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Hematopoietic Cell Transplantation in Myelodysplastic Syndromes after Treatment with Hypomethylating Agents

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The prognosis of patients with myelodysplastic syndromes (MDS) after failure of hypomethylating agent (HMA) therapy is poor. Allogeneic hematopoietic cell transplantation (HCT) can be effective in curing patients who have failed therapy with HMA. However, published results have not addressed the outcomes with HCT in this setting. We identified 125 MDS patients who had been treated with HMA and underwent subsequent HCT. Among these, 68 were considered HMA failures and 57 responders. Failure was defined as progression to higher grade MDS or acute myeloid leukemia, lack of hematologic improvement after at least 4 HMA cycles, or loss of response after initial improvement. Response was defined as showing at least hematologic improvement. Outcomes were compared using Cox regression. Overall, 73 of 125 HMA-treated patients (58%) had died by the time of last contact. Median follow-up of survivors, measured from HCT, was 41.9 months (range, 2.7 to 98.5). The estimated probability of relapse at 3 years was 56.6% and 34.2% among failing and responding patients, respectively (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.2 to 3.66; $P < .01$). The estimated probability of relapse-free survival at 3 years was 23.8% and 42% in failing and responding patients, respectively (HR for relapse/death, 1.88; 95% CI, 1.19 to 2.95; $P < .01$). The risk of nonrelapse mortality was similar for both groups (HR, 1.12; 95% CI, .52 to 2.39; $P = .77$). Failure of treatment with HMA was associated with higher risk of post-HCT relapse than observed in patients responding to HMA. Prospective trials are needed to evaluate the efficacy of novel conditioning regimens and post-HCT maintenance strategies in patients who have failed HMA pre-HCT.

INTRODUCTION

The hypomethylating agents (HMAs) azacitidine (AZA) and 2-deoxy-azacytidine (decitabine) have shown clinical activity in myelodysplastic syndromes (MDS) [1,2]. They are nucleoside analogues with direct cytotoxicity and the ability to interfere within epigenetic regulation processes. Although AZA treatment was associated with overall survival (OS) benefit when compared with conventional care in MDS patients, the median prolongation of survival was on the order of only 9 months [3], and in most patients the life expectancy is reduced by more than 90% compared with control subjects. Hematopoietic cell transplantation (HCT) remains the only therapeutic approach with curative potential in this setting [4].

Retrospective analyses have confirmed a very poor prognosis for patients who failed to respond or whose disease progressed on HMAs [5,6]. Salvage options are limited but include low or higher dose chemotherapy, investigational agents, HCT, or supportive care. Although HCT may be the treatment associated with the best outcome based on retrospective analyses, only a third of patients with HMA failure experienced prolonged relapse-free survival [5]. Although prior studies have evaluated the use of hypomethylating therapy before HCT [7,8], no studies to date have focused on the population of patients who have failed HMA. The aim of the current study was to compare post-HCT outcomes among patients who failed HMA therapy to outcomes of patients who responded to HMAs before HCT, with a focus on the risk of relapse.

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METHODS

Patients

Between June 2004 (US Food and Drug Administration approval of AZA) and December 2013, 125 patients with MDS or chronic myelomonocytic leukemia who had been treated with HMAs underwent HCT at the Fred

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Hutchinson Cancer Research Center. The diagnosis was confirmed according to World Health Organization 2008 criteria [9]. The disease risk was assessed using the International Prognostic Scoring System (IPSS) [10] and the revised IPSS (IPSS-R) [11]. All patients or their legal guardians had given informed consent to use medical information for research purposes as approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center in accordance with the Declaration of Helsinki.

In addition to the 5-group cytogenetic classification by Schanz et al. [12] that has been incorporated into the IPSS-R, we also identified patients with monosomal karyotype as defined elsewhere [13]. MDS was considered "secondary" if preceded by cytotoxic therapy for hematologic or nonhematologic disorders.

Definition of HMA Failures and Responders

Response to HMA was determined using the International Working Group 2006 criteria [14]. Treatment failure was defined as loss of response after initial improvement, progression to higher risk MDS or acute myeloid leukemia (AML), or no hematologic improvement after at least 4 HMA cycles.

Assessment of Transplant Outcomes

The day of engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $\geq .5 \times 10^9$/L. Primary graft failure was defined as not reaching an absolute neutrophil count of $.5 \times 10^9$/L by day 28 (day 55 in case of cord blood HCT). Secondary graft failure was defined as a progressive decline in peripheral neutrophil counts after initial recovery. In addition, donor $CD3^+$ T cells < 5% on day 28 or donor T cell decline to <5% after previous evidence of engraftment were considered evidence of primary or secondary graft failure, respectively [15]. The analyses were performed on days 28, 56, 84, 180, and 365 and then as clinically indicated.

Survival time was the time from HCT until death or date of last contact. Relapse-free survival was the time from HCT until death, relapse, or date of last contact. All patients were scheduled for marrow aspiration and biopsy on day 28, day 84, and 1 year post-HCT with morphology, flow cytometric, and cytogenetic analyses. Relapse was defined as the recurrence of any cytogenetic abnormality or immunophenotypic markers that were present pre-HCT or by a recurrence of dysplasia or increased bone marrow myeloblast count detected by morphology. Acute and chronic graft-versus-host disease (GVHD) were diagnosed, graded, and treated as previously described [16,17]. In patients who died after relapse, relapse was considered the cause of death, regardless of the proximal cause of death. Causes of death were attributed using previously described criteria [18].

Statistical Analysis

Estimates of OS and progression-free survival probabilities were obtained using the method of Kaplan and Meier [19]. Probabilities of relapse, nonrelapse mortality, and GVHD were summarized using cumulative incidence estimates [20], where death without relapse was considered a competing risk for relapse and relapse a competing risk for nonrelapse mortality. Death and relapse without GVHD were considered competing risks for GVHD.

Cox regression models were fit to compare the cause-specific hazards of failure between treatment failures and responders for each of the above endpoints. Variables considered for inclusion into each regression model included gender, age at HCT, secondary nature of MDS, IPSS-R, AML evolution, minimal identifiable disease by cytogenetics at HCT [21], conditioning regimen intensity, and presence of monosomal karyotype [22] at diagnosis. No adjustments were made for multiple comparisons.

RESULTS

Patient and Transplant Characteristics

Patient characteristics are summarized in Table 1. Patients who failed HMA treatment were more likely to have a higher stage World Health Organization classification, evidence of disease at the time of HCT, and evolved to AML than the patients who did not fail HMA treatment. The median age at HCT was 61 years (range, 30 to 76) among HMA failures and 61 years (range, 34 to 77) in HMA responders. Patients who failed to respond received a median of 5 HMA cycles (range, 1 to 20) compared with 4 HMA cycles (range, 1 to 40) in responders. The cytogenetic risk profiles at diagnosis were similar for failures and responders, as were the proportions of patients with secondary MDS, at 24% and 23%, respectively. A monosomal karyotype [13] was detected in 14 patients who failed to respond (21%) and 17 patients (30%) who responded.

Patients were prepared for HCT with various conditioning regimens, categorized on the basis of treatment components and dose intensities (Table 2). The 2 cohorts were balanced in regards to regimen intensity, donor, and stem cell source. GVHD prophylaxis consisted of mycophenolate mofetil and cyclosporine or tacrolimus in 68 patients (54%), plus sirolimus in 7 patients (6%); methotrexate and cyclosporine or tacrolimus in 40 patients (32%), plus sirolimus in 2 patients (2%); and post-transplant cyclophosphamide with or without cyclosporine or tacrolimus in 8 patients (6%).

HMA Failures and Responders

Among the 125 patients who had received at least 1 cycle of HMAs before HCT, 68 (54%) were classified as HMA failures and 57 (46%) as responders. AZA was given at 75 mg/m^2/day for 7 days every 28 days. Decitabine was administrated at 20 mg/m^2/day for 5 days every 28 days. Ninety-nine patients (79%) were treated with AZA, 19 patients (15%) with decitabine, and 7 patients (6%) received both.

Among the 68 patients who experienced treatment failure, HMA therapy was given as a first-line approach in 64 (94%). Four patients (6%) received HMAs as salvage therapy after induction-type chemotherapy. Thirty-one patients who failed first-line HMA therapy were subsequently treated with induction-type chemotherapy before HCT. The decision to initiate induction-type chemotherapy was primarily driven by an increase in bone marrow myeloblast percentage. Among these 31 patients, 26 achieved complete remission or marrow complete remission and directly underwent HCT and 5 patients showed no response or disease progression. The other 33 patients who failed first-line HMA therapy went directly to HCT (Figure 1).

Among the 68 patients who experienced treatment failure, 7 (10%) lost the response after initial improvement, 53 (78%) progressed to higher risk MDS or AML, and 8 (12%) had no hematologic improvement after at least 4 HMA cycles. Twenty-six of 68 patients (38%) received less than 4 HMA cycles, all of them because of progression to higher risk MDS or AML.

Among 57 responding patients, 4 (7%) had failed to respond to induction-type chemotherapy before HMA therapy. The remaining 53 patients (93%) received HMAs as first-line treatment. The best responses to HMAs included complete remission or marrow complete remission in 44 patients (77%) and partial remission in 1 patient (2%). Responders included 3 patients (5%) who had progressed to AML before being treated with HMAs.

Overall Outcome

Overall, 73 patients (58.4%) had died by the time of last contact, including 46 patients who had relapsed post-HCT. The median time between HCT and relapse was 2.8 months (range, .2 to 27.6). Twenty-seven patients died from nonrelapse causes. Median follow-up from HCT among the 52 survivors was 41.9 months (range, 2.7 to 98.5). OS and relapse-free survival at 3 years were 40.8% and 32.1%, respectively, and relapse and nonrelapse mortality 46.4% and 21.5%, respectively (Figure 2). Eight patients received a second HCT, 2 for graft failure and 6 as salvage after relapse.

The estimated probability of grades II to IV and III to IV acute GVHD was 59.8% and 13%, respectively. The 3-year estimate of chronic GVHD was 43.1%.