Approval Summary: Azacitidine for Treatment of Myelodysplastic Syndrome Subtypes


Abstract
Purpose: This article summarizes data submitted to the U.S. Food and Drug Administration for marketing approval of azacitidine as injectable suspension (Vidaza, Pharmion Corporation, Boulder, CO) for treatment of patients with myelodysplastic syndrome.

Experimental Design: In one phase 3 controlled trial, 191 study subjects were randomized to treatment with azacitidine or to observation; an additional 120 patients were treated with azacitidine in two phase 2 single arm studies. The primary efficacy end point was the overall response rate, defined as complete or partial normalization of peripheral blood counts and bone marrow blast percentages for at least 4 weeks.

Results: In the controlled trial, the overall response rate was 15.7% in the azacitidine treatment group; there were no responders in the observation group (P < 0.0001). Response rates were similar in the two single arm studies. During response patients stopped being red cell or platelet transfusion dependent. Median duration of responses was at least 9 months. An additional 19% of azacitidine-treated patients had less than partial responses, most becoming transfusion independent. The most common adverse events attributed to azacitidine were gastrointestinal, hematologic, local (injection site), and constitutional. There were no azacitidine-related deaths.

Conclusions: On May 19, 2004 the U.S. Food and Drug Administration approved azacitidine as injectable suspension for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia. Full prescribing information is available at http://www.fda.gov/cder/foi/label/2004/050794lbl.pdf. Azacitidine is the first agent approved for treatment of myelodysplastic syndrome.
hypermethylation of the p15INK4B gene in MDS (9, 10) suggested that azacitidine may be effective in the treatment of MDS.

Azacitidine is also a cytotoxic agent in proliferating cells, but the concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not suppress synthesis of replicating DNA (11).

**Regulatory history**

The original Investigational New Drug application for azacitidine was submitted by the National Cancer Institute in 1971 for various antineoplastic indications. By 1976 more than 800 patients with AML, chronic myelogenous leukemia, and various solid tumors had been treated with a variety of azacitidine regimens (12). Patients with severe β-thalassemia or with homozygous sickle cell disease treated with lower doses of azacitidine showed an increased fetal hemoglobin synthesis (13, 14), suggesting an effect of azacitidine on cell differentiation.

Three multicenter Cancer and Leukemia Group B (CALGB) trials (15–17) and seven single center trials (18–24) carried out between 1985 and 2002 documented azacitidine activity in MDS patients. Pharmion Corporation submitted a New Drug Application based on the data of the three CALGB trials.

**Chemistry**

The active ingredient of Vidaza (Pharmion Corporation, Boulder, CO) is azacitidine (5-azacytidine), an analogue of cytidine. The chemical structures of azacitidine and of cytidine are shown in Fig. 1. Azacitidine differs from cytidine in containing a nitrogen atom in the 5 position of the heterocyclic ring instead of a carbon atom. The chemical name of azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2-(1H)-one, the empirical formula of azacitidine is C₈H₁₂N₄O₅, and the molecular weight is 244.

Azacitidine is a white to off-white solid that is stable at 25°C, not light sensitive, sparingly soluble in water, and unstable when reconstituted in aqueous solution. Hydrolytic degradation at 25°C to 30°C results in a 21% to 36% loss over 8 hours; at 5°C the loss is 2% to 3% over 8 hours.

**Toxicology**

Acute and repeated dose toxicology studies have identified bone marrow, liver, kidney, and lymphoid tissues as the target organs and tissues. Mortality was due to bone marrow failure. Azacitidine was found to be mutagenic (25), carcinogenic (25), and embryotoxic when females were dosed during gestation or treated males were mated to untreated females (27, 28). Teratogenicity induced by azacitidine included central nervous system, limb, and skeletal anomalies and other fetal abnormalities (29).

**Clinical pharmacology**

Azacitidine is rapidly absorbed following s.c. administration. Maximum plasma concentration is attained in about 30 minutes. Azacitidine is widely distributed, and is rapidly eliminated, with a mean plasma half-life of about 41 minutes.

Metabolism of azacitidine involves deamination by cytidine deaminase followed by opening of the ring structure (30). Azacitidine and its metabolites are primarily excreted by the kidneys.

The effects of intrinsic factors such as age, gender, race, renal impairment, or hepatic impairment on the pharmacokinetics of azacitidine have not been studied. In vivo drug-drug interaction studies have not been conducted. In vitro studies in cultured human hepatocytes indicate that azacitidine at a clinically relevant concentrations is not an inducer of CYP 1A2, 2C19, or 3A4/5.¹

**Clinical trials**

**Study design.** The controlled trial (CALGB 9221) was a multicenter, randomized, open-label trial designed to compare the safety and efficacy of s.c. administered azacitidine (azacitidine group) with supportive care (observation group) in patients with any of the five subtypes of MDS. RA and RARS patients were included if they required packed RBC transfusions for ≥3 months for symptomatic anemia, had platelet counts of <10⁹/L or significant hemorrhage, required platelet transfusions, or were neutropenic (absolute neutrophil count <1 × 10⁹/L) with infections requiring treatment with antibiotics. Patients randomized to the observation group were allowed to cross over to azacitidine treatment after two to four cycles of therapy if they met prespecified criteria of disease progression. Blocked randomization included stratification by the five MDS subtypes. Patients with hepatic or renal impairment were excluded from the trials.

The two supporting studies were open-label, multicenter single arm studies, one treating patients with azacitidine administered s.c. (CALGB 8921), the other i.v. (CALGB 8421).

**Treatment.** The starting azacitidine dose, administered s.c. or i.v., was 75 mg/m² for 7 days every 28 days. The dose was to be decreased for hematologic toxicity and renal function abnormalities, and increased for lack of efficacy in absence of toxicity. Patients with no response after four azacitidine treatment cycles were to be taken off the study.

**Efficacy end points.** Overall response rate [complete response (CR) + partial response (PR)] was the primary efficacy end point. CR was defined as complete normalization of blood cell counts and bone marrow blast percentages for at least 4 weeks. PR was defined as ≥50% restoration in the deficit from normal levels of baseline blood cell counts, absence of blasts in peripheral blood,

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¹ Pharmion Corporation, unpublished data.
Randomized to the observation arm had major protocol arm and 9 in the observation arm). Thirty-four patients at study entry (there were 10 such subjects in the azacitidine subjects who were adjudicated to have had a diagnosis of AML rate in all azacitidine-treated subjects was 14.7%. The overall response rate in subjects who crossed over to azacitidine treatment was 16.2%; there were no responses among subjects who remained in observation arm without crossing over. The overall response rate in the intent-to-treat population was 18.8%. Exclusion of the one subject with baseline diagnosis of AML did not change the response rate (19.1%). Exclusion of subjects with AML and of subjects with protocol violations resulted in a response rate of 20.0%.

In summary (Table 2), the response rate among all 270 patients treated with azacitidine in the three trials was 15.2%. The response rate among 238 patients with MDS was 15.1%

Response rates were similar in subjects with all MDS subtypes and with AML (Table 3). Response rates were similar in both genders and across all age groups. There were 26 responders among 183 males (14.2%) and 15 responders among 87 females (17.2%). There were 15 responders among 100 patients less than 65 years of age (15.0%), 19 responders among 115 patients of ages 65 to 74 years (16.5%), and 7 responders among 55 patients of ages 75 years or more (12.7%). Racial or ethnic differences in response rates could not be detected because >95% of subjects were white. Response rates were not related to azacitidine dose.

CRs generally occurred after 5 to 15 cycles of therapy. PRs occurred after 1 to 21 cycles of therapy. During the period of CR or PR, patients who had been dependent on packed RBC and/or platelet transfusions became transfusion independent. Responses were generally long lasting: 75% of the responding patients were still in response at the completion of all three studies. In the controlled trial, the median duration of response was at least 330 days and the mean duration was at least 512 days. In the two single-arm trials, the median duration was at least 430 days in CALGB 8921 study and at least 281 days in CALGB 8421 study, with mean duration of at least 810 days in CALGB 8921 and of at least 512 days in CALGB 8421.

In addition to patients with CR or PR, about 19% of azacitidine-treated patients in the three trials had lesser responses termed “improvement” (defined as ≥50% restoration

| Table 1. Response rates to azacitidine in the controlled trial* |
|------------------|----------------|----------------|----------------|----------------|
| **Response**     | **Azacitidine** | **Observation before crossover** | **Observation without crossover** | **Azacitidine after crossover** |
| 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%)        |

* All randomized patients (intent-to-treat population).
in the deficit from normal in one or more peripheral blood cell lines or a ≥50% decrease in RBC or platelet transfusion requirements). About two thirds of transfusion-dependent patients became transfusion independent with improvement response. The median duration of improvement responses was 195 days. In the observation arm, 6% of patients met the criteria for improvement as a result of increases in platelet or neutrophil counts. All of these patients were anemic, but none of them had an increase in hemoglobin values.

Azacitidine treatment could not be shown to result in a survival benefit or in delay in progression to AML because of the crossover of observation arm patients to azacitidine treatment.

Safety. In the controlled trial, >95% patients in both groups reported treatment-associated adverse events. Azacitidine-treated subjects reported more frequently than observation arm subjects gastrointestinal events (nausea, vomiting, diarrhea, constipation, and anorexia), neutropenia, febrile neutropenia, thrombocytopenia, injection site events, arthralgia, dizziness, dyspnea, cough, and myalgia. Serious adverse events occurred more frequently in azacitidine-treated patients (60%) than in observation patients (36%). Serious adverse events most commonly resulting in hospitalization were thrombocytopenia, febrile neutropenia, fever, and pneumonia. There were no deaths attributed to azacitidine treatment. During the study periods, half of the deaths in the three trials were probably related to MDS and the other half were unrelated to MDS.

The most common reasons for azacitidine discontinuation, dose reduction, or therapy interruption were leukopenia, neutropenia, and thrombocytopenia. Patients who developed CR or PR first had further decreases in hematologic parameters. Most patients in both treatment arms received packed RBC and/or platelet transfusions and medications to treat adverse events. The frequency of adverse events decreased after the first two cycles of azacitidine therapy.

Liver function abnormalities, which coincided with intercurrent illnesses including hepatobiliary disorders, occurred in about 16% of azacitidine-treated subjects and in 8% of observation subjects. Three patients in the azacitidine arm developed hepatic impairment; two of them had been previously diagnosed with liver cirrhosis. Renal failure developed in five azacitidine arm patients and in one observation arm patient, in settings of sepsis, hypotension, heart failure, and diabetes mellitus.

Adverse events occurred at about the same frequency in males and females and in all age groups.

**Discussion**

The three CALGB trials were the largest trials of azacitidine in MDS to date, and the effects of azacitidine on CR + PR and transfusion requirements were reproducible. Although only one trial had a control group, it is clear that spontaneous remissions do not occur in MDS, so that the single arm studies are convincing with respect to response. Other single-arm trials of azacitidine in MDS with similar or higher efficacy have been reported in the literature (18–24). The clinical benefit of response to azacitidine treatment was shown in long-lasting increases in peripheral blood cell counts, which made transfusions unnecessary. Decreased bone marrow blast percentages were similarly long lasting. However, improvement in survival or delay in progression to AML could not be shown.

Azacitidine seems to be a relatively safe drug for a premalignant or malignant condition such as MDS, although adverse events were common. The most common adverse events were gastrointestinal, which were prevented or controlled with concomitant medications, and hematologic, which exacerbated the hematopoietic cytopenias characteristic of MDS. The latter finding is consistent with all published

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**Table 3. Response rates to azacitine in all three trials by in MDS subtypes and in AML**

<table>
<thead>
<tr>
<th>MDS subtypes and AML</th>
<th>CALGB 9221</th>
<th>CALGB 8921</th>
<th>CALGB 8421</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>7/35</td>
<td>—</td>
<td>—</td>
<td>7/35 (20.0%)</td>
</tr>
<tr>
<td>RARS</td>
<td>1/8</td>
<td>—</td>
<td>—</td>
<td>1/8 (12.5%)</td>
</tr>
<tr>
<td>RAEB</td>
<td>8/58</td>
<td>4/26</td>
<td>4/23</td>
<td>16/107 (15.5%)</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>2/23</td>
<td>2/20</td>
<td>5/24</td>
<td>9/67 (13.4%)</td>
</tr>
<tr>
<td>CMML</td>
<td>2/10</td>
<td>1/9</td>
<td>—</td>
<td>3/19 (15.8%)</td>
</tr>
<tr>
<td>AML</td>
<td>2/16</td>
<td>3/17</td>
<td>0/1</td>
<td>5/34 (14.7%)</td>
</tr>
</tbody>
</table>

*All randomized patients.
studies citing hematologic toxicity as dose limiting. No deaths were attributed to azacitidine in these studies. However, azacitidine was a possible or probable contributor to 21 deaths in cancer patients reported by National Cancer Institute. Most deaths were due to infections, neutropenia, and thrombocytopenia.

Hepatic and renal adverse events were rare, possibly because patients with hepatic or renal impairment were excluded from participation in these studies. Prior reports described hepatic coma developing in patients with hepatic metastases from solid tumors (12). Renal function abnormalities had been previously reported in patients treated with combination chemotherapy, some with preexisting renal impairment (12). Hence, caution is advisable in treating patients with hepatic or renal impairment.

The trial protocols specified that subjects should be dismissed from the trial if no response occurred after four cycles of therapy. Fifty of 270 patients (18.5%) in the azacitidine treatment groups in the three trials were discontinued for this reason. However, four cycles of therapy were too few to conclude a lack of efficacy for some patients. CR or PR took longer time to develop.

The CALGB protocols also specified that patients who achieved a CR were to be withdrawn from the study after three further cycles. Most of the CR patients followed this instruction; however, some CR and most PR patients continued to receive azacitidine until they were withdrawn from the study for other reasons. The instructions in the label state that treatment may be continued as long as the patient continues to benefit.

In summary, On May 19, 2004 the U.S. Food and Drug Administration approved azacitidine as injectable suspension (Vidaza) for treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T, and CMML. Azacitidine is the first agent approved for treatment of myelodysplastic syndrome. Full prescribing information is available at http://www.fda.gov/cder/foi/label/2004/050794lbl.pdf.

References

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