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Allogeneic: Adult

Allogeneic Stem Cell Transplantation for Patients Age ≥ 70 Years with Myelodysplastic Syndrome: A Retrospective Study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT



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A B S T R A C T

In this retrospective analysis we evaluated the outcome of 313 patients aged ≥ 70 years in the registry of the European Group for Blood and Marrow Transplantation with myelodysplastic syndrome (MDS; $n = 221$) and secondary acute myeloid leukemia ($n = 92$) who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from related ($n = 79$) or unrelated ($n = 234$) donors. Median age at HSCT was 72 years (range, 70 to 78). Conditioning regimen was nonmyeloablative ($n = 54$), reduced intensity ($n = 207$), or standard intensity ($n = 52$). Allogeneic HSCT for MDS patients ≥ 70 years was increasingly performed over time. Although during 2000 to 2004 only 16 patients received HSCT, during 2011 to 2013 the number of transplantations increased to 181. The cumulative incidence of nonrelapse mortality at 1 year and relapse at 3 years was 32% and 28%, respectively, with a 3-year overall survival rate of 34%. Good performance, determined by Karnofsky performance status, and recipients' seronegativity for cytomegalovirus was associated with 3-year estimated overall survival rates of 43% ($P = .01$) and 46% ($P = .002$), respectively. Conditioning intensity did not impact survival. After careful patient selection, allogeneic HSCT can be offered to patients older than 70 years with MDS.

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INTRODUCTION

Myelodysplastic syndrome (MDS) defines a group of clonal hematopoietic stem cell disorders that presents with cytopenias, abnormal blast counts, and the risk of progression into acute myeloid leukemia (AML). It is diagnosed at a median age of 70 [1,2] with a peak at 80 years [1,3]. Incidence is 4 to 5 per 100,000 per year [1,4], and prevalence is 11 in 100,000 with a peak at 80 years [1–3]. The choice of treatment for MDS depends on risk stratification [5–9], transfusion needs, age, and responsiveness to specific treatment modalities. Patients with low risk scores are the treated to achieve reduction of transfusion requirements and improvement of quality of life, whereas the treatment goal for intermediate- and high-risk MDS is the reduction of the risk for transformation into AML [10]. In this situation, demethylating agents as azacitidine or decitabine provide a survival benefit [11–15].

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment option, but the decision for HSCT depends on the right timing, mental and physical fitness of the patient, available donors, comorbidities, and patient preference. Treatment guidelines recommend HSCT for intermediate-II and high-risk stages up to the age of 65 years, and reduced-intensity conditioning (RIC) regimens are commonly used up to 70 years of age. However, there is a development toward a more frequent use of HSCT for elderly patients because of increasing life expectancy in general, availability of conditioning regimens with decreased toxicity, and the observation that numerous MDS patients 70 years and older have a high performance status at time of diagnosis. To investigate outcome after HSCT in MDS patients aged ≥ 70 years, we performed a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT) registry.

METHODS

Patient Population

In this analysis we included all patients in the EBMT registry ≥ 70 years with MDS and secondary AML (sAML) with a first allogeneic transplantation between 2000 and 2013. Patients were excluded if no data on outcome, patient sex, or conditioning were available; if they had received a cord blood graft; or if they had a diagnosis of MDS/myeloproliferative disorder overlap or bone marrow failure. The remaining 313 patients were further analyzed (Table 1). Cytogenetic data were available for only 68 patients and allocated to cytogenetic risk according to the revised International Prognostic Scoring System (IPSS-R) [6].

Conditioning Regimens

We reviewed the allocation of conditioning regimen to standard (myeloablative conditioning [MAC]) or RIC as reported by the transplant center

and implemented the category of nonmyeloablative (NMA) conditioning (Table 2). NMA conditioning was defined as 2 Gy total body irradiation and fludarabine [16] or 4 mg/kg busulfan alone. MAC was considered as total body irradiation > 500 cGy single dose or ≥ 800 cGy fractionated $\pm$ cyclophosphamide [16,17], busulfan > 9 mg/kg [17,18], melphalan > 150 mg/kg plus additional agents other than fludarabine [17] and conditioning regimens using treosulfan or thiotepa if no dose reduction $\geq 50\%$ from standard had been applied [19]. RIC was defined as every regimen with intensity between NMA and MAC.

Statistical Analysis

Comparisons between patient characteristics in subgroups were performed by chi-square or Fisher Exact test (categorical variables) and *t*-test (continuous variables). Complete remission before HSCT was defined by marrow blast count below 5% and a normalization of peripheral blood counts for at least 4 weeks. Primary endpoints were overall survival (OS), relapse-free survival (RFS), relapse incidence, and nonrelapse mortality (NRM). OS was defined as the probability of survival since transplantation; death from any cause was considered as an event. Patients alive at time of last follow-up were censored at this date. RFS was calculated as time from HSCT to death or relapse, whatever occurred first, with patients surviving relapse-free censored at time of last follow-up. Probabilities of OS and RFS were estimated using the Kaplan-Meier product limit method, and differences in subgroups were assessed by the log-rank test. NRM was defined as any death in the absence of relapse since HSCT. Estimates of NRM and relapse incidence were calculated using cumulative incidence curves to accommodate competing risks (relapse considered a competing risk for NRM and vice versa), and comparisons among subgroups were assessed using Gray's test. Cumulative incidences of acute graft-versus-host disease (aGVHD; grades II to IV and III to IV) and chronic GVHD (cGVHD) were also analyzed in competing risks models, considering relapse and death without occurrence of relapse and GVHD (aGVHD grades II to IV and III to IV and cGVHD, respectively) as competing events. For cGVHD all cases were included independently from time of onset according to National Institutes of Health 2006 criteria. Median follow-up was calculated by means of the reversed Kaplan-Meier method.

Cox proportional hazards regression was used to assess the impact of potential prognostic factors in multivariate analyses. The impact of these factors on OS, RFS, NRM, and relapse incidence was modeled by means of (cause-specific) hazards models. The variables included in the multivariate analyses were chosen based on clinical considerations. The missing cases for Karnofsky performance status (KPS) and disease status were kept in the analysis in separate categories. Age was not included in the multivariate analysis because of a lack of significance in the univariate analysis. The impact of GVHD on outcomes was assessed by Cox models in which aGVHD grades II to IV and III to IV and cGVHD, respectively, were included as time-dependent covariates.

All *P* values are 2-sided, and $P < .05$ is considered significant. All analyses were performed in R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) using packages “prolim” and “cmprsk.”

RESULTS

Patient Characteristics

Median age of patients at transplantation was 72 years (range, 70 to 78), and 226 patients were men. NMA, RIC, or

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