JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Hematologic Response to Three Alternative Dosing Schedules of Azacitidine in Patients With Myelodysplastic Syndromes

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Submitted March 19, 2008; accepted November 19, 2008; published online ahead of print at www.jco.org on March 2, 2009.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007, and at the 49th Annual Meeting of the American Society of Hematology, Atlanta, GA, December 8-11, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/09/9999-1/$20.00

DOI: 10.1200/JCO.2008.17.1058

ABSTRACT

Purpose
Azacitidine (AZA) is effective treatment for myelodysplastic syndromes (MDS) at a dosing schedule of 75 mg/m^2/d subcutaneously for 7 days every 4 weeks. The initial phase of this ongoing multicenter, community-based, open-label study evaluated three alternative AZA dosing schedules without weekend dosing.

Patients and Methods
MDS patients were randomly assigned to one of three regimens every 4 weeks for six cycles: AZA 5-2-2 (75 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 75 mg/m^2/d for 2 days); AZA 5-2-5 (50 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 50 mg/m^2/d for 5 days); or AZA 5 (75 mg/m^2/d subcutaneously for 5 days).

Results
Of patients randomly assigned to AZA 5-2-2 (n = 50), AZA 5-2-5 (n = 51), or AZA 5 (n = 50), most were French-American-British (FAB) lower risk (refractory anemia [RA]/RA with ringed sideroblasts/chronic myelomonocytic leukemia with < 5% bone marrow blasts, 63%) or RA with excess blasts (30%), and 79 (52%) completed ≥ six treatment cycles. Hematologic improvement (HI) was achieved by 44% (22 of 50), 45% (23 of 51), and 56% (28 of 50) of AZA 5-2-2, AZA 5-2-5, and AZA 5 arms, respectively. Proportions of RBC transfusion–dependent patients who achieved transfusion independence were 50% (12 of 24), 55% (12 of 22), and 64% (16 of 25), and of FAB lower-risk transfusion-dependent patients were 53% (nine of 17), 50% (six of 12), and 61% (11 of 18), respectively. In the AZA 5-2-2, AZA 5-2-5, and AZA 5 groups, 84%, 77%, and 58%, respectively, experienced ≥ 1 grade 3 to 4 adverse events.

Conclusion
All three alternative dosing regimens produced HI, RBC transfusion independence, and safety responses consistent with the currently approved AZA regimen. These results support AZA benefits in transfusion-dependent lower-risk MDS patients.

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INTRODUCTION

The hypomethylating agent, azacitidine (Vidaza; Celgene Corporation, Summit, NJ), the first medication approved for treatment of myelodysplastic syndromes (MDS), has been shown to alter the natural history of the disease.[1,2] The Cancer and Leukemia Group B study showed azacitidine significantly reduced transfusion dependence, decreased risk of transformation to acute myeloid leukemia (AML), improved quality of life (QOL), and showed a trend for prolonged survival compared with best supportive care (BSC) in all French-American-British (FAB) subtypes of MDS.[1,3] The Cancer and Leukemia Group B findings and data from two phase II studies, using the WHO classifications[4] and International Working Group (IWG)[5] response criteria, support these benefits of azacitidine.[6] Moreover, recent data demonstrate that azacitidine is the first therapy to significantly prolong survival in higher-risk MDS patients versus conventional care regimens (24.5 *v* 15 months, respectively; $P = .0001$).[2]

Transfusion benefits with azacitidine have been seen in both lower- and higher-risk MDS patients.[1,6] Azacitidine is approved for all five FAB subtypes of MDS,[7] and National Comprehensive Cancer Network guidelines[8] support its use in higher-risk MDS patients, who have increased disease-related mortality, and in lower-risk patients, most of whom require RBC transfusions for anemia.

Transfusion dependence is associated with significant clinical and economic burdens.[9,10] The newly developed WHO based time-dependent prognostic scoring system[11] identifies transfusion requirements as predictive of survival and leukemic evolution. RBC transfusions are also associated with significant complications, including alloimmunization, likelihood of febrile and allergic reactions, hemosiderosis, and transmission of infectious agents.[9,10] In addition, long-term transfusion support for patients with MDS is costly, often requiring specially processed blood products and premedications. Thus, transfusion independence is a clinically significant treatment objective.[5]

The currently approved azacitidine regimen is 75 mg/m^2/d subcutaneously (SC) or intravenously for 7 days every 28 days. Alternative dosing regimens that eliminate weekend dosing would increase convenience for patients and clinicians. To this end, three alternative azacitidine dosing regimens, which avoid weekend dosing, were selected to assess their relative effectiveness in MDS patients.

This report describes the safety and efficacy of these three alternative azacitidine dosing regimens administered for six treatment cycles, which comprised the treatment phase of this study. A maintenance phase of this study is ongoing at the time of this writing.

PATIENTS AND METHODS

Patient Eligibility

Male and female MDS patients ≥ 18 years of age with a diagnosis of FAB criteria-defined refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RA with excess blasts in transformation (RAEB-T), or chronic myelomonocytic leukemia (CMML), and life expectancy longer than 7 months were included. RA or RARS patients must have met at least one of the following criteria: hemoglobin lower than 110 g/L with requirements for at least one RBC transfusion every 28 days; thrombocytopenia with platelet count lower than 100×10^9/L; or neutropenia with absolute neutrophil count lower than 1.5×10^9/L. Bone marrow samples were required within 30 days of the first azacitidine dose and reviewed by local pathologists for diagnosis and assessment of patient eligibility. Confirmation of baseline cytopenias (defined earlier) for all patients was based on a single measurement taken on or before initial azacitidine dosing.

Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3. In addition, on laboratory screening, serum bilirubin level ≤ 1.5 × the upper limit of normal (ULN); AST or ALT level ≤ 2 × ULN; and serum creatinine level ≤ 1.5 × ULN were required. Only patients deemed unlikely to proceed to transplantation after remission were enrolled.

Patients were excluded if they had secondary MDS, a history of AML, or other malignant disease. Also excluded were those with uncorrected red cell folate deficiency or vitamin B_{12} deficiency. All patients provided written, informed consent and the study protocol was approved by the appropriate institutional review boards.

Study Design

This phase II, multicenter, randomized, open-label trial comprised three treatment arms. Patients were randomly assigned to one of three alternative dosing regimens, administered in 28-day cycles for six treatment cycles. In the AZA 5-2-2 arm, azacitidine was administered at 75 mg/m^2/d SC for 5 days, followed by a 2-day weekend break, followed by azacitidine 75 mg/m^2/d SC for 2 days (total cumulative dose 525 mg/m^2 per cycle). In the AZA 5-2-5 arm, azacitidine was administered at 50 mg/m^2/d SC for 5 days, followed by a 2-day weekend break, followed by azacitidine 50 mg/m^2/d SC for 5 days (total cumulative dose 500 mg/m^2 per cycle). In the AZA 5 arm, azacitidine was administered at 75 mg/m^2/d SC for 5 days (total cumulative dose 375 mg/m^2 per cycle). Per protocol, intravenous administration of AZA was not allowed at any time during the study.

After at least two cycles, the azacitidine dose could be increased if the patient was not responding, defined as treatment failure or disease progression according to IWG 2000 MDS criteria.[5] Conversely, the dose could be delayed or decreased based on hematologic recovery and adverse events.

Erythropoiesis stimulating agents (ESAs) could be continued at a fixed dose in patients receiving a stable dose of an ESA for 4 weeks before study randomization. ESAs could not be started or titrated once azacitidine treatment was initiated. Myeloid growth factors were allowed for treatment of neutropenic infection but were stopped within 4 days of resolution of the febrile episode. Hematologic response to azacitidine was not assessed until ≥ 3 weeks had passed since the last dose of myeloid growth factor. Further supportive care was provided to patients at the investigators' discretion.

Response Criteria

This was a community-based trial. Thus, cytogenetic data were not required or collected and follow-up bone marrows were not routinely performed. All patients who received azacitidine were evaluated for safety and all randomly assigned patients were evaluated for efficacy (intent to treat [ITT] analysis).

Efficacy was measured based on hematologic improvement (HI) and transfusion independence rates, as defined by IWG 2000 criteria[5] and determined by computer-generated assessments. To be considered transfusion dependent at baseline, patients required at least one transfusion during the 28-day baseline period. Transfusion independence rates were measured in patients with baseline transfusion dependence. Transfusion (RBC or platelet) independence was defined as a transfusion-free period of ≥ 56 consecutive days, starting the first day after the last transfusion. The duration of transfusion independence was measured as the first day after the last transfusion until transfusion requirements returned.

Safety

Adverse events were coded using MedDRA version 10.0. All baseline conditions, including cytopenias, that worsened after treatment initiation were graded using the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical Methods

This trial was not designed to achieve statistically significant results or formal hypothesis testing among the three alternative regimens. Patients were randomly assigned to one of the three regimens using a stratified blocked randomization schedule (ie, patients were randomly assigned within each of the five FAB-defined subtype strata resulting in a balanced allocation of patients to the three treatment arms). Number, proportion, and 95% CIs for patients achieving HI are summarized for the ITT population and for FAB-defined lower-risk (RA, RARS, and CMML with < 5% bone marrow blasts) patients (FAB-defined higher risk patients were RAEB, RAEB-T, and CMML with ≥ 5% blasts). Onset of HI by azacitidine treatment cycle is reported descriptively.

Number and percent (with 95% CI) of RBC and platelet transfusion-dependent patients at baseline, who achieved transfusion independence, were assessed in the group of all ITT patients and in FAB-defined lower-risk patients in each alternative dosing regimen. Onset of transfusion independence by azacitidine treatment cycle is reported descriptively. A multivariate logistic regression analysis was performed to compare the occurrence of transfusion independence among the three treatment arms. A stepwise selection procedure was used to investigate the influence of prognostic variables on achievement of transfusion independence; covariates included age (continuous), baseline ESA use (yes or no), presence of baseline neutropenia ($< 1.5 \times 10^9$/L $v \geq 1.5 \times 10^9$/L), presence of baseline thrombocytopenia ($< 100 \times 10^9$/L $v \geq 100 \times 10^9$/L), and numbers of RBC transfusions (continuous) and RBC units (≤ 2 v > 2 units) in the 56 days before study entry.

RESULTS

Patient Accounting

Of 184 patients screened, 151 were eligible to enroll and comprised the ITT population. Baseline patient demographics and disease characteristics are presented in Table 1. Most patients were FAB lower risk (63%) or RAEB (30%) with an ECOG status of 0 to 1 (n = 129; 85%). After random assignment, three patients did not receive study drug but are included in the ITT analyses (n = 151) but excluded from the safety-assessable population (n = 148). A total of 139 patients (92%) received at least two treatment cycles and 79 patients (52%) completed the six treatment cycles. Reasons for withdrawal during the first six cycles (n = 72) included adverse events (n = 20; 13%) and disease progression/relapse (n = 10; 7%). In all, 68% (34 of 50), 63% (30 of 48), and 34% (17 of 50) of patients in the AZA 5-2-2, AZA 5-2-5, and AZA 5 groups, respectively, discontinued or delayed treatment during the first six cycles due to an AE.

HI

In all, 44% to 56% of patients achieved major or minor HI (Table 2). For those who achieved HI, onset occurred during the first two cycles for 82%, 56%, and 90% of patients in the AZA 5-2-2, AZA 5-2-5, and AZA 5 groups, respectively (Table 3). Of FAB lower-risk patients, 49% (16 of 33), 41% (12 of 29), and 50% (16 of 32) of the AZA 5-2-2, AZA 5-2-5, and AZA 5 groups achieved major or minor HI. In addition, 11 (34%) of 32, five (21%) of 24, and 10 (33%) of 30 patients with baseline multilineage cytopenias experienced multilineage HI in the AZA 5-2-2, AZA 5-2-5, and AZA 5 groups.

Transfusion Independence

Among baseline RBC transfusion-dependent patients, 12 (50%; 95% CI, 29 to 71), 12 (55%; 95% CI, 32 to 76), and 16 (64%; 95% CI, 43 to 82) in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing arms, respectively, achieved transfusion independence within the six-cycle treatment phase of the trial (Table 3). The median numbers of prestudy transfusions in patients who achieved transfusion independence were 2 (range, 2 to 5), 2 (range, 2 to 4), and 2 (range, 2 to 6) in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing arms. Among baseline transfusion-dependent patients who did not achieve transfusion independence, median numbers of prestudy transfusions were 2 (range, 2 to 6), 4 (range, 2 to 7), and 3 (range, 2 to 6) in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing arms.

RBC transfusion independence was compared among the three treatment arms using a logistic-regression analysis adjusted for baseline neutropenia, thrombocytopenia, and number of baseline RBC transfusion units. The analysis showed that overall, the absence of baseline neutropenia ($\geq 1.5 \times 10^9$/L) or thrombocytopenia ($\geq 100 \times 10^9$/L) and lower transfusion requirements ($\leq$ 2 units/56 days) were predictive of higher rates of RBC transfusion independence. No statistically significant differences among the three dose schedules were observed. There was a treatment interaction detected for the presence of thrombocytopenia at baseline in the AZA 5-2-5 dosing group: patients did equally well whether or not they had baseline thrombocytopenia, whereas those in the AZA 5-2-2 and AZA 5 dosing arms fared better if they were not thrombocytopenic at baseline.

The majority of baseline RBC transfusion-dependent patients who achieved transfusion independence during the study were FAB lower-risk patients: nine (75%) of 12, six (50%) of 12, and 11 (69%) of 16 patients in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing arms,

Table 1. Patient Demographic and Disease Characteristics for All Randomly Assigned Patients (N = 151) at Baseline

Characteristic	AZA 5-2-2		AZA 5-2-5		AZA 5	
	No.	%	No.	%	No.	%
No. of patients	50		51		50	
Median age, years	73		76		76	
Range	37-88		54-91		47-93	
Sex						
Male	28	56	37	73	33	66
Female	22	44	14	28	17	34
ECOG status by grade						
0	19	38	14	28	12	24
1	23	46	29	57	32	64
2	5	10	7	14	3	6
3	3	6	1	2	3	6
RBC transfusion dependent	24	48	22	43	25	50
Platelet transfusion dependent	2	4	1	2	4	8
FAB classification						
RA	22	44	21	41	22	44
RARS	7	14	7	14	7	14
RAEB	14	28	17	33	14	28
RAEB-T	1	2	1	2	2	4
CMML	6	12	5	10	5	10

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AZA 5-2-2, 75 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 75 mg/m^2/d for 2 days; AZA 5-2-5, 50 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 50 mg/m^2/d for 5 days; AZA 5, 75 mg/m^2/d subcutaneously for 5 days; FAB, French-American-British; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-T, RA with excess blasts in transformation; CMML, chronic myelomonocytic leukemia.

Table 2. HI Evaluated Using IWG 2000 Criteria

	Treatment Arm								
	AZA 5-2-2 (n = 50)			AZA 5-2-5 (n = 51)			AZA 5 (n = 50)		
HI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
HI-E									
Major	19/43	44	29 to 60	19/43	44	29 to 60	20/44	46	30 to 61
Minor	1/29	3	0.1 to 18	0		0 to 11	1/28	4	0.1 to 18
HI-P									
Major	12/28	43	25 to 63	8/30	27	12 to 46	11/22	50	28 to 72
Minor	0		0 to 11	0		0 to 10	1/27	4	0.1 to 19
HI-N									
Major	4/23	17	5 to 39	4/23	17	5 to 39	9/24	38	19 to 59
Minor	0		0 to 15	0		0 to 15	0		0 to 14
Any HI*	22/50	44	31 to 60	23/51	45	32 to 61	28/50	56	41 to 70

Abbreviations: HI, hematologic improvement; IWG, International Working Group; AZA 5-2-2, 75 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 75 mg/m^2/d for 2 days; AZA 5-2-5, 50 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 50 mg/m^2/d for 5 days; AZA 5, 75 mg/m^2/d subcutaneously for 5 days; E, erythroid; P, platelet; N, neutrophil.
*Patients were counted only once for best response within an improvement category.

respectively. For baseline transfusion-dependent patients in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing arms with onset of transfusion independence during the first six cycles, independence was ongoing at the end of the treatment phase in 12 (100%), 11 (92%), and 10 (63%) of them. Median duration of transfusion independence was 473 days and 387 days, respectively, in the AZA 5-2-2 and AZA 5-2-5 arms, and was not reached in the AZA 5 dosing arm. The onset of RBC transfusion independence occurred within the first two cycles for at least 75% of patients in each of the three dosing arms (Table 3). Seven patients were platelet transfusion-dependent at baseline (AZA 5-2-2, n = 2; AZA 5-2-5; n = 1, AZA 5, n = 4); all but one (an AZA 5-2-5 patient) achieved transfusion independence during the study.

Safety and Tolerability

The three azacitidine alternative dosing regimens were generally well tolerated, with 52% of patients completing all six treatment cycles. Safety was fairly consistent among dosing arms, although fewer AEs were observed with the AZA 5 regimen. More patients in the AZA 5 arm completed six cycles of treatment (n = 32; 64%) than in the AZA 5-2-2 (n = 22; 44%) or AZA 5-2-5 (n = 25; 49%) dosing arms. The most commonly reported hematologic AEs were neutropenia (38%), anemia (29%), thrombocytopenia (25%), and leukopenia (18%). The most commonly reported nonhematologic AEs were fatigue (56%), nausea (55%), injection site erythema (55%), constipation (51%), and injection site pain (34%). Grade 3 and 4 treatment-related AEs of special interest are listed in Table 4. The majority of treatment-emergent grade 3 or 4 AEs were reported during the first three treatment cycles and then tended to decline. Similarly, anemia, neutropenia, leukopenia, and thrombocytopenia were primarily reported during cycles one and two and infrequently thereafter (Table 5).

The numbers of patients with at least one treatment-emergent AE that led to study discontinuation were 11 (22%), 10 (21%), and seven (14%) in the AZA 5-2-2, AZA 5-2-5, and AZA 5 dosing arms, respectively. Serious AEs were reported in 27 (54%), 19 (40%), and 15 (30%) patients in the AZA 5-2-2, AZA 5-2-5, and AZA 5 groups, respectively. The most common (≥3%) serious AEs involved anemia (n = 7), febrile neutropenia (n = 9), congestive heart failure (n = 5, all pre-existed azacitidine treatment and worsening was not thought to be study drug related), and pneumonia (n = 6). Three patients died

Table 3. Onset of HI or TI by Treatment Cycle

	AZA 5-2-2				AZA 5-2-5				AZA 5			
	Any HI (n = 22)		RBC TI (n = 12)		Any HI (n = 23)		RBC TI (n = 12)		Any HI (n = 28)		RBC TI (n = 16)	
Cycle No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	9	41	6	50	6	26	4	33	15	54	9	56
2	9	41	5	42	7	30	5	42	10	36	3	19
3	1	5	0		7	30	3	25	2	7	1	6
4	0		1	8	2	9	0		1	4	2	13
5*	2	9	0		1	4	0		0		1	6
6*	1	5	0		0		0		0		0	

Abbreviations: HI, hematologic improvement; TI, transfusion independence; AZA 5-2-2, 75 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 75 mg/m^2/d for 2 days; AZA 5-2-5, 50 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 50 mg/m^2/d for 5 days; AZA 5, 75 mg/m^2/d subcutaneously for 5 days.
*In these patients, HI and TI (by definition, maintained for 2 months) were confirmed after the first 6 cycles of treatment.

Table 4. Selected Grade 3 or 4 Adverse Events

Event	AZA 5-2-2 (n = 50)		AZA 5-2-5 (n = 48)		AZA 5 (n = 50)		Total (N = 148)	
	No.	%	No.	%	No.	%	No.	%
≥ 1 grade 3 or 4 adverse event	42	84	37	77	29	58	108	73
Hematologic disorders	33	66	24	50	17	34	74	50
Anemia	12	24	7	15	5	10	24	16
Febrile neutropenia	4	8	4	8	1	2	9	6
Leukopenia	7	14	4	8	4	8	15	10
Neutropenia	21	42	15	31	11	22	47	32
Thrombocytopenia	13	26	7	15	6	12	26	18
Infections	11	22	14	29	5	10	30	20
Candida sepsis	0		0		1	2	1	1
Cellulitis	1	2	1	2	1	2	3	2
Pneumonia	0		4	8	1	2	5	3
Urinary tract infection	0		3	6	0		3	2

Abbreviations: AZA 5-2-2, 75 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 75 mg/m^2/d for 2 days; AZA 5-2-5, 50 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 50 mg/m^2/d for 5 days; AZA 5, 75 mg/m^2/d subcutaneously for 5 days.

during the treatment period (one patient in each dosing arm). One death (5-2-5 treatment arm) was considered to be possibly related to study treatment and was due to septic shock and neutropenia in a patient with baseline bilineage cytopenias and an ECOG status of 3. The patient had received two cycles of azacitidine treatment.

DISCUSSION

Transfusion dependence exerts a detrimental effect on survival and diminishes patients' health-related QOL.[11] Therefore, achieving transfusion independence may be especially meaningful for MDS patients. In this study, approximately 55% of all patients, including FAB-defined lower-risk patients, with baseline RBC transfusion dependence became transfusion independent.

The transfusion independence rates in this study compare favorably with those of other MDS treatments. Two trials of lenalidomide in lower-risk MDS patients (International Prognostic Scoring System low or intermediate [Int]-1) have reported a 26% transfusion-independence rate in patients without chromosome 5q31 deletion and 67% in patients with chromosome 5q31 deletion.[12,13] In addition, a trial of decitabine in MDS patients (69% International Prognostic Scoring System Int-2 or high; 31% Int-1) reported a transfusion independence rate of 17%, all in patients with complete response or partial response.[14]

Table 5. Frequency of Grade 3 and 4 Hematologic Adverse Events of Interest by Cycle

Regimen	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
AZA 5-2-2												
Total No. of patients/cycle	50		46		44		37		31		29	
Anemia	10	20	4	9	1	2	2	5	0		1	3
Leukopenia	5	10	0		0		1	3	1	3	0	
Neutropenia	12	24	8	17	3	7	3	8	2	7	1	3
Thrombocytopenia	9	18	3	7	1	2	1	3	0		0	
AZA 5-2-5												
Total No. of patients/cycle	48		44		40		36		34		31	
Anemia	5	10	3	7	1	3	0		0		1	3
Leukopenia	3	6	1	2	1	3	0		0		0	
Neutropenia	8	17	1	2	3	8	0		2	6	4	13
Thrombocytopenia	5	10	3	7	2	5	0		0		0	
AZA 5												
Total No. of patients/cycle	50		49		48		44		43		37	
Anemia	2	4	3	6	1	2	1	2	0		1	3
Leukopenia	4	8	1	2	0		0		0		0	
Neutropenia	9	18	0		2	4	2	5	0		0	
Thrombocytopenia	4	8	2	4	1	2	2	5	1	2	0	

Abbreviations: AZA 5-2-2, 75 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 75 mg/m^2/d for 2 days; AZA 5-2-5, 50 mg/m^2/d subcutaneously for 5 days, followed by 2 days no treatment, then 50 mg/m^2/d for 5 days; AZA 5, 75 mg/m^2/d subcutaneously for 5 days.

In this study, the onset of transfusion independence and hematologic improvement was relatively rapid in all three dosing arms, occurring within the first two cycles in the majority of patients who achieved these responses. Onset of HI and transfusion independence in the 5-2-5 arm was somewhat delayed relative to the other two dosing arms, however, possibly due to this regimen's delivery of lower daily doses of azacitidine over a longer period. Nevertheless, by cycle 3, 60% of patients in this dosing arm, who achieved hematologic improvement, had experienced onset of this response. Interestingly, the presence or absence of baseline thrombocytopenia had no effect on the likelihood of achieving RBC transfusion independence in the AZA 5-2-5 dose group. In contrast, patients in the AZA 5-2-2 and AZA 5 dose groups did better if they were not thrombocytopenic at baseline. This finding suggests that prolonged exposure to a lower daily dose of azacitidine may benefit patients with multiple cytopenias at baseline. Although patient numbers in this analysis were small and this finding bears further scrutiny in a larger patient sample, it could have implications for an oral azacitidine formulation (currently under investigation[15]), which would also allow administration of lower azacitidine doses over a longer period.

Data suggest prolonged exposure to lower doses of a demethylating agent may increase or sustain response rates.[16] The continued duration of RBC transfusion independence in patients with baseline dependence observed in our results suggest a maintenance of treatment effect. The 12-month maintenance phase of this trial is ongoing, and continuing patients were transitioned to AZA 5 (75 mg/m^2/d SC for 5 days) repeated every 28 days or every 42 days. Results of this maintenance phase will further clarify the durability of hematologic responses with continued azacitidine treatment at lower cumulative drug levels per cycle.

In the three alternative dosing regimens, continued azacitidine therapy appears to be warranted because, as presented in Table 3, some patients achieved hematologic improvement and transfusion independence during later cycles. Azacitidine dosing for a median of 9 cycles (75 mg/m^2/d SC for 7 days every 28 days) has been associated with a significant survival benefit in higher-risk MDS patients in the recently reported international, multicenter, randomized, open-label AZA-001 trial.[2] Although overall survival was not an end point of this trial, further study is needed to elucidate whether survival benefits in higher-risk MDS patients are also conferred to lower-risk MDS patients receiving either 75 mg/m^2/d SC for 7 days or an alternative azacitidine dosing schedule. Because transfusion requirements increase morbidity and mortality in MDS patients,[11] a drug that reduces transfusion requirements in lower-risk patients may extend survival.

Though a community-based study has the advantage of providing real world clinical information, it also has limitations and this setting does not lend itself to rigid protocol requirements. For example, while cytogenetic data would have been informative, obtaining serial bone marrow samples from these patients was not feasible. Not having cytogenetic data prevented collection of International Prognostic Scoring System information, which could have better characterized this patient population.

The three azacitidine alternative dosing regimens were generally well tolerated and similar to that observed with the approved azacitidine dosing regimen. The majority of grade 3 and 4 hematologic AEs were reported during early treatment cycles suggesting that patient tolerance to azacitidine increases as treatment continues.

In this study of primarily lower-risk MDS patients, the benefits of treatment on transfusion independence and hematologic improvement were similar among the three alternative dosing groups. However, results suggest that the AZA 5 dosing regimen may be better tolerated, with a more convenient dosing schedule than the other two alternative dosing regimens.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Heidi J. McIntyre, Celgene (C); Indra J. Fernando, Celgene (C); Jay T. Backstrom, Celgene (C); C.L. Beach, Celgene (C) **Consultant or Advisory Role:** Roger M. Lyons, Pharmion (C) **Stock Ownership:** Heidi J. McIntyre, Pharmion; Indra J. Fernando, Celgene; Jay T. Backstrom, Celgene; C.L. Beach, Celgene **Honoraria:** Roger M. Lyons, Pharmion; Thomas M. Cosgriff, Pharmion; Allen L. Cohn, BMS, Amgen **Research Funding:** Roger M. Lyons, Pharmion; Sanjiv S. Modi, Pharmion; John D. Hainsworth, Pharmion **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

Linda Lintz, BA, study management; EMB Statistical Solutions, statistical support, PRA International, study management; Sheila Owens, BS, editorial assistance; Neil Malone, MA, editorial assistance; and the Azacitidine Alternative Dosing Study Investigators: Thomas Anderson, MD, Bedford, TX; Barry Brooks, MD, Dallas, TX; David Dong, MD, PhD, Seattle, WA; David Loesch, MD, Indianapolis, IN; Jose Lopez, MD, Fredericksburg, TX; Robert Raju, MD, Kettering, OH; Robert Randolph, MD, Burien, WA; Gerald Robbins, MD, New Port Richey, FL; Robert Ruxer, MD, Fort Worth, TX; Joseph Catlett, MD, Washington, DC; Anas Al-Janadi, MD, Lansing, MI; David Headley, DO, Colorado Springs, CO; Kelly McCaul, MD, Sioux Falls, SD; Dorothy Park, MD, Beverly Hills, CA; James Gerstner, MD, Peoria, IL; Richard Conklin, MD, Aberbeen, SD; Carlos Alemany, MD, Ocoee, FL; John Eckardt, MD, St. Louis, MO. We thank Barry Skikne, MD, for review of the pathology reports.