

FDA Drug Approval Summary: Azacitidine (5-azacytidine, Vidaza™) for Injectable Suspension

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Key Words. Azacitidine · Vidaza™ · Myelodysplastic syndromes · Refractory Anemia · Leukemia

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe indication and rationale for using azacitidine.
2. Discuss the relative effectiveness of azacitidine.
3. Identify the limitations of treatment with azacitidine.

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ABSTRACT

On May 19, 2004, azacitidine (5-azacytidine; Vidaza™; Pharmion Corporation, Boulder, CO, <http://www.pharmion.com>) for injectable suspension received regular approval by the U.S. Food and Drug Administration (FDA) for the treatment of all subtypes of myelodysplastic syndrome (MDS). This report summarizes the basis for this approval. Effectiveness was demonstrated in one randomized, controlled trial comparing azacitidine administered s.c. with best supportive care (observation group) and in two single-arm studies, one in which azacitidine was administered s.c. and in the other in which it was administered i.v. The dose of azacitidine, 75 mg/m²/day for 7 days every 28 days, was the same in all three studies. In the randomized trial, study participants were well matched with respect to age, sex, race,

performance status, MDS subtype, and use of transfusion during the 3 months before study entry. Patients in the observation arm were permitted by protocol to cross over to azacitidine treatment if their disease progressed according to prespecified criteria. During the course of the study, more than half of the patients in the observation arm did cross over to the azacitidine treatment arm. The primary efficacy end point was the overall response rate. Response consisted of complete or partial normalization of blood cell counts and of bone marrow morphology. The response rate in the azacitidine arm was about 16%; there were no responses in the observation arm. The response rates in the two single-arm studies were similar (13% and 19%). The responses were sustained, with median durations of 11 months

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and 17 months respectively. Responding patients who were transfusion dependent at study entry lost the need for transfusions. In addition, about 19% of patients had less than partial responses (termed improvement), and two-thirds of them became transfusion independent. Common adverse events associated with azacitidine treatment were gastrointestinal (nausea, vomiting, diarrhea, constipation, and anorexia), hematologic (neutropenia, thrombocytopenia), fevers, rigors, ecchymoses, petechiae, injection site events, arthralgia, headache, and dizziness. Liver function abnormalities

occurred in 16% of patients with intercurrent hepatobiliary disorders and in two patients with previously diagnosed liver cirrhosis. Renal failure occurred in patients during sepsis and hypotension. There were no deaths attributed to azacitidine. Azacitidine, the first drug approved by the U.S. FDA for MDS, has a favorable safety profile and provides a clinical benefit of eliminating transfusion dependence and complete or partial normalization of blood counts and bone marrow blast percentages in responding patients. *The Oncologist* 2005;10:176–182

INTRODUCTION

Azacitidine (5-azacytidine, Vidaza™; Pharmion Corporation, Boulder, CO, <http://www.pharmion.com>) is an analogue of the naturally occurring pyrimidine nucleoside cytidine (Fig. 1). Azacitidine is thought to have two main mechanisms of antineoplastic action—cytotoxicity, resulting from incorporation into RNA and DNA, and DNA hypomethylation, restoring normal growth control and differentiation in hematopoietic cells [1]. Induction of DNA hypomethylation appears to require lower azacitidine doses than does cytotoxicity, as the concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not suppress DNA synthesis [2].

Upon uptake by cells, azacitidine is phosphorylated to 5-azacytidine monophosphate by uridine-cytidine kinase and

then to diphosphate and triphosphate by pyrimidine monophosphate and diphosphate kinases, respectively. 5-Azacitidine triphosphate is incorporated into RNA, disrupting nuclear and cytoplasmic RNA metabolism and inhibiting protein synthesis [2]. 5-Azacytidine diphosphate is reduced by ribonucleotide reductase to 5-aza-deoxycytidine diphosphate, which is then phosphorylated by nucleoside diphosphate kinases to 5-azadeoxycytidine triphosphate, which is incorporated into DNA. As a result, DNA synthesis is inhibited. Azacitidine is most toxic during the S-phase of the cell cycle, but the predominant mechanism of cytotoxicity has not been established [3, 4].

Azacitidine inhibits methylation of replicating DNA by stoichiometric binding with DNA methyltransferase 1, resulting in DNA hypomethylation [1, 5]. DNA hypermethylation at the CpG islands has been described in myelodysplastic syndrome (MDS) [6], acute myelogenous leukemia (AML) [7], and other malignancies.

Azacitidine is rapidly absorbed after s.c. administration. Maximum plasma concentrations occur 30 minutes after s.c. administration and 11 minutes after a 10-minute i.v. infusion. The mean plasma concentration following i.v. infusion is approximately fourfold higher than that following s.c. administration. The bioavailability after s.c. administration is 89% of that after i.v. administration, as determined by the area under the concentration-time curve (AUC). The plasma half-life is approximately 22 minutes after i.v. infusion and about 41 minutes after s.c. administration. The drug is widely distributed in tissues; the mean volume of distribution after i.v. administration is about 76 liters, which is greater than the total body water volume (42 liters).

Azacitidine undergoes spontaneous hydrolysis in aqueous solutions, as well as rapid deamination by cytidine deaminase and subsequent degradation [8]. Human pharmacokinetic data are derived from studies of [¹⁴C]-labeled drug, not from determinations of azacitidine metabolite concentrations. Urinary excretion is the main elimination route of azacitidine and its metabolites (85% after i.v. dosing and about 50% after s.c. administration). Less than 1% of the radiolabeled azacitidine

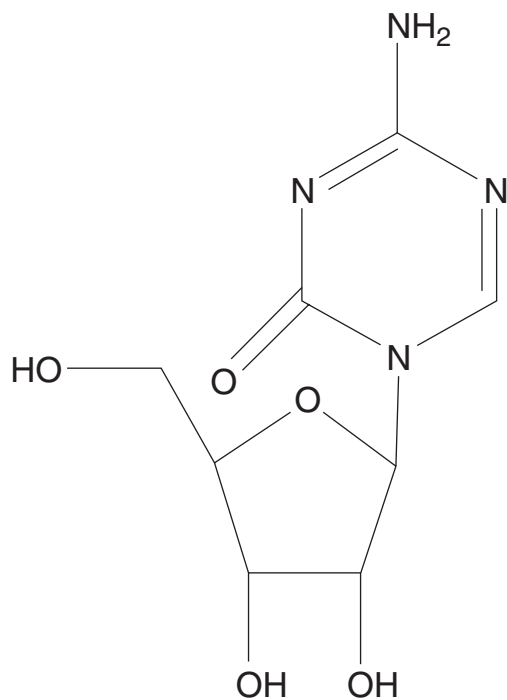


Figure 1. Molecular structure of azacitidine (5-azacytidine).

dose is excreted in the feces. The mean elimination half-life of radiolabeled azacitidine is about 4 hours after either i.v. or s.c. administration. Azacitidine, like other pyrimidine or purine nucleosides, is unlikely to be a substrate, an inhibitor, or an inducer of cytochrome P450 enzymes, but the available information is incomplete. Interactions with other drugs have not been tested.

Azacitidine has been used primarily in the treatment of AML [9] and MDS through the National Cancer Institute (NCI) expanded-access program to investigational drugs and in studies sponsored by the NCI Cancer Therapy Evaluation Program.

The submitted new drug application (NDA) sought approval of azacitidine for the treatment of patients with all five subtypes (French-American-British [FAB] classification) of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL) [10]. No therapeutic agents were approved for MDS prior to azacitidine.

CLINICAL STUDIES

In the NDA, the sponsor submitted the results of three clinical studies, originally conducted by the Cancer and Leukemia Group B (CALGB) [11–13]. Two studies were single-arm trials; the third study had a control arm. The controlled study was a randomized, open-label, phase III, multicenter trial, in which 99 patients were randomized to azacitidine treatment and 92 were randomized to best supportive care (observation). Azacitidine was administered s.c. at a starting dose of 75 mg/m²/day for 7 days in each 28-day cycle. Dose adjustments were prespecified. The dose was to be decreased for hematological toxicities or decreased renal function and increased for lack of beneficial effect without toxicity. The protocol did not permit the use of growth factors.

Study participants included patients with all five MDS subtypes, by the FAB classification listed above. Patients with RA or RARS were eligible for the trial only if they had neutropenia or thrombocytopenia or required transfusions. Randomization criteria included stratification by MDS subtype. The initial diagnosis at the study site was adjudicated by the CALGB central laboratory. Patients with adjudicated diagnoses of AML at study entry were excluded from the analysis of efficacy end points, but they were included in the intent-to-treat (ITT) analyses of all patients randomized. Observation arm patients were permitted to cross over to treatment with azacitidine if they met prespecified criteria of disease progression (increasing cytopenias and transfusion needs, major hemorrhages requiring platelet transfusions,

clinical infections with neutropenia requiring antibiotics) at prespecified crossover time points (after two or four 28-day cycles). About 55% of patients in the observation arm crossed over to the azacitidine treatment arm.

Patient demographics and disease characteristics at study entry are summarized in Table 1. Patients in the azacitidine and the observation arms were well matched by gender, race, age, MDS subtype, and transfusion history. The study population was typical of MDS patients. The male:female patient

Table 1. Patient demographics and disease characteristics

Characteristic	Azacitidine n = 99 (%)	Observation n = 92 (%)
Age group		
18–64 years	36 (36)	33 (36)
65–74 years	39 (39)	33 (36)
75 years and older	24 (24)	25 (27)
Sex		
Male	72 (73)	60 (65)
Female	27 (27)	32 (35)
Race		
Caucasian	93 (94)	85 (92)
African American	1 (1)	1 (1)
Asian	2 (2)	1 (1)
Hispanic	3 (3)	5 (5)
Performance status		
0 Normal	35 (35)	26 (28)
1 Fatigue	34 (34)	39 (42)
2 Impaired	8 (8)	6 (7)
3 Bed rest	1 (1)	0
4 Not recorded	21 (21)	21 (23)
MDS subtypes and AML as adjudicated by the central laboratory		
RA	21 (21)	18 (20)
RARS	6 (6)	5 (5)
RAEB	38 (38)	39 (42)
RAEB-T	16 (16)	14 (15)
CMMoL	8 (8)	7 (8)
AML	10 (10)	9 (10)
Use of transfusion products during 3 months before study entry		
Any product	70 (71)	59 (64)
RBC	66 (67)	55 (60)
Platelets	15 (15)	12 (13)
Plasma/hetastarch	1 (1)	1 (1)
Unknown	2 (2)	2 (2)

Abbreviations: AML = acute myelogenous leukemia; CMMoL = chronic myelomonocytic leukemia; MDS = myelodysplastic syndrome; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts.

Table 2. Response criteria**Complete response**

Peripheral blood: Normal CBC, absence of myeloblasts.

Bone marrow: Less than 5% myeloblasts.

Duration: At least 4 weeks.

Partial response

Peripheral blood: Greater than 50% restoration in the deficits from normal levels of baseline hemoglobin, WBC, and platelets, and absence of myeloblasts. For CMMoL, if WBC was elevated at baseline, a 75% reduction in the excess count above normal.

Bone marrow: Greater than 50% decrease in myeloblasts from baseline in patients with RAEB, RAEB-T, and CMMoL. Decrease in myeloblasts is not applicable for patients with RA and RARS.

Duration: At least 4 weeks.

Abbreviations: CMMoL = chronic myelomonocytic leukemia; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts.

ratio was about 3:1, and the average age was >67 years. Patients who were adjudicated by the central laboratory to have had AML at study entry were equally distributed between the two arms.

The primary efficacy end point was the overall response rate (complete response [CR] plus partial response [PR] rates). The response criteria are shown in Table 2. The overall response rate for all randomized patients in the azacitidine treatment arm, excluding those adjudicated to have AML, was 15.7%; no patient had a response in the observation arm. The overall response rate for all patients randomized to azacitidine (ITT population), including those adjudicated to have had AML at study entry, was 16.2%. The overall response rate in patients randomized to azacitidine, excluding patients with adjudicated diagnoses of AML at study entry and patients with major protocol violations (hematopoietic growth factor or corticosteroid use), was 20.4%. Each of

these differences between the azacitidine treatment group and the observation group was highly statistically significant. In the crossover from the observation to the azacitidine treatment group, excluding patients with adjudicated diagnoses of AML, the overall response rate to azacitidine treatment was 12.8%; 11.8% in the ITT population had responses. These response data are summarized in Table 3.

Similar response rates were reported in the two single-arm trials. In one trial, 72 patients with RAEB, RAEB-T, and CMMoL were treated with the above azacitidine dosage regimen administered s.c. On review, 17 of those patients were adjudicated to have had AML at study entry. The response rate was 12.7% excluding patients with adjudicated diagnoses of AML and 13.9% including all patients. In the second study, 48 patients with RAEB and RAEB-T were treated with the above azacitidine dosage regimen, administered i.v. instead of s.c. The response rate was 19.1% excluding patients

Table 3. Response rates to azacitidine in the randomized trial

Response	Azacitidine	Observation before crossover	Observation without crossover	Azacitidine after crossover
All randomized patients (ITT population)				
CR + PR	16/99 (16.2%)	0/92 (0%)	0/41 (0%)	6/51 (11.8%)
CR	6 (6.1%)	0	0	3 (5.9%)
PR	10 (10.1%)	0	0	3 (5.9%)
Excluding patients with adjudicated diagnoses of AML at study entry				
CR + PR	14/89 (15.7%)	0/83 (0%)	0/36 (0%)	6/47 (12.8%)
CR	5 (5.6%)	0	0	3 (6.4%)
PR	9 (10.1%)	0	0	3 (6.4%)
Excluding patients with adjudicated diagnoses of AML at study entry or with major protocol violations				
CR + PR	11/54 (20.4%)	0/48 (0%)	0/22 (0%)	5/26 (19.2%)
CR	5 (9.3%)	0	0	3 (11.5%)
PR	6 (11.1%)	0	0	2 (7.7%)

Abbreviations: AML = acute myelogenous leukemia; CR = complete response; ITT = intent-to-treat; PR = partial response.

Table 4. Response rates in azacitidine-treated patients in all three studies

Response	CALGB 9221 Azacitidine arm	CALGB 9221 Azacitidine after crossover	CALGB 8921	CALGB 8421	Total
All randomized patients (ITT population)					
CR + PR	16/99 (16.2%)	6/51 (11.8%)	10/72 (13.9%)	9/48 (18.8%)	41/270 (15.2%)
CR	6	3	4	3	16 (5.9%)
PR	10	3	6	6	25 (9.3%)
Excluding patients with adjudicated diagnoses of AML at study entry					
CR + PR	14/89 (15.7%)	6/47 (12.8%)	7/55 (12.7%)	9/47 (19.1%)	36/238 (15.1%)
CR	5	3	3	3	14 (5.9%)
PR	9	3	4	6	22 (9.2%)

Abbreviations: AML = acute myelogenous leukemia; CALGB = Cancer and Leukemia Group B; CR = complete response; ITT = intent-to-treat; PR = partial response.

with adjudicated diagnoses of AML at study entry and 18.8% including all patients. Response rates from all three trials are summarized in Table 4.

Exploratory analyses showed that response rates were similar in males and females, all age groups, and all MDS subtypes. Patients adjudicated to have had AML at study entry had about the same response rate as MDS patients (17.9%).

The most evident benefit of a response (CR or PR) was in transfusion-dependent patients. The patients who were dependent on RBC and/or platelet transfusions at study entry lost the need for transfusions during the duration of CR or PR. The responses were long lasting. The median response duration could only be estimated as >330 days, since most (75%) of the responding patients were still in response at treatment completion. Likewise, the mean response duration could only be estimated as >512 days.

Delay in progression to AML could not be established as a treatment benefit, despite the persistence of decreased bone marrow blast percentages during CRs and PRs in the azacitidine treatment arm, because crossover of observation arm patients to the azacitidine treatment arm rendered the two arms no longer comparable with respect to percentages of patients with each MDS subtype.

A survival benefit of azacitidine treatment could not be established because of crossover of observation arm patients and because the trial was insufficiently powered to detect a survival benefit.

Initial changes indicating the beginning of a CR or PR to azacitidine treatment, such as a decrease in blast count or an increase in platelet count, hemoglobin, or WBC were observed by the fifth treatment cycle in greater than 90% of patients. Maximal responses (CR or PR) took longer to develop.

In addition to CRs and PRs, lesser responses not meeting the CR or PR criteria, termed improvement (less than 50% restoration of normal blood counts and less than 50%

decreases in RBC or platelet transfusion requirements), occurred in about 24% of azacitidine-treated patients, and two-thirds of them became transfusion independent. About 6% of observation arm patients achieved the criteria for improvement by increased platelet or neutrophil counts; none of them became RBC transfusion independent. In the three studies, about 19% of azacitidine-treated patients met the criteria for improvement. The median duration of improvement (195 days) was shorter than that of CR or PR.

The treatment strategy of starting azacitidine at dose of 75 mg/m² and adjusting it during subsequent cycles was effective. About 46% of the patients with best responses of CRs or PRs received 75 mg/m² for the majority of cycles before achieving a response, 37% received less than 75 mg/m², and 17% received more than 100 mg/m².

SAFETY

Safety evaluation of azacitidine was confounded by the pathophysiology of MDS, which overlaps, to a great extent, the most common toxicities of azacitidine. Serious adverse events (SAEs) occurred in about 60% of azacitidine-treated patients and in about 36% of observation-arm patients. The most common SAEs resulting in hospitalization in both arms were thrombocytopenia, febrile neutropenia, fever, and pneumonia. No deaths were attributed to azacitidine. Virtually all (99%) azacitidine-treated patients and over 96% of the observation-arm patients reported adverse events. Gastrointestinal events (nausea, vomiting, diarrhea, constipation, and anorexia), hematologic events (neutropenia, fever, rigors, ecchymoses, and petechiae), injection site events, arthralgia, cough, dyspnea, headache, weakness, dizziness, and insomnia were more commonly reported by patients treated with azacitidine than by patients in the observation arm. However, the duration of exposure was almost twice as long in the azacitidine-treatment arm as in the observation arm in the controlled trial (mean

duration of 11.4 months in the azacitidine arm versus 6.1 months in the observation arm).

The highest proportion of patients reporting adverse events occurred in the first two cycles of therapy; this proportion decreased in subsequent cycles with the use of appropriate concomitant medications. The most common reasons for azacitidine discontinuation, dose reduction, or therapy interruption (besides the main reason of lack of effectiveness) were neutropenia, leukopenia, and thrombocytopenia. The main indications for concomitant medications to treat adverse events were gastrointestinal symptoms and fever in the azacitidine-treated patients and fever, hypokalemia, and nausea in observation-arm patients.

Blood cell counts were low at baseline in all patients and decreased further in patients treated with azacitidine. Blood cell counts increased in patients who showed responses or improvements. Patients with hepatic or renal impairment were excluded from the clinical trials. Liver function abnormalities occurred, for the most part, in patients with intercurrent illnesses, including hepatobiliary disorders. More severe abnormalities developed in patients with previously diagnosed liver cirrhosis. In previous literature reports, hepatic coma occurred in patients with extensive metastases to the liver [9]. Renal failure was reported in patients during periods of sepsis and hypotension.

Some adverse events, such as vomiting, diarrhea, headache, injection site erythema, arthralgia, tachycardia, and postprocedural hemorrhage, were reported more frequently by females than males. The proportion of patients with adverse events was not greater in older age groups.

COMMENTS AND CONCLUSIONS

Most MDS patients die from bleeding or infection and from progression to AML. Prior to this approval, no single agent was approved for the treatment of MDS. The mainstay of therapy has been supportive care, including RBC and platelet

transfusions and treatment with hematopoietic growth factors, if serum erythropoietin levels were decreased. Because of their advanced age, most MDS patients are not candidates for more aggressive therapy, such as hematopoietic stem cell transplantation or high-dose chemotherapy.

As described in the clinical trials in this NDA, treatment with azacitidine resulted in consistent responses in about 16% (11.8%–18.8%) of patients. There were no responses in patients who received only supportive care. The statistical significance of the response rate in the controlled trial persisted after patients with adjudicated diagnoses of AML and patients with major protocol violations (which consisted mainly of pretransfusion steroid injections) were excluded. The response rate was reproducible among the three trials and is consistent with other published reports [14–18].

The responses (CRs and PRs) had the direct clinical benefit of transfusion-dependent patients losing the need for RBC and/or platelet transfusions for the duration of the response. In addition, about 19% of patients in the three studies whose responses did not meet the CR or PR response criteria also had clinical benefit.

Clinical benefits of the decreased incidence of bleeding or infections requiring antibiotics could not be established because of low incidences of these events during the trial period. Likewise, survival benefit or delay in progression to AML could not be established because crossover of control patients to the active treatment arm confounded these time-to-event end points.

In summary, azacitidine is an active agent that provides a benefit to patients with MDS. Its use is accompanied by adverse events that appear to be relatively easily controlled in most patients by appropriate medications. It is a relatively safe drug for a malignant or premalignant condition such as MDS for which there previously were no approved drugs. Azacitidine was approved because the benefits of its use clearly outweigh the accompanying risks.

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