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Pretransplantation Therapy with Azacitidine vs Induction Chemotherapy and Posttransplantation Outcome in Patients with MDS

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Although allogeneic hematopoietic cell transplantation (HCT) has proven curative potential for myelodysplastic syndrome, relapse after HCT remains a problem. Pretransplantation cytoreduction with induction chemotherapy (IC) has been used to reduce relapse rates but is associated with significant toxicity and mortality. Hypomethylating agents may achieve cytoreduction with limited toxicity; however, data on the effect of pre-HCT hypomethylation on post-HCT outcomes are limited. We retrospectively reviewed results in 68 patients who underwent allogeneic HCT for myelodysplastic syndrome or acute myeloid leukemia transformed from MDS. Thirty-five patients had received cytoreduction with azacitidine before HCT with either a high-dose (40%) or a reduced-intensity (60%) conditioning regimen, and 33 had undergone IC before HCT with high-dose conditioning. The estimated 1-year overall survival (OS) was 57% in the azacitidine group and 36% in the IC group. The risk of post-HCT mortality (hazard ratio, 0.68; 95% confidence interval, 0.35-1.30), nonrelapse mortality (hazard ratio, 0.99; 95% confidence interval, 0.41-2.34), and relapse (hazard ratio, 0.34; 95% confidence interval, 0.41-2.34) were lower in the azacitidine group compared to the IC group, but only the hazard for relapse was significantly lower. After adjustment for cytogenetic risk, International Prognostic Scoring System, and donor, the rates of post-HCT relapse for the 2 cohorts were similar. Although the current study was retrospective and nonrandomized and needs to be interpreted in this context, the results add to the growing evidence that pre-HCT therapy with azacitidine is associated with less toxicity than IC and may allow for similar post-HCT outcomes.

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INTRODUCTION

Myelodysplastic syndrome (MDS) represents a group of clonal myeloid stem cell disorders with a heterogeneous spectrum of presentation ranging from an indolent course over several years to rapid progression to acute myeloid leukemia (AML). The natural history of patients with MDS is varied with a median survival ranging from 5.7 years for patients with low-risk International Prognostic Scoring System (IPSS), to 0.4 years for those with high-risk scores at the time of diagnosis. The only known curative treatment modality for MDS is allogeneic hematopoietic cell transplantation (HCT). Yet, despite the demonstrated benefit of HCT, patients with advanced MDS are at a substantial risk of relapse after HCT [1-3]. A central question, therefore, is whether patients should receive pre-HCT "debulking" therapy to reduce the risk of post-HCT relapse, and if so, what is the optimum modality to achieve that objective? As MDS is primarily a disease of older age, often complicated by medical comorbidities, a major concern is toxicity and mortality related to intensive treatment. Several retrospective studies have explored the efficacy of induction chemotherapy (IC) before HCT aimed at decreasing the rate of relapse and improving post-transplantation outcomes [4-6]. Pretransplantation IC may reduce the incidence of post-HCT relapse but is associated with considerable morbidity and mortality, and patients may not come to HCT. In fact,

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a prospective study of 259 patients with high-risk MDS or AML over the age of 50 years found that of the 99 patients who achieved complete remissions after IC, only 53 had a consultation considering HCT, and just 14 patients ultimately received an HCT [7]. The remaining patients were not considered well enough for HCT for various reasons, including their clinical status before IC.

Administration of the azanucleosides, azacitidine and decitabine, is associated with only mild toxicity and has been shown to delay progression to AML and, in the case of azacitidine, to extend survival by 9.5 months as compared to conventional care [8-10]. Given their activity against MDS and the low toxicity profile, azanucleosides represent an attractive alternative to traditional IC as a pre-HCT cytoreductive modality.

The ideal strategy to discern the post-HCT benefit of pre-HCT cytoreductive therapy, and to identify the optimal agent, would be in the form of a randomized prospective study. Patients enrolled would be randomized to 1 of 3 arms; either proceed to immediate HCT, or receive pre-HCT cytoreduction with IC, or with azacitidine. Such a study has not been conducted and may not be feasible or practical. In fact, several studies designed and launched to answer similar questions have been closed due to poor accrual. With the lack of randomized prospective data, and despite the inherent limitations, retrospective analyses provide the only means to generate evidence on which to base clinical practice. Thus, to compare the usefulness of pre-HCT azacitidine and IC for post-HCT outcome, we conducted a retrospective analysis of post-HCT results in patients with advanced MDS who underwent pre-HCT cytoreduction at our institution.

PATIENTS AND METHODS

Patients

Consecutive patients with advanced MDS or AML developing from antecedent MDS (transformed acute myelogenous leukemia [tAML]) who received an allogeneic HCT between August 2004 and May 2010 were screened for treatment with azacitidine before HCT. Included were patients who received other chemotherapeutic interventions before azacitidine. However, patients who received other chemotherapy after azacitidine and before HCT were excluded. A historical cohort comprising patients with advanced MDS or tAML, who received IC before HCT at our center from December 1992 to October 2002, was included in the analysis as a comparator group [5].

Patients who received azacitidine were older than IC-treated patients (median, 60 vs 47 years). The majority of patients in both groups had de novo disease. The median time from diagnosis to HCT was similar for the 2 groups. Patients for whom bone marrow biopsies were available to evaluate cellularity before cytoreductive therapy, all showed hypercellular marrows with a cellularity >60%. There were more patients with advanced MDS/tAML in the IC-treated group. However, there were no significant differences between the groups regarding marrow myeloblast count at the time of HCT (Table 1).

Pretransplantation Therapy

The initiation and duration of treatment with azacitidine or IC was at the discretion of the treating physician. Azacitidine was administered at doses of 75 mg/m^2/day on days 1 through 7 of a 28-day cycle [8]. A minimum of 1 cycle of azacitidine was administered before proceeding to HCT. The median cycles of azacitidine administered was 3 (range, 1-11). Among the patients who received IC, most (61%) were given cytarabine for 7 days and an anthracycline for 3 days (7+3). Other patients received topotecan and cytarabine (21%), dexamethasone, cytarabine, thioguanine, etoposide, daunorubicin (12%), fludarabine, cytarabine, filgrastim (3%), and high-dose cytarabine (3%). Patients received IC 1 to 6 months (median, 2 months) before HCT.

Transplantation Conditioning Regimens

All patients in the IC group were conditioned with high-dose regimens, whereas in the azacitidine group, 14 patients (40%) underwent conditioning with high-dose regimens, and 21 (60%) received reduced-intensity conditioning (RIC), as previously defined ($P < .001$) [11]. Overall, 33 patients were conditioned with a previously described regimen comprising targeted busulfan (tBu) and cyclophosphamide (Cy; tBuCy) [12].

Twelve patients, all in the IC group, were conditioned with Bu and total body irradiation (TBI; BuTBI) [13]. TBI and Cy were used for 1 patient in the azacitidine group [14]. Fludarabine (Flu) and targeted Bu (FluBu) was used to condition 1 patient in the azacitidine group [15]. Eleven patients in the azacitidine group were conditioned with Flu and low-dose TBI (FluTBI) [16], while 6 received treosulfan (Treo), Flu, and low-dose TBI (TreoFluTBI; 3 × 14 g/m^2 of Treo, 5 × 30 mg/m^2 of intravenous [IV] Flu, and 200 cGy TBI).

Two patients were conditioned with radiolabeled anti-CD45 antibody plus Flu and low-dose TBI (FluTBI + I-131) [17]. One patient in the azacitidine group received radiolabeled anti-CD45 antibody with Flu, low-dose TBI, and cyclophosphamide before and after stem cell infusion (FluCyTBI + I-131; 0.5 mg/kg of ^{131}I-anti-CD45 antibody, 2 × 14.5 mg/kg of Cy, 5 × 30 mg/m^2 of IV Flu, 200 cGy TBI, and 50 mg/kg Cy post-HCT), and 1 patient was