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Upfront Allogeneic Stem Cell Transplantation after Reduced-Intensity/Nonmyeloablative Conditioning for Patients with Myelodysplastic Syndrome: A Study by the Société Française de Greffe de Moelle et de Thérapie Cellulaire

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A B S T R A C T

Cytoreduction before allogeneic stem cell transplantation (allo-SCT) for patients with myelodysplastic syndromes remains a debatable issue. After excluding patients who had received preconditioning induction chemotherapy, we analyzed 128 consecutive patients with myelodysplastic syndrome who received reduced-intensity or nonmyeloablative conditioning (RIC/NMA) allo-SCT. Among them, 40 received azacitidine (AZA) before transplant (AZA group) and 88 were transplanted up front (best supportive care [BSC] group). At diagnosis, 55 patients had intermediate 2 or high-risk scores per the International Prognostic Scoring System and 33 had a high cytogenetic risk score. Progression to a more advanced disease before allo-SCT was recorded in 22 patients. Source of stem cells were blood (n = 112) or marrow (n = 16) from sibling (n = 78) or HLA-matched unrelated (n = 50) donors. With a median follow-up of 60 months, 3-year overall survival, relapse-free survival, cumulative incidence of relapse, and nonrelapse mortality were, respectively, 53% versus 53% ($P = .69$), 37% versus 42% ($P = .78$), 35% versus 36% ($P = .99$), and 20% versus 23% ($P = .74$), for the AZA group and BSC group, respectively. Multivariate analysis confirmed the absence of statistical differences in outcome between the AZA and BSC groups, after adjusting for potential confounders using the propensity

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score approach. The absence of cytoreduction before RIC/NMA allo-SCT did not seem to alter the outcome. However, our results emphasize the need to perform prospective protocols to delineate the role of debulking strategy and to identify subsets of patients who may benefit from this approach.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-SCT) remains the only potentially curative therapeutic approach in patients with myelodysplastic syndrome (MDS).

Because the disease affects more often elderly than young patients, reduced-intensity or nonmyeloablative conditioning (RIC/NMA), which gives similar results to myeloablative conditioning with less toxicity, appeared to be more convenient in this category of patients. Despite the beneficial effects of allo-SCT, these patients are at substantial risk of relapse after transplant, especially in cases of RIC/NMA [1]. High disease burden at transplant has been shown to be correlated with poor outcome and may increase the post-transplant relapse risk [2-4].

Pretransplant induction-type chemotherapy has been recommended in young patients when MDS was associated with more than 5% marrow blasts [5]. The benefit of induction chemotherapy before allo-SCT is not well established, however. Although some studies suggested that upfront allo-SCT with no prior cytoreduction gave the same results as those in patients who received induction chemotherapy [6-8], other studies suggested a beneficial effect of induction chemotherapy before transplant [2,4,9]. Thus, there is no definitive evidence of a survival benefit associated with cytoreductive treatment before allo-SCT in MDS. We and others showed that demethylating agents, which have emerged as the current standard of care for most patients with intermediate 2 and high-risk MDS, were a valid “debulking” approach and showed similar outcomes when compared with induction chemotherapy [10-13].

The aim of the current study was to assess the impact of best supportive care (BSC) compared with before transplant treatment with azacitidine (AZA) on patient outcome after allo-SCT following RIC/NMA for MDS. To perform this retrospective study, we used a propensity score-based approach that can control for potentially confounding biases.

METHODS

The study was approved by the French Society of Bone Marrow Transplantation and Cell Therapy board and conducted according to the Declaration of Helsinki.

Patient Selection

Transplantation modalities were made as homogeneous as possible using the following inclusion and exclusion criteria: (1) patients older than 18 years referred for first allo-SCT after RIC or NMA according to the standard definition published by Bacigalupo et al. [14] and (2) source of stem cell was marrow or blood from either a sibling or an HLA-A, -B, -Cw, -DR, and -DQ identical unrelated donor at the allelic level (so-called 10/10). Patients who received allo-SCT from an HLA-mismatched donor, cord blood, or T cell–depleted graft and patients with chronic myelomonocytic leukemia were excluded.

Participating centers were asked to verify the data recorded for each patient in the French Bone Marrow Transplantation Registry and to provide additional information. Quality of the data was controlled using a computerized search for discrepancy errors and vigorous onsite data verification of each file. HLA matching was cross-checked with the data from the French Bone Marrow Donor Registry as previously described [15].

Consequently, 283 consecutive patients with MDS who underwent allo-SCT between January 1999 and December 2009 in 24 French and Belgian centers were identified. Twenty-seven patients were excluded because their files lacked at least 1 of the following: initial French-American-British (FAB)/World Health Organization (WHO) category or International Prognostic Scoring System (IPSS) classification, treatment before transplantation, and disease status at transplant. In addition, we excluded 128 patients who received induction-type chemotherapy or cytoreduction treatment other than AZA. Based on local physicians' decisions, the 128 remaining patients received either best supportive care (BSC group, n = 88), which included blood transfusion, hormones, growth factors (erythropoietin, granulocyte colony-stimulating factor), and immunosuppressive treatment, or AZA alone (AZA group, n = 40) (Figure 1).

Patient and Donor Characteristics and Transplantation Modalities

Morphological classification, according to FAB and WHO classifications [16,17], was documented as a separate variable at initial diagnosis and at time of transplantation. IPSS at diagnosis was calculated [18], and all progressions to more advanced disease between diagnosis and transplantation were recorded. Responses to treatment and disease status at transplant were reevaluated according to International Working Group 2006 criteria [19].

At diagnosis (Table 1), 42 of 128 patients (33%) had refractory anemia, refractory anemia with ringed sideroblasts, or refractory cytopenia with multilineage dysplasia, 46 (36%) patients had refractory anemia with excess of blasts (RAEB-1), 34 patients (26%) had RAEB-2, and 6 patients (5%) had RAEB in transformation/acute myeloid leukemia (with marrow blasts between 20% and 30%). Cytogenetic analysis was, according to IPSS classification [18], favorable, intermediate, and poor risk in 65 (51%), 30 (23%), and 33 patients (26%), respectively. IPSS was low or intermediate 1 in 73 patients (lower risk category, 57%) or intermediate 2 and high in 55 patients (higher risk category, 43%). Patients in the AZA group had significantly higher IPSS at diagnosis compared with the BSC group ($P = .003$).

In the AZA group, the drug was started after a median time from diagnosis of 192 days (range, 38 to 941) and discontinued at a median time of 54 days before transplant (range, 6 to 438 days). The median number of AZA cycles was 4.5 (range, 2 to 26). The median time from diagnosis to transplant was 22.8 months. Thirty-three patients (26%) were transplanted before 7.3 months, 63 (49%) received allo-SCT between 7.3 and 22.8 months after diagnosis, and 32 (25%) were transplanted after 26.7 months.

Table 2 depicts patients' characteristics at transplant and transplantation modalities according to treatment group before allo-SCT. Thus, median age at transplant was higher in the AZA group compared with the BSC group (60 versus 56 years; $P = .0001$). Overall, 22 of 128 patients (17%) had progressed to a more aggressive disease before transplantation: 7 patients (17.5%) in the AZA group and 15 (17%) in the BSC group. According to International Working Group 2006 criteria [19], 29 patients (23%) were responders (including complete remission, partial remission, or marrow complete remission): 26 patients (65%) in the AZA group and 3 (3%) in the BSC group ($P = .0001$).

Patients of the AZA group received more allo-SCT from an HLA-matched unrelated donor than those of the BSC group ($P = .0001$). There was no

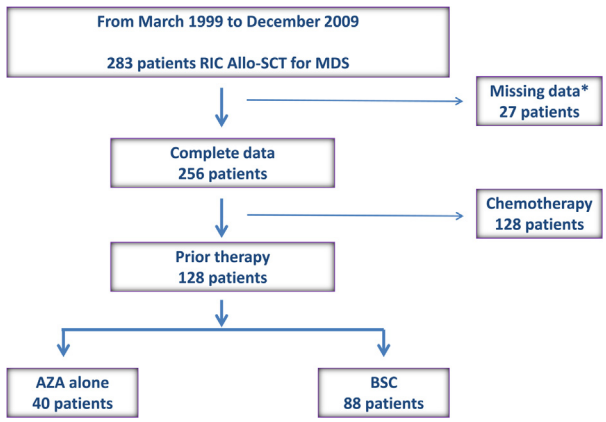

Figure 1. Flow chart for patient selection strategy. Patients whose files were missing at least 1 of the following data were excluded: initial FAB/WHO diagnosis, IPSS at diagnosis, before-transplantation treatment, WHO criteria, and disease status at transplant.