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Comparison of Intensive Chemotherapy and Hypomethylating Agents before Allogeneic Stem Cell Transplantation for Advanced Myelodysplastic Syndromes: A Study of the Myelodysplastic Syndrome Subcommittee of the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplant Research

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A B S T R A C T

The European Society for Blood and Marrow Transplant Research data set was used to retrospectively analyze the outcomes of hypomethylating therapy (HMA) compared with those of conventional chemotherapy (CC) before hematopoietic stem cell transplantation (HSCT) in 209 patients with advanced myelodysplastic syndromes. Median follow-up was 22.1 months and the median age of the group was 57.6 years with 37% of the

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population older than > 60 years. The majority of patients (59%) received reduced-intensity conditioning and 34% and 27% had intermediate-2 and high international prognostic scoring system (IPSS) scores. At time of HSCT, 32% of patients did not achieve complete remission (CR) and 13% had primary refractory disease. On univariate analysis, outcomes at 3 years were not significantly different between HMA and CC for overall survival (OS), relapse-free survival (RFS), cumulative incidence of relapse (CIR), and nonrelapse mortality (NRM): OS (42% versus 35%), RFS (29% versus 31%), CIR (45% versus 40%), and NRM (26% versus 28%). Comparing characteristics of the groups, there were more patients < 55 years old, more patients in CR (68% versus 32%), and fewer patients with primary refractory disease in the CC group than in the HMA group (10% versus 19%, $P < .001$). Patients with primary refractory disease had worse outcomes than those in CR with regard to OS (hazard ratio [HR], 2.42; 95% confidence interval [CI], 1.41 to 4.13; $P = .001$), RFS (HR, 2.27; 95% CI, 1.37 to 3.76; $P = .001$), and NRM (HR, 2.49; 95% CI, 1.18 to 5.26; $P = .016$). In addition, an adverse effect of IPSS-R cytogenetic risk group was evident for RFS. In summary, outcomes after HSCT are similar for patients receiving HMA compared with those receiving CC, despite the higher proportion of patients with primary refractory disease in the HMA group.

INTRODUCTION

Myelodysplastic syndromes (MDS) are potentially life-threatening clonal hematological disorders for which hematopoietic stem cell transplantation (HSCT) is the only curative therapy. The advent of reduced-intensity protocols has expanded the applicability of this procedure to those of advanced age and those who have comorbidities. This is particularly relevant given the older median age of the majority of the population diagnosed with MDS. Current data suggest that transplantation outcomes are influenced by a number of factors, with pretransplantation blast percentage, cytogenetic risk group, and remission status considered of particular importance. Traditional attempts to provide pretransplantation therapy for this group of patients have centered on the use of conventional induction chemotherapy, a process which may not be tolerated by those of advanced age or with significant other comorbidities. The demonstration of the utility of azacitidine (AZA) and other hypomethylating (HMA) agents for the treatment of higher risk MDS in recent years [1,2] has provided an alternative approach to pretransplantation induction therapy. Potential advantages include decreased toxicity and provision of time while an appropriate HLA-matched donor is identified. The impact of pre-HSCT AZA has been assessed in a limited number of studies [3-7], but these are retrospective and most include small numbers of patients. Overall, these appear to demonstrate similar overall survival (OS), relapse-free survival (RFS), relapse, and nonrelapse mortality (NRM) in patients receiving AZA compared with those who received traditional induction chemotherapy. To contribute to the debate in this area, we conducted a large retrospective analysis of patients with advanced MDS referred to the European Society for Blood and Marrow Transplant Research (EBMT) registry between 2004 and 2011.

METHODS

The EBMT data set was retrospectively analyzed to assess the outcomes of patients receiving HMA compared with those treated with conventional chemotherapy (CC) before HSCT. HMA was approved in early 2000; consequently, we selected MDS patients who received their first allogeneic stem cell transplantation between 2004 and 2011 reported to the EBMT. To include a homogeneous group of patients with blasts at time of diagnosis, we included only patients classified as having either refractory anemia with excess blasts or refractory anemia with excess blasts in transformation at time of diagnosis, with sufficient data on anthracycline-containing chemotherapy (n = 132) or HMA (n = 77). As the aim was to compare conventional induction chemotherapy with HMA, patients receiving only cytarabine (ara-C) were excluded from the analysis.

Variables analyzed included remission status at time of HSCT, donor type (HLA-identical sibling versus unrelated donor), conditioning type (myeloablative [MAC] versus reduced-intensity [RIC]), age, calendar period of transplantation, the presence of normal versus abnormal cytogenetics (*normal* being defined as 46 XX or XY and *abnormal* as all other karyotypic abnormalities), and international prognostic scoring system (IPSS) score [8] at diagnosis and at time of transplantation. Because of the recent introduction of the Revised International Prognostic Scoring System (IPSS-R) [9], patients were additionally classified according to this model and results analyzed according to IPSS-R category.

Statistical Methodology

OS was defined as time between transplantation and death or last follow-up for patients alive (censored). *RFS* was defined as time between transplantation and first relapse or death without relapse, or last follow-up for patients alive relapse-free (censored). OS and RFS probabilities were estimated by the Kaplan-Meier estimator and compared in univariate analysis by the log-rank test. Relapse and nonrelapse death were analyzed as competing risks, the cumulative incidence rates were estimated applying the proper nonparametric estimator, and the univariate comparisons were done using the Gray test. All variables considered in univariate analysis were candidates to enter the multivariate model as adjustment factors, together with the treatment group. The latter was retained even if not significant, and for the others, only the significant variables were included in the final model. All endpoints were analyzed in multivariable analysis applying Cox regression. The difference of characteristics between groups were assessed by the Fisher exact test or the chi-squared test (categorical variables) or by the Mann-Whitney or Kruskal-Wallis test (continuous variables).

RESULTS

Patients

Patient characteristics for the 2 groups are presented in Table 1. The median follow-up of the cohort was 22.1 months (95% confidence interval [CI], 16.8 to 31.3) and the median age of the population was 57.6 years (range, 20.0 to 69.6). The majority of patients were male (n = 120, 57.4%) and 37% of the population was older than 60 years. Seventy-seven patients (37%) received HMA and 132 (63%) received CC. Donors were HLA identical in 92 (44%) and matched unrelated in 117 (56%). One hundred twenty-four (59%) patients received a RIC HSCT. At the time of HSCT, 55% of patients were in complete remission (CR), with 32% not in morphological CR and 13% of patients with primary refractory disease. Of note, there were more patients in the CC group in CR at the time of HSCT (68% in CC group versus 32% in HMA group, $P < .001$). When comparing the median age between the 2 groups, although the difference in medians is small (56.8 versus 58.8), the CC group had significantly more younger patients ($P = .024$) than the HMA group. There were no significant differences between the 2 groups with regard to gender, type of donor (sibling versus HLA-matched unrelated donor), type of transplantation conditioning (MAC versus RIC),