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Low-Dose Azacitidine After Allogeneic Stem Cell Transplantation for Acute Leukemia

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Abstract

BACKGROUND—The authors hypothesized that low doses of the hypomethylating agent 5-azacitidine may maximize the graft-versus-leukemia effect and may be tolerated well after allogeneic transplantation (HSCT).

METHODS—The drug was given to 17 patients with acute leukemia as salvage for disease recurrence after HSCT (n = 9 patients) or as maintenance therapy (n = 8 patients). 5-Azacitidine was given subcutaneously daily for 5 days and was repeated every 4 weeks at doses of 16 mg/m^2 (n = 4 patients), 24 mg/m^2 (n = 9 patients), and 40 mg/m^2 (n = 4 patients). A median of 8 cycles was delivered. The median follow-up was 16 months and 11 months after HSCT and 5-azacitidine treatment, respectively.

RESULTS—Five of 9 patients with recurrent disease responded. Four of 13 responding patients developed disease recurrence while they were receiving 5-azacitidine after a median of 10 months. The actuarial 1-year event-free and overall survival rates were 55% and 90%, respectively. There were no extramedullary toxicities, and no graft-versus-host disease exacerbation was observed.

CONCLUSIONS—Low-dose 5-azacitidine may induce durable remissions for patients who develop disease recurrence after HSCT. Further follow-up and a larger group of patients will be necessary to confirm these observations.

Keywords

acute leukemia; transplantation; azacitidine; survival

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Conflict of Interest Disclosures

The authors made no disclosures.

Disease recurrence is a major cause of treatment failure in patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) who undergo allogeneic hematopoietic stem cell transplantation (HSCT) to treat recurrent and/or refractory disease.[1,2] Modifications of the preparative regimen using multiple combinations of chemotherapy and physical agents have failed to reduce the risk of recurrence without an increase in nonrecurrence mortality.[3,4] Outcomes after early recurrence of acute leukemia usually are dismal given the toxicity of salvage chemotherapy, donor lymphocyte infusions, and second transplants. Therefore, novel strategies are needed to prevent and treat disease recurrence.

5-Azacidine is a DNA hypomethylating agent that appears to induce leukemic cell differentiation and increase the expression of human leukemic antigen DR-1 (HLA-DR) and several tumor-associated antigens. We have hypothesized that such actions may increase the graft-versus-leukemia (GVL) effect.[5–12] The drug also has significant activity in MDS and AML.[13–15] It is interesting to note that lower doses appear to promote hypomethylation more effectively than higher doses.[16] Lower doses are likely to be tolerated better after HSCT given the high risk of myelosuppression and other toxicities in the post-HSCT period. Therefore, we used 5-azacitidine to treat and prevent disease recurrence after HSCT, and here we present the results of this intervention.

MATERIALS AND METHODS

Between November 2004 and January 2008, 17 patients were treated sequentially (16 patients at the University of Texas M. D. Anderson Cancer Center and 1 patient at Vanderbilt University). They represent all patients who received azacitidine in our institutions outside a clinical trial. Nine patients with AML received 5-azacydine as salvage therapy, and 8 patients (7 with myeloid leukemia and 1 with lymphoid leukemia) received it as maintenance of remission. Patients with disease recurrence were chosen on the basis of having an “indolent” disease recurrence, whereas maintenance was offered to patients who were perceived to have a very high risk of disease recurrence but were in remission after transplantation, as described in Table 1. In addition, patients did not have uncontrolled graft-versus-host disease (GVHD), elevated liver function tests, or creatinine levels above the normal range. The drug was given 5 times daily and was repeated every 4 weeks at doses of 16 mg/m^2 (n = 4 patients), 24 mg/m^2 (n = 9 patients), and 40 mg/m^2 (n = 4 patients). The intent was to administer azacitidine until loss of response or upon completion of 2 years of therapy. Doses were chosen on the basis of an ongoing dose-finding study in which these patients did not participate (either they were not eligible or the protocol was not available in the institution).

Donors were HLA-compatible related (n = 5 donors), unrelated (n = 11 donors; double cord blood, n = 2 donors), or syngeneic (n = 1 donor). HLA typing consisted of allele level resolution for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1, except for cord blood donor-recipient pairs, in which the donor was typed with intermediate resolution for HLA-A and HLA-B and with high-resolution for HLA-DRB1. All donor-recipient pairs were fully matched except for recipients of cord blood transplantation, who received units

with 2 mismatches. GVHD prophylaxis was tacrolimus-based in all patients, and all recipients of unrelated stem cell transplantation received antithymocyte globulin as part of the conditioning regimen. Patients who were receiving azacitidine also received granulocyte–colony-stimulating factor (G-CSF) intermittently at the discretion of the treating physician for those with absolute neutrophil counts $<1 \times 10^9$/L. No G-CSF was given during administration of the drug. Toxicity was graded according to National Cancer Institute criteria. GVHD was graded according to consensus criteria.[17] Bone marrow aspirations were performed 30 days after transplantation and approximately every 3 months thereafter. Chimerism was studied in bone marrow and peripheral blood samples obtained at approximately 3-month intervals using cytogenetics for sex-mismatched donor-recipient pairs (bone marrow) or analysis of microsatellite DNA polymorphism (bone marrow and peripheral blood; in the latter, we also analyzed lymphoid and myeloid chimerism). A complete remission (CR) was defined as bone marrow with <6% blasts, granulocyte count $>1 \times 10^9$/L, and platelet count $>100 \times 10^9$/L. Patients who met these criteria but had from 6% to 25% bone marrow blasts were considered to have a partial remission (PR). Event-free survival (EFS) was measured from start of 5-azacitidine until loss of response, progression, or death from any cause during treatment. Overall survival (OS) was defined from the date of HSCT to the date of death or last follow-up. Survival probabilities were estimated by using the Kaplan-Meier method and were compared using the log-rank test.[18] Informed consent was obtained for 5-azacitidine treatment in all patients for treatment off protocol. The institutional review board of the University of Texas M. D. Anderson Cancer Center approved this retrospective study.

RESULTS

The median patient age was 48 years (range, 21–67 years). Cytogenetics were low-risk, intermediate-risk, and high-risk in 1 patient (5%), 11 patients (65%), and 5 patients (30%), respectively. Six patients (35%) had failed a previous HSCT. At the time of HSCT, 10 patients (59%) had refractory disease with a median bone marrow blast percentage of 51% (range, 20%–98%) (Table 1). All 17 patients were in CR after HSCT. Nine patients then developed a disease recurrence after a median of 8 months (range, 2–23 months).

5-Azacidine was started at a median of 8 months (range, 2–26 months) after HSCT in patients with recurrent disease and at a median of 2 months (range, 1–6 months) when it was given as maintenance therapy. The median number of cycles delivered was 8 (range, 1–22 cycles delivered). Of the 9 patients who had recurrent disease, 6 patients had a medullary recurrence (median bone marrow blasts, 25%), and 3 patients had extramedullary disease (leukemia cutis in 2 patients and blastic pleural effusion in 1 patient). Five of 9 patients who developed recurrent disease responded (55%); 3 patients achieved a CR that was ongoing for ≥4 months and ≥17 months in 2 patients and that was lost after 4 months in 1 patient (Table 2). Two patients had a PR that was sustained for ≥2 months and ≥4 months. Eight patients who received 5-azacitidine as maintenance therapy remained in CR for a median of 17 months (range, from ≥14 months to ≥26 months). Three of those patients developed disease recurrence after 4 months, 14 months, and 18 months of therapy after they received 3 cycles, 12 cycles, and 12 cycles, respectively. All but 1 patient in the maintenance group were full donor chimeras at the beginning of azacitidine therapy and remained complete chimeras

unless they developed a recurrence. The patient who was a mixed chimera in an unfractionated bone marrow sample became a complete donor chimera after therapy. Among the patients with recurrent disease, those who achieved a CR with azacitidine converted to full donor chimerism in the lymphoid and myeloid populations.

Five of 9 patients in the recurrent disease subgroup were off immunosuppressants at the time of disease recurrence, whereas 2 patients underwent immunosuppression withdrawal to treat recurrence (before initiation of the drug); and, in 2 patients, azacitidine was given concomitantly with the process of tacrolimus discontinuation. Ten patients developed grade 1/2 GVHD post-HSCT (before the initiation of 5-azacitidine); 4 of them had persistent grade 1/2 GVHD after the initiation of 5-azacitidine, and no new episodes occurred afterward.

Azacitidine was tolerated well with no extramedullary toxicities and with no apparent increase in the rate of infectious complications. Grade 1/2 hematologic toxicities were noted in most patients. After a median follow-up of 16 months (range, 3–40 months) and 11 months (range, 1–26 months) after HSCT and 5-azacitidine therapy, respectively, 14 patients (82%) remained alive, including 7 patients (41%) who were in CR and 2 patients (13%) who were in PR for a median of 20 months (range, from ≥7 months to ≥40 months) and 12 months (range, from ≥2 months to ≥26 months), respectively. The 1-and 2-year actuarial EFS and OS rates were 55% and 30%, and 90% and 80%, respectively.

DISCUSSION

To our knowledge, this is the first report on the efficacy of 5-azacitidine given to a large number of patients after allogeneic HSCT. Specifically, we demonstrated the safety of the drug administered at low doses and the lack of GVHD exacerbation. The efficacy of this approach is suggested by the high response rate in patients with recurrent disease who had failed after 1 or 2 HSCTs.

The most important predictor of survival for patients who develop disease recurrence after allogeneic HSCT is the duration of remission after transplantation.[1,2,12,19–21] Our cohort had a short median CR duration of 8 months, and 6 patients had undergone 2 transplantations. Patients who received maintenance therapy were unlikely to remain in CR otherwise given the advanced stage of their disease at the time they underwent HSCT.

To our knowledge, there is little information on the use of 5-azacytidine at the doses that we used in the current study. However, there is clinical and laboratory evidence that the other US Food and Drug Administration (FDA)-approved hypomethylating agent, decitabine, may be more active in lower than “standard” doses. The FDA-approved dose of 5-azacytidine is 75 mg/m^2 daily for 7 days, a dose that is unlikely to be tolerated in the post-HSCT period because of high likelihood of myelosuppression and other toxicities.[14–16]

Immunosuppression withdrawal alone was not responsible for the results described here. In our previous experience treating similarly high-risk patients, the response rate to that intervention was zero.[22] In addition, some of our patients remained on immunosuppressants while they were on azacitidine, although we have avoided administering the drug in the presence of more than minimal manifestations of GVHD. The response rate observed in the

current study was comparable to that achieved any salvage strategy used in similar patient populations in the past with a very favorable toxicity profile.[23] It is interesting to note that some patients never achieved a CR but remained with stable disease for a period. In addition, all treatments were conducted in the outpatient setting. Most responders, however, had relatively indolent recurrences, whereas rapidly evolving disease was less likely to respond. It is unclear whether the drug has an inhibitory effect on GVHD, although there is preclinical evidence of its influence on regulatory T lymphocytes.[24,25]

Our cohort demonstrated that low-dose azacitidine can be given safely after allogeneic transplantation. We hypothesize that our results were caused by an effect of the drug as an antileukemic agent and as a potentiator of the GVL effect. Although this speculation remains to be proven formally, low-dose azacitidine may provide us with a tool with which to decrease the rates of disease recurrence and to improve mixed chimerism after HSCT when it is given as maintenance or possibly as an adjuvant to donor lymphocyte infusions to treat disease recurrence. We are concluding a dose and schedule finding study that will be followed by a controlled, randomized evaluation of azacitidine as maintenance therapy after HSCT for patients who are at high risk of a recurrence of AML and MDS.[26]

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Table 1

Patient Characteristics and Treatment

PIN	Age, y	Phenotype	Disease Status at Time of HSCT	% Bone Marrow Blasts	Conditioning*	No. of Allogeneic HSCT	Donor Type	Indication	Remission Duration After HSCT, mo	Bone Marrow Blasts at Recurrence	Chimerism Before 5-AC	GVHD Before 5-AC	Immunosuppression Withdrawal as Treatment of Recurrence†
1	36	ALL	CR3	2	FM	1	MUD	Maintenance	NA	NA	100% Donor	Yes	NA
2	48	AML	Refractory	37	GOFM	1	MUD	Maintenance	NA	NA	100% Donor	Yes	NA
3	49	AML	Refractory	92	BuCy	1	Syngeneic	Maintenance	NA	NA	NA	No	NA
4	58	AML	Refractory	30	FluBu	2	MUD	Maintenance	NA	NA	100% Donor	No	NA
5	66	AML	Refractory	25	FM	2	MUD	Maintenance	NA	NA	100% Donor	Yes	NA
6	29	AML	CR3 after CNS relapse	3	GOFM	2	MUD	Maintenance	NA	NA	100% Donor	Yes	NA
7	33	AML	CR2	3	FM	2	MUD	Maintenance	12	NA	Mixed	No	Yes
8	26	AML	Refractory	80	GOFM	1	MRD	Maintenance	NA	NA	100% Donor	Yes	NA
9	67	AML	Refractory	20	GOFM	1	MRD	Salvage	8	30%	Mixed	No	Yes
10	65	AML	CR2	1	FCyTBI	1	UCB	Salvage	5	Extramedullary	Mixed	Yes	No
11	62	AML	CR2	5	GOFM	2	MRD	Salvage	23	6%	Mixed	Yes	No
12	44	AML	Refractory	51	FM	1	MUD	Salvage	5	Extramedullary	100% Donor	Yes	No
13	57	AML	CR1	1	CyTBI	1	UCB	Salvage	7	38%	Mixed	No	Yes
14	52	AML	Refractory	31	GOFM	1	MRD	Salvage	10	Extramedullary	100% Donor	No	Yes/incomplete
15	53	AML	CR2	3	FluBu	1	MRD	Salvage	6	15%	Mixed	Yes	No
16	24	AML	Refractory	90	Bu/clofarabine	2	MUD	Salvage	2	9%	Mixed	No	Yes/incomplete
17	21	AML	Refractory	45	GOFM	1	MUD	Salvage	2	55%	Mixed	Yes	No

PIN indicates patient identification number; HSCT, hematopoietic stem cell transplantation; 5-AC, 5-azacitidine; GVHD, graft-versus-host disease; ALL, acute lymphocytic leukemia; CR3, third complete remission; FM, fludarabine and melphalan; MUD, matched unrelated donor; NA, not applicable; AML, acute myeloid leukemia; GOFM, combined gemtuzumab ozogamicin (2 mg/m^2), fludarabine (40 mg/m^2 intravenously daily for 4 d), and melphalan (140 mg/m^2); BuCy, busulfan (3.2 mg/Kg intravenously daily for 4 d) and cyclophosphamide (120 mg/Kg); FluBu, busulfan (130 mg/m^2 intravenously daily for 2 d) and fludarabine (40 mg/m^2 intravenously daily for 4 d); CNS, central nervous system; CR2, second complete remission; MRD, matched related donor; FCyTBI, fludarabine (40 mg/m^2 intravenously daily for 4 d), cyclophosphamide (50 mg/Kg), and total body irradiation (2 Grays); UCB, unrelated cord blood; CyTBI, cyclophosphamide (120 mg/Kg) and total body irradiation (12 Grays); Bu/clofarabine, busulfan (130 mg/m^2 intravenously daily for 4 d) and clofarabine (40 mg/m^2 intravenous daily for 4 d).

*All patients who underwent unrelated donor transplantation had antithymocyte globulin added to the preparative regimen.

[†]Among the patients who developed recurrent disease, 5 already were off immunosuppressants at the time they started 5-AC; in 4 patients, 5-AC was started after or during the process of immunosuppression withdrawal.

Table 2

Outcomes After Azacitidine Treatment

PIN	Indication	Time from HSCT to 5-AC, mo	Dose*/No. of Treatment Cycles	Response	Response Duration, mo†	GVHD After 5-AC	Chimerism After 5-AC	Recurrence	Status at LFU	Survival, mo‡
1	Maintenance	3	16/8	CCR	≥14	Yes	100% Donor	No	CR	≥17
2	Maintenance	6	24/12	CCR	18	Yes	100% Donor	Yes	Died	25
3	Maintenance	1	24/3	CCR	4	No	NA	Yes	AWD	≥6
4	Maintenance	2	24/12	CCR	14	No	100% Donor	Yes	AWD	≥19
5	Maintenance	3	24/22	CCR	≥26	Yes	100% Donor	No	CR	≥29
6	Maintenance	2	24/20	CCR	≥23	No	100% Donor	No	CR	≥25
7	Maintenance	12	24/15	CCR	≥17	No	100% Donor	No	CR	≥29
8	Maintenance	2	40/5	CCR	≥6	No	100% Donor	No	CR	≥7
9	Salvage	8	16/2	NR	NA	No	NA	NA	AWD	≥22
10	Salvage	5	16/2	PR	≥2	No	Mixed	No	PR	≥7
11	Salvage	23	16/13	CR	≥15	No	100% Donor	No	CR	≥40
12	Salvage	5	24/2	NR	NA	No	NA	NA	Died	8
13	Salvage	7	24/4	PR	≥5	No	Mixed	No	PR	≥12
14	Salvage	10	24/3	CR	4	No	100% Donor	Yes	Died	17
15	Salvage	6	40/3	CR	≥4	No	100% Donor	No	CR	≥9
16	Salvage	2	40/1	NR	NA	No	Mixed	NA	AWD	≥3
17§	Salvage	2	40/2	NR	NA	Yes	Mixed	NA	AWD	≥4

PIN indicates patient identification number; HSCT, hematopoietic stem cell transplantation; 5-AC, 5-azacitidine; GVHD, graft-versus-host disease; LFU, last follow-up; CCR, continuous complete remission; AWD, alive with disease; NR, nonresponse; PR, partial remission; NA, not applicable.

*Doses shown are in mg/m^2 per d×5.

‡Response was measured from the start of 5-AC for patients who received 5-AC as maintenance therapy and from the time a response was achieved for patients who received 5-AC as salvage therapy.

‡Survival was calculated from the last HSCT.

§5-AC was given combined with sorafenib (FMS-like tyrosine kinase 3-positive patient).