ASBMT
American Society for Blood and Marrow Transplantation

5-Azacytidine as Salvage Treatment in Relapsed Myeloid Tumors after Allogeneic Bone Marrow Transplantation

Javier Bolaños-Meade, B. Douglas Smith, Steven D. Gore, Michael A. McDevitt, Leo Luznik, Ephraim J. Fuchs, Richard J. Jones

Relapse after allogeneic blood or marrow transplantation carries a very poor prognosis. Current strategies for management that include donor lymphocyte infusions (DLIs) and salvage chemotherapies are usually toxic and ineffective. Here we report the outcome of 10 patients with myeloid malignancies that received 5-azacytidine after a failed allogeneic bone marrow transplant. Of the 10 patients, 6 achieved a complete remission, 1 had stable disease, and 3 progressed after a median of 6 cycles administered. Only 1 patient has died (of disease progression), and no flares of graft-versus-host disease (GVHD) were observed with 5-azacytidine. As of latest follow-up, the median overall survival (OS) for the group was 422.5 days (127-1411). These results further suggest that 5-azacytidine is an active agent after failing an allogeneic bone marrow transplant, and prospective studies are warranted.

Biol Blood Marrow Transplant 17: 754-758 (2011)

KEY WORDS: Acute myeloid leukemia, Donor lymphocyte infusion, 5-Azacytidine, Myelodysplastic syndrome, Graft-versus-host disease

INTRODUCTION

Patients who relapse after allogeneic blood and marrow transplant (BMT) for acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) have very poor prognoses [1]. Survival is generally short with traditional salvage therapies such as further chemotherapy or donor lymphocyte infusions (DLI) [1,2]. Thus, there is a great need for new therapeutic approaches in this setting.

The DNA methyltransferase inhibitor 5-azacytidine is effective treatment for MDS, with 20% to 30% complete and partial responses as well as improved survival compared to best supportive care [3,4]. Preliminary data suggest that 5-azacytidine has similar activity in some subsets of AML [5,6]. Hypomethylating agents may play a role in effectively stabilizing MDS prior to allogeneic BMT [7,8]. Moreover, it appears that the drug may have immunolomodulatory properties that could potentially enhance the graft-versus-leukemia effect associated with allogeneic BMT [9,10]. Recent reports also suggest that 5-azacytidine may have activity in patients with relapse after allogeneic BMT [11-13]. On the basis of this information, 5-azacytidine has been used at our institution to treat patients with progressive AML or MDS after BMT.

MATERIALS AND METHODS

We retrospectively identified all patients with myeloid malignancies who were treated with 5-azacytidine for relapse after allogeneic BMT between 2007 and 2009 at Johns Hopkins Hospital. There was a programmatic decision to consider treatment of relapses of myeloid malignancies after allogeneic BMT with 5-azacytidine in 2007, but the final decision on treatment was determined by the primary physician caring for the patient (whether to enroll on a clinical trial, give 5-azacytidine, or refer to hospice care, for instance). Evidence of recurrent disease was defined as decreasing or loss of donor chimerism usually with morphologic or cytogenetic persistence of the primary disease. Patients received supportive care including blood product support as needed. Patients were followed for morphological response, chimerism, and

From the "George W. Santos" Bone Marrow Transplant Service, Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, and the Division of Hematology, Department of Medicine, the Johns Hopkins University School of Medicine, Baltimore, Maryland.

Financial disclosure: See Acknowledgments on page 757.

Correspondence and reprint requests: Javier Bolaños-Meade, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans, CRB-I 2M87, Baltimore, MD 21231 (e-mail: fbolano2@jhmi.edu).

Received July 30, 2010; accepted October 11, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.10.008

survival. This analysis was approved as being exempt from human subjects research by the Johns Hopkins Hospital institutional review board and written and electronic medical records were retrospectively analyzed. The survival analyses were completed as of May 1, 2010.

Chimerism was measured as follows. Unsorted and $CD3^+$ cells are separated from peripheral blood, or unsorted bone marrow cells, using the RoboSep automated instrument (StemCell Technologies, Vancouver, Canada). This assay consists of PCR amplification of (15) microsatellite markers and the amelogenin locus using AmpFlSTR Identifiler PCR Amplification Kit (Applied Biosystems, Foster City, CA, USA). The resulting PCR products are analyzed by capillary electrophoresis and the peak heights of the informative alleles are compared to calculate a percentage engraftment. In general, engraftment is calculated using 2 different microsatellite loci from a single PCR reaction. The true limit of detection for an individual reaction is both locus and PCR dependent. The formal limit of detection is 5% [14,15].

RESULTS

Patients

Between 2007 and 2009, 154 allogeneic transplants for 149 patients with myeloid malignancices were performed at Johns Hopkins Hospital. A total of 37 relapses were identified during that time frame, and 10 of these patients were identified as having received 5-azacytidine for disease progression after BMT (Table 1). One was previously reported [13]. Their median age was 55 years (range: 25-67). Three were males, and 7 females. None of the patients were known to be positive for a FLT3 ITD, patients 1, 7, 9, and 10 were FLT3 ITD negative, and the rest were not tested. None of the patients had active graft-versus-host disease (GVHD) or were on immunosuppression at the time of starting therapy. None of the patients had blasts in peripheral blood at the time of starting therapy.

Therapy

Patients received 5-azacytidine following different schedules as per the treating physician (Table 2), but most patients received 75 mg/m^2/day for either 5 or 7 days. One patient received 5-azacytidine in combination with the histone deacetylase inhibitor entinostat as previously reported [16]. The median number of cycles administered was 6 (range: 2-27).

Outcome

Therapy was well tolerated with no unexpected or severe toxicities. One of the patients (a nonresponder) was admitted to the hospital for neutropenic fevers

Table 1. Characteristics of the Patients

ID	Patient	Diagnosis	Karyotype before Starting 5-aza	Type of Transplant	Time between BMT and Progression	Conditioning	Prior Therapies
1	61 YOM	AML/CMML	46,XY	NMA haploidentical	36 months	Flu-Cy-TBY-Cy	Induction with cytotoxics
2	57 YOF	MDS/AML primary refractory	50,XX,+X,add(2)(q37),7,del(7)(q22),del(9)(q13q32),+13,+14,+21,+22[11]/46,XX[9]	MUD	132 months	Bu-Cy	Induction with cytotoxics
3	25 YOF	2o MDS	46,XX,del(20)(q12)[9]/46,XX[11]	NMA haploidentical	6 months	Flu-Cy-TBY-Cy	None
4	48 YOF	MDS	46,XY	Matched sibling	14 months	Bu-Cy-Cy	Lenalidomide
5	61 YOF	MDS/AML	46,XY	MUD	18 months	Bu-Cy-Cy then Flu-Alem	Hydroxyurea
6	67 YOM	MDS	46,XY	NMA MUD	5 months	Flu-Cy-TBY-Cy	5-Azacytidine; lenalidomide; 5-azacytidine
7	47 YOF	MDS	46,XX[4]/46,XY[16]	MUD	36 months	Bu-Cy	Induction
8	71 YOF	MDS/AML	46,XX,del(5)(q13q33),add(7)(q11.2),−13,+14,t(17;20)(p13;q11.2),-18,inv(21)(q21q22)[cp9]/46,XX[11]	NMA sibling	0 months	Flu-Cy-TBY-Cy	Etoposide-tipifarnib; cytarabine
9	57 YOM	MDS/MPD	46,XY	Matched sibling	0 months	Bu-Cy-Cy	Hydroxyurea
10	53 YOF	MDS	44,XX,der(3;5)(q10;p10),+8, −9, −10[2]/54,X,-X,+1,add(3)(q21),der(3;5)(q10;p10),+5,+7,+8,+9,+17,+22,+2r,+mar[1]/46,XX[4]	Matched sibling	18 months	Bu-Cy-Cy	5-Azacytidine

NMA indicates nonmyeloablative; MUD, matched-unrelated; BMT, bone marrow transplant; MDS/MPD, myelodysplastic syndrome/myeloproliferative disorder; Bu-Cy, busulfan and cyclophosphamide; Bu-Cy-Cy, busulfan, cyclophosphamide, and post-BMT cyclophosphamide as described by Luznik et al. [28]; Flu-Cy-TBI-Cy, fludarabine, cyclophosphamide, total=body irradiation, and post-BMT cyclophosphamide as described by Luznik et al. [29]; Flu-Alem, fludarabine and alemtuzumab as described by Bolaños-Meade et al. [30].