normal karyotype [6]. Before 2007, our therapeutic strategy was to pursue allo in CR1 for patients with cytogenetically defined IR-AML. From 2007, the same strategy was applied for patients with IR-AML with either *FLT3*-ITD or triple-negative genotype. Patients with cytogenetic abnormalities not classified as favorable or adverse and a favorable genotype (mutated *NPM1* without *FLT3*-ITD or mutated *CEBPA*) were not included in our comparative study because we always chose to treat them with nonallogeneic SCT therapies in CR1 without looking for a donor. As a consequence, the unique reason for not performing allo in our study was the absence of a suitable donor at the time of CR1. From 2001 to 2006, patients underwent transplantation only with MRDs. From 2007, patients underwent transplantation in priority with MRD, then matched-unrelated donor, and finally mismatched-unrelated donor (C or DQB1) in the absence of MRD or matched-unrelated donor. Cord blood units were used from 2008 in the absence of any related or unrelated donor. Finally, to minimize potential biases favoring patients who underwent transplantation, patients ineligible for allo because of a poor performance status or a severe comorbidity were excluded, as were patients deceased or in relapse before the median time between CR1 and allo.

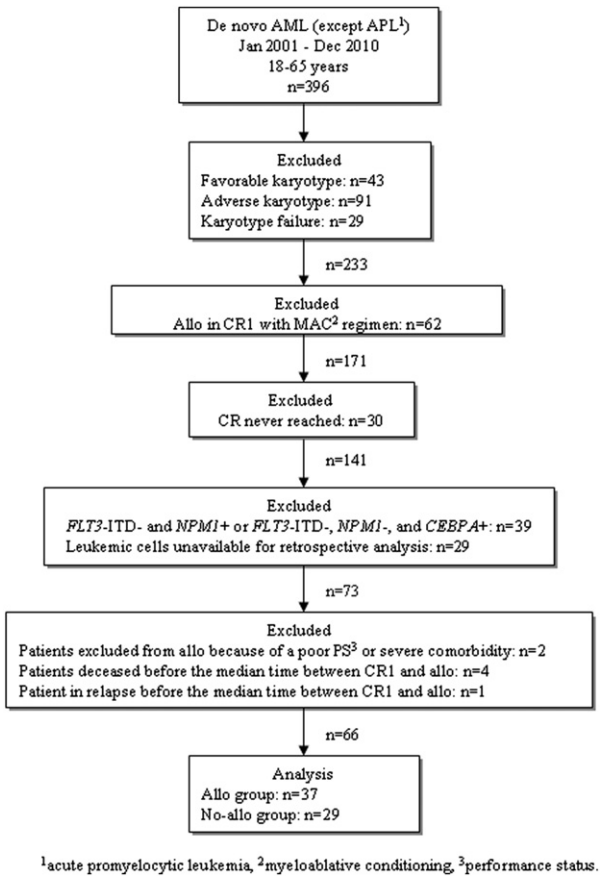

Figure 1. Selection of patients included in the study.

Materials

Bone marrow samples were used whenever available. In all other cases, peripheral blood samples were examined if the percentage of blasts in peripheral blood was >25%. Genomic DNA was extracted from mononuclear cells separated by Ficoll gradient. Genomic DNA (gDNA) was extracted using a QIAamp DNA Blood miniKit (Qiagen, Courtaboeuf, France), according to the manufacturer's protocol.