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Factors Determining Responses to Azacitidine in Patients with Myelodysplastic Syndromes and Acute Myeloid Leukemia with Early Post-Transplantation Relapse: A Prospective Trial

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Retrospective analyses suggest a benefit of therapy with hypomethylating agents in patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) who relapse after allogeneic hematopoietic cell transplantation (HCT). We conducted a prospective trial in 39 patients with MDS or AML who relapsed within 100 days of HCT. Relapse was documented by morphology, flow cytometry, or cytogenetics. Treatment consisted of 5-azacitidine, 75 mg/m^2/day for 7 days, administered every 28 days. Patients were followed by sequential marrow examinations, and responses were assessed at 6 months. There were 3 complete remissions and 9 partial remissions (30%); an additional 3 patients had stable disease by International Working Group criteria. In multivariate analysis, only the type of induction chemotherapy given before HCT was significantly associated with post-HCT response to 5-azacitidine and overall survival ($P = .004$). These data support the use of hypomethylating therapy for post-HCT relapse in patients with MDS and AML and suggest that pre-HCT therapy may affect the likelihood of response to this salvage approach.

INTRODUCTION

Although improved antimicrobial and graft-versus-host-disease (GVHD) prophylaxis have reduced nonrelapse mortality, relapse-related mortality has not significantly declined over the past decade [1] and is a major cause of failure in patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML), particularly but not only after reduced-intensity conditioning [2]. Current therapeutic interventions for post-transplantation relapse include withdrawal of immunosuppression, administration of chemotherapy, donor lymphocyte infusion (DLI), and second stem cell transplantation. Regardless of the type of intervention, outcomes after post-transplantation relapse have remained dismal, particularly among adult patients [3]. An analysis of results at our center showed 2-year overall survival (OS) rates of 3%, 9%, and 19% for patients who relapsed <100 days, 100 to 200 days, or >200 days, respectively, after hematopoietic cell transplantation (HCT) [3]. A recent Center for International Blood and Marrow Transplant Research study reported comparable outcomes: survival probability at 3 years of 4%, 12%, and 26% for patients who relapsed <6 months, 6 months to 2 years, and 2 to 3 years after HCT, respectively [4]. Novel strategies for the treatment of post-transplantation relapse are needed. The first dose-finding study on the use of hypomethylating agents (HMA) after HCT was conducted by de Lima and colleagues [5] to prevent relapse in high-risk patients in a maintenance setting. Subsequent retrospective studies [6-9] have shown the safety and potential efficacy of HMAs in patients with post-HCT relapse. Here we report the results of a larger prospective trial of azacitidine in patients with MDS or AML with recurrent or persistent disease early after HCT.

METHODS

Study Design

"Treatment of Post-Transplant Relapse and Persistent Disease in Patients with MDS and AML with Azacitidine" was a prospective, open-label, single-center phase II study performed at Fred Hutchinson Cancer Research Center (FHCRC) and the University of Washington, Seattle. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the FHCRC (National Cancer Institute number NCI01083706). Written informed consent was given by all

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patients. The primary endpoint was 6-month OS. Secondary endpoints included the rate of response by International Working Group (IWG) criteria.

Patients

Patient and disease characteristics are summarized in Table 1. Patients with MDS or AML had undergone HCT from related or unrelated donors after various conditioning regimens. Major exclusions were refractory disease at the time of HCT (patients who received chemotherapy before transplantation with no evidence of response by IWG criteria); the presence of ≥10% bone marrow myeloblasts by morphology; serum creatinine >2× the upper limit of normal; aspartate aminotransferase/alanine aminotransaminase >2× upper limit of normal; Eastern Cooperative Oncology Group performance status >2; patients with severe comorbidities other than MDS or AML, which would be expected to prevent compliance with treatment; and patients with active severe infections within 2 weeks before the start of protocol treatment. Also excluded were patients with evidence of central nervous system disease at time of relapse by cerebrospinal fluid morphology or flow cytometry. Patients with acute GVHD or prior history of acute GVHD were not excluded from the study.

Diagnosis of Relapse or Persistent Disease

Bone marrow aspirates were obtained between days 28 and 100 after HCT. The diagnosis of disease recurrence or persistence was based on the presence of significant morphologic dysplasia (>10% in myeloid lineage, >10% in erythroid lineage, >40% in megakaryocyte lineage) or abnormal myeloblasts or aberrant maturation patterns in the myeloid lineages by flow cytometry in marrow or the appearance of blasts in peripheral blood, or reappearance of cytogenetic abnormalities (identified before HCT) as determined by standard cytogenetics and fluorescein in situ hybridization (FISH), or extramedullary relapse (local radiotherapy was allowed). Patients were enrolled between July 2010 and December 2013. During this period, 76 patients were diagnosed with early post-HCT relapse or persistent disease, and 39 of these (51%) were enrolled in the present trial.

Table 1
Patient and Disease Characteristics

Characteristic	Value
No. of patients	39
Age, median (range), yr	52 (23-76)
Gender: male/female	21/18
Diagnosis /disease stage at transplantation	
AML	26 (67)
CR	11
MRD	11
RD	4
MDS (IPSS)	13 (33)
Low	1
Int-1	6
Int-2	2
High	1
Missing	3
Cytogenetic risk group*	
Favorable	0
Intermediate	16 (41)
Unfavorable	23 (59)
Donor	
HLA-matched relative	11 (28)
Unrelated	28 (72)
Source of stem cells	
Peripheral blood	30 (77)
Marrow	3 (8)
Cord blood	6 (15)
Conditioning regimen	
tBu4 Flu/CY	10 (26)
Treo Flu (TBI)	3 (8)
CY/TBI (13.2 Gy)	2 (4.5)
Clo/TBI	3 (8)
BC8 RIT	2 (4.5)
Flu/TBI (2-4 Gy)	19 (49)
Indication for post-HCT treatment	
Persistent disease	11 (28)
Relapse	28 (72)

Data presented are n (%) unless otherwise indicated.
MRD indicates minimal residual disease (<1% by flow cytometry); RD, residual disease (≥1% by morphology or flow cytometry); IPSS, International Prognostic Staging System; int, intermediate; tBU4 Flu/CY, busulfan, 16 mg.kg over 4 days with targeting of trough levels, combined with fludarabine or cyclophosphamide; Treo Flu (TBI), treosulfan + fludarabine, with or without 2 Gy total body irradiation; CY, cyclophosphamide; TBI, total body irradiation; clo/TBI, clofarabine + low dose TBI (3 Gy); BC8RIT, radioimmunotherapy with 131I conjugated anti-CD45 antibody BC8; Flu/TBI, fludarabine + low dose TBI (2-3 Gy).
* By International Prognostic Staging System criteria for MDS.

Treatment

Azacitidine was started within 2 weeks of the diagnosis of disease progression/relapse and was given at a dose of 75 mg/m^2/day s.c. or i.v., ×7 every 28 (±3) days for at least 6 cycles unless there was no evidence of response, the disease progressed, or toxicity occurred. Patients who relapsed again while on therapy could be offered alternative treatment. The abrupt withdrawal of immunosuppressive medications was not encouraged. At the discretion of the attending physician, a slow taper could be instituted. DLI was allowed at any time during treatment at the attending physician's discretion. However, if DLI were to be given, it was to be administered in the week after administration of azacitidine.

Evaluation

Patients were followed on a monthly basis. Complete blood cell counts with differential were obtained at least weekly for the first 2 months and thereafter at least monthly while treatment was ongoing. Bone marrow examination was performed at 3, 6, 9, and 12 months (±14 days) after initiating treatment with azacitidine. The clinical testing performed on these marrows included morphologic analysis, flow cytometry, and cytogenetics, including FISH, and molecular studies, as indicated.

Statistical Analysis

The design parameters for this study are based on historical data from the FHCRC regarding outcomes after post-transplantation relapse/progression. The 6-month OS in patients who relapsed less than 100 days after transplantation was 15% [3]. For patients who received chemotherapy and relapsed before 100 days the 6-month OS was 20% and for patients treated with withdrawal of immunosuppression alone, the 6-month OS was 10%. Therefore, the trial was considered a success if we were to demonstrate with reasonable confidence that the 6-month OS rate with the present regimen exceeded 10%.

Survival was measured from the time of the bone marrow evaluation determining relapse; patients started azacitidine within less than 14 days of this date. OS was estimated by the Kaplan-Meier method. Association of covariates with survival was analyzed using Cox regression. Association of covariates with response at 6 months was analyzed using logistic regression.

RESULTS

The trial enrolled 39 patients with MDS or AML who had undergone allogeneic HCT from related or unrelated donors after conditioning with various high-intensity or reduced-intensity preparative regimens. Patient and transplantation characteristics are shown in Table 1. All patients had evidence of recurrent or persistent malignancy by morphology, flow cytometry, or cytogenetics including FISH on marrow samples obtained at ≥day 28 and <day 100 after HCT. The study was designed specifically for early relapse (or persistent disease), and the diagnosis of relapse was made by flow cytometry or FISH of marrow cells in 34 of 39 patients (87%). The median blast percentage in bone marrow was 1.38%. Although blasts might appear in peripheral blood eventually, the diagnosis of relapse or persistent disease was based on marrow findings (median time to relapse, 56 days; range, 28 to 91 days).

The spectrum of clinical responses is shown in Table 2. At 6 months, 25 of 39 patients (64%) were alive, and 12 of 39 (30.7%) had responded to azacitidine, 3 achieving a complete remission (CR), and 9 a partial remission (PR). Responses were achieved after a median of 6 (range, 5 to 11) cycles of azacitidine, whereas patients who failed to respond received a median of 2 (range, 1 to 5) cycles. Three patients developed grade III acute GVHD during treatment. One patient interrupted treatment because of an episode of pulmonary hemorrhage) but was able to continue azacitidine subsequently without further complication. Less than one-third of