**National PBM Drug Monograph**

# Azacitidine (Vidaza™)

**May 2005**

**VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel**

## Executive Summary:

- Azacitidine is a pyrimidine analog believed to exert its effects through hypomethylation of DNA, restoring normal function to tumor suppressor genes, and through direct cytotoxicity of abnormal hematopoietic cells.
- It is indicated for patients with the following myelodysplastic disease subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia requiring IV antibiotics or thrombocytopenia with clinical hemorrhage requiring platelet transfusions or RBC transfusions for anemia), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.
- In a randomized trial compared to best supportive care, azacitidine produced better responses, delayed time to treatment failure, delayed transformation to acute myelogenous leukemia, increased QoL scores, and eliminated transfusion requirements in patients achieving a CR or PR.
- In patients who crossed over to azacitidine, a CR or PR was seen in 14% of patients.
- Overall survival showed a trend towards the azacitidine arm that was not statistically significant, although the results are confounded by the high number of best supportive care patients who crossed over to azacitidine therapy.
- Azacitidine is administered as a subcutaneous dose at 75mg/$m^2$ per day for 7 days, and repeated every 28 days.
- The majority of adverse events were GI (nausea, vomiting, diarrhea), myelosuppression (leukopenia, thrombocytopenia, neutropenia), and injection site reactions.
- Myelosuppression was generally reversible and blood counts returned to normal in many patients by the next treatment cycle. At a minimum, blood counts should be monitored before each treatment cycle.
- For patients with profound blood count nadirs, a dose reduction table is provided.
- Assessment of cytopenias is difficult because MDS causes cytopenias in some patients. For patients starting therapy with a cytopenia, a table is provided to assess nadir blood counts on a relative basis based on percentage decreased from baseline.
- Renal impairment, likely to occur in the elderly, may increase adverse events due to decreased excretion of azacitidine and its metabolites and should be monitored carefully with each treatment cycle.

## Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating azacitidine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

## Pharmacology/Pharmacokinetics[1,2,3]

Azacitidine is an analog of the pyrimidine nucleoside cytidine. It has two main mechanisms of action: 1) cytotoxicity from incorporation into RNA, inhibiting protein synthesis, and into DNA, inhibiting DNA synthesis and 2) inhibition of DNA methylation resulting in cell differentiation. Azacitidine was developed because of its antileukemic activity at high concentrations and its differentiation potential at low concentrations due to hypomethylation. Cytosine hypermethylation of genes plays a role in gene expression and is thought to be important in cell proliferation and maturation; it is frequently found in myelodysplastic syndrome (MDS), acute myelogenous leukemia, and other malignancies.

**Table #1 Azacitidine Pharmacokinetics**

| Parameter | Azacitidine |
|---|---|
| Metabolism | Spontaneous hydrolysis in aqueous solutions and rapid deamination by cytidine deaminase |
| Elimination | Primarily renal (85% after IV dose, 50% after subcutaneous dose); <1% excreted in feces |
| Half-life | After subcutaneous injection mean plasma half-life is 41 ±8 minutes; Mean elimination half-life is 4 hours for both IV and subcutaneous dose |
| Bioavailability | Bioavailability after subcutaneous injection compared to IV injection is 89% based on AUC ratio of least square means<br>Subcutaneous $AUC_{0\rightarrow\infty}$ ng•h/mL = 960.53 ± 458.06<br>Intravenous $AUC_{0\rightarrow\infty}$ ng•h/mL = 1044.26 ± 285.67 |

## FDA Approved Indication(s) and Off-label Uses

Azacitidine is approved for initial therapy in patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with 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.

Off-label uses: Acute Myelogenous Leukemia (AML)

## Current VA National Formulary Alternatives

Currently, there is no alternative therapeutic agent for treatment of MDS. Current treatment standards are primarily supportive care unless the patient is eligible for a stem cell bone marrow transplant.

## Dosage and Administration

Dosage in MDS: Starting dose of 75mg/$m^2$ subcutaneously daily for 7 days, repeat every 4 weeks. Patients should be premedicated with an antiemetic. About 50% of patients achieve control of nausea and vomiting with prochlorperazine, but use of an HT3 antagonist may be required.

If no benefit after 2 cycles and no toxicity other than nausea and vomiting, dose may be increased to 100mg/$m^2$

Cycles: a minimum of 4 cycles is recommended to evaluate response, however complete or partial responses may require more than 4 cycles. Treatment cycles are continued as long as there is benefit.

Dose Adjustments:

**Table #2: Dose Adjustment if Baseline (start of therapy) counts are: WBC≥3.0 X10$^9$/L, ANC ≥ 1.5 X10$^9$/L, and platelets ≥75 X 10$^9$/L Based on Nadir Counts**

| Nadir Counts | | % Dose in the Next Course |
|---|---|---|
| ANC (X10$^9$/L) | Platelets (X10$^9$/L) | |
| <0.5 | <25 | 50% |
| 0.5-1.5 | 25 – 50 | 67% |
| >1.5 | >50 | 100% |

**Table #3: Dose Adjustment if Baseline counts are: WBC <3.0 X10$^9$/L, ANC <1.5 X10$^9$/L, or platelets <75 X10$^9$/L Based on Nadir Counts and Bone Marrow Biopsy Cellularity at time of Nadir***

| **IF WBC or Platelet nadir % decrease in counts from baseline is:** | **AND Bone Marrow Biopsy Cellularity at Time of Nadir (%)** | | |
|---|---|---|---|
| | 30-60 | 15-30 | <15 |
| | **THEN % Dose in Next Course** | | |
| 50-75% | 100 | 50 | 33 |
| >75% | 75 | 50 | 33 |

*If there has been improvement in differentiation (% of mature granulocytes is higher and ANC is higher than at onset of course) at the start of the next cycle, give the same dose as before. If the nadir has occurred as defined in the table, start the next course at 28 days only if both the WBC and platelet counts are >25% above the nadir count and rising. If not, reevaluate counts every 7 days. If counts have not increased at least 25% by day 42, treat with 50% of the scheduled dose.

Dose Adjustment for Renal Function:

Serum bicarbonate levels <20mEq/L – Reduce dose by 50% on the next course

Unexplained Elevations of BUN or serum creatinine – delay next course until values return to normal or baseline then reduce dose by 50% on next course

Safety in patients with hepatic impairment has not been studied.

Use in Geriatric Patients: In clinical trials more than half of the patients were over 65 years old. No differences in efficacy were observed in this population. No significant differences in observed adverse events in this subpopulation. Because azacitidine and its metabolites are excreted by the kidney, and geriatric patients may have reduced renal function, it is useful to carefully monitor renal function during therapy with azacitidine.

Preparation and Stability:

1. Reconstitute each 100mg vial with 4ml sterile water for injection to make a suspension containing 25mg/mL. Invert the vial 2-3 times and gently swirl to form a suspension.
2. Doses greater than 4mL (100mg) should be divided equally into two syringes.
3. The suspension may be held at Room Temperature for up to 1 hour before administration.

4. For delayed administration, the suspension may be kept in the vial or syringe(s) at Refrigerated Temperatures (2°C - 8°C, 36°F - 46°F) for up to 8 hours if refrigerated immediately after reconstitution.

Administration:

1. Contents of syringes should be re-suspended by inverting 2-3 times and gently rolling the syringe in the hands for 30 seconds before injecting.

2. When injecting 2 syringes, inject into 2 separate sites. Rotate sites on the thigh, abdomen, or upper arm so that new injections are given at least one inch from an old injection site.

## Efficacy [4,5]

**Efficacy Measures**
Primary Endpoint is Response Rate

**Table#4 Efficacy Parameters**

| Response | Site | Criteria |
|---|---|---|
| Complete Response (CR)<br>Duration ≥4 weeks | Marrow | <5% blasts |
| | Peripheral Blood | Normal CBC if abnormal at baseline<br>Absence of blasts in peripheral circulation |
| | Transfusions | None |
| Partial Response (PR)<br>Duration ≥4 weeks | Marrow | RA, RARS: no marrow requirements<br>RAEB, RAEB-T, CMMoL: ≥50% decrease in blasts; improvement of marrow dyspoiesis |
| | Peripheral Blood | ≥50% restoration in the deficit from normal levels of baseline white cells, hemoglobin, and platelets if abnormal at baseline<br>No blasts in peripheral circulation<br>For CMMoL, if WBC is elevated at baseline, a ≥75% reduction in the excess count over the upper limit of normal |
| | Transfusions | None |
| Improved | Marrow | No requirements |
| | Peripheral Blood | Monolineage or bilineage response that does not meet criteria for PR |
| | Transfusions | ≤50% of baseline requirements |

Secondary Endpoints:

1. Time-to AML Transformation or Death
2. Time to Treatment Failure
3. Overall Survival
4. Quality of Life-1) EORTC QoL Questionnaire C30 (general physical symptoms, physical functioning, fatigue and malaise, and social and emotional functioning); 2) Mental Health Inventory (anxiety, depression, positive affect, emotional ties, loss of behavioral and emotional control); 3) Patient's perspective of improvement in their condition using a VAS.

**Summary of efficacy findings**

A randomized, multicenter, open-label trial compared the safety and efficacy of subcutaneous azacitidine plus best supportive care (BSC) with best supportive care alone in patients with any of the five subtypes of myelodysplastic syndromes. Patients with the refractory anemia (RA) and refractory anemia with ringed sideroblasts (RAEB) subtypes were included if they also met at least one of the following criteria: required RBC transfusions in the past 3 months, had platelet counts ≤50,000 or with clinical bleeding requiring platelet transfusions, or were neutropenic (ANC< 1.0 x $10^9$/L) with infections requiring IV antibiotics.

**Table #5 Primary Outcome**

| Result | AzaC N=99 | BSC N=92 | Cross-over N=49 |
|---|---|---|---|
| CR | 7%* | 0% | 10% |
| PR | 16* | 0 | 4 |
| Improved | 37* | 5† | 33 |
| Total | 60* | 5 | 47 |
| Trilineage Response | 23 | 0 | 14 |

† all 5 patients had improved counts while transforming to AML

*differences in arms in CR rate (P=0.01), CR+PR (P<0.0001), CR+PR+improvement (P<0.0001)

**Table #6 Secondary Outcomes**

| Event | AzaC | BSC |
|---|---|---|
| TT initial response | 64 days | - |
| TT best response | 93 days | - |
| Duration of response | 15 months | - |
| TTF | 9.1 mos* | 3.8 mos |
| TT AML or death | 21 mos** | 12 mos |
| AML as first event | 15%† | 38% |
| Overall survival | 20 mos‡ | 14mos |

*P<0.0001, **P=0.007, †P=0.001

‡P=0.1

**Table #7 Effect on RBC's and Platelets**

| Effect | AzaC |
|---|---|
| RBC lineage response | 51% |
| Elimination of RBC transfusion | 45% |
| Reduce RBC transfusion by 50% | 9% |
| Platelet response | 47% |
| WBC response | 40% |

**Table #8 Quality of Life Analysis versus Best Supportive Care**

| QoL Parameter | P value |
|---|---|
| Fatigue | 0.001 |
| Dyspnea | 0.0014 |
| Physical function | 0.002 |
| Positive affect | 0.0077 |
| Psychological distress | 0.015 |

- The first study to report a treatment for MDS is better than best supportive care when assessed by multiple endpoints
- Response to Azacitidine was independent of MDS classification.
- The first drug in MDS that delays and decreases the transformation to AML
- Increased Quality of Life (QoL) parameters in several physical function and psychological parameters versus best supportive care
- Approximately 53% of patients on best supportive care crossed over to receive azacitidine as per the trial design.

- This crossover confounds the overall survival results, which favor azacitidine but did not reach statistical significance.
- A landmark analysis was performed to eliminate the effect of the BSC patients who crossed over to azacitidine. Survival in three patient subgroups was compared from a 6-month landmark date. Patients initially randomized to azacitidine survived an additional 18 months versus 11 months for patients who never crossed over or crossed over after 6 months (p=0.03).
- Patients on azacitidine had an increase in the mean number of RBC transfusions during the first month of treatment. Patients with CR or PR, by definition, had an elimination of RBC and platelet transfusions. Of the patients in the improved category, 22% had an elimination of RBC transfusions and 16% had a decrease by 50% or greater in transfusion requirements.

Other Studies:
Subcutaneous Administration of azacitidine
CALGB 8921: Phase II trial to determine which subcategories of MDS would respond to subcutaneous azacitidine. Sixty-seven patients were evaluated. A CR was achieved in 12%, a PR in 12% and improvement in 28%.

An additional six uncontrolled trials have been published.

IV administration
CALGB 8421 used azacitidine as a continuous infusion over 7 days plus supportive care. A CR was seen in 12%, a PR in 25%, and improvement in 12%. One third required a dose reduction because of myelosuppression.

Additional small trials using IV azacitidine have been published.
For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 14).

## Adverse Events (Safety Data)

**Table#9 : Adverse Events in ≥5% of patients**

| Event | Azacitidine (N=220) | Observation (N=92) |
|---|---|---|
| Nausea | 70.5% | 17.4 |
| Anemia | 69.5 | 64.1 |
| Thrombocytopenia | 65.5 | 45.7 |
| Vomiting | 54.1 | 5.4 |
| Pyrexia | 51.8 | 30.4 |
| Leukopenia | 48.2 | 29.3 |
| Diarrhea | 36.4 | 14.1 |
| Fatigue | 35.9 | 25 |
| Injection site erythema | 35 | 0 |
| Constipation | 33.6 | 6.5 |
| Neutropenia | 32.3 | 10.9 |
| Ecchymosis | 30.5 | 15.2 |
| Cough | 29.5 | 15.2 |
| Dyspnea | 29.1 | 12 |
| Weakness | 29.1 | 20.7 |
| Rigors | 25.5 | 10.9 |
| Petechiae | 23.6 | 8.7 |
| Injection site pain | 22.7 | 0 |
| Arthralgia | 22.3 | 3.3 |
| Headache | 21.8 | 10.9 |
| Anorexia | 22.3 | 6.5 |
| Pain in limb | 20 | 5.4 |
| Pharyngitis | 20 | 7.6 |
| Back pain | 18.6 | 7.6 |
| Contusion | 18.6 | 9.8 |

| | | |
|---|---|---|
| Dizziness | 18.6 | 5.4 |
| Edema peripheral | 18.6 | 10.9 |
| Erythema | 16.8 | 4.3 |
| Chest pain | 16.4 | 5.4 |
| Epistaxis | 16.4 | 9.8 |
| Febrile Neutropenia | 16.4 | 4.3 |
| Myalgia | 15.9 | 2.2 |
| Weight decreased | 15.9 | 10.9 |
| Abdominal pain | 15.5 | 13 |
| Pallor | 15.5 | 7.6 |
| Nasopharyngitis | 14.5 | 3.3 |
| Pitting edema | 14.5 | 9.8 |
| Skin lesion | 14.8 | 8.7 |
| Dyspnea exertional | 14.1 | 16.3 |
| Injection site bruising | 14.1 | 0 |
| Rash | 14.1 | 9.8 |
| Injection site reaction | 13.6 | 0 |
| Anxiety | 13.2 | 3.3 |
| Appetite decreased | 12.7 | 8.7 |
| Fatigue aggravated | 12.7 | 4.3 |
| Hypokalemia | 12.7 | 13 |
| URI | 12.7 | 4.3 |
| Pruritus | 12.3 | 12 |
| Abdominal tenderness | 11.8 | 1.1 |
| Depression | 11.8 | 7.6 |
| Productive cough | 11.4 | 4.3 |
| Insomnia | 10.9 | 4.3 |
| Malaise | 10.9 | 1.1 |
| Pain | 10.9 | 3.3 |
| Pneumonia | 10.9 | 5.4 |
| Upper abdominal pain | 10.5 | 3.3 |
| Crackles lung | 10.5 | 8.7 |
| Sweating increased | 10.5 | 2.2 |
| Cardiac murmur | 10 | 8.7 |
| Rhinorrhea | 10 | 2.2 |
| Gingival bleeding | 9.5 | 4.3 |
| Lymphadenopathy | 9.5 | 3.3 |
| Herpes simplex | 9.1 | 5.4 |
| Hematoma | 8.6 | 0 |
| Night sweats | 8.6 | 3.3 |
| Rales | 8.6 | 8.7 |
| Tachycardia | 8.6 | 6.5 |
| Wheezing | 8.6 | 2.2 |
| Cellulitis | 8.2 | 4.3 |
| Dysuria | 8.2 | 2.2 |
| Breath sounds decreased | 7.7 | 1.1 |
| Lethargy | 7.7 | 2.2 |
| Oral mucosal petechiae | 7.7 | 3.3 |
| Stomatitis | 7.7 | 0 |
| Urinary tract infection | 7.7 | 5.4 |
| Peripheral swelling | 7.3 | 5.4 |
| Dyspepsia | 6.8 | 4.3 |
| Hemorrhoids | 6.8 | 1.1 |
| Injection site pruritus | 6.8 | 0 |
| Transfusion reaction | 6.8 | 0 |
| Pleural effusion | 6.4 | 6.5 |
| Abdominal distension | 5.9 | 4.3 |
| Muscle cramps | 5.9 | 3.3 |
| Post procedural hemorrhage | 5.9 | 1.1 |
| Postnasal drip | 5.9 | 3.3 |
| Rhonchi | 5.9 | 2.2 |
| Syncope | 5.9 | 5.4 |
| Urticaria | 5.9 | 1.1 |
| Anemia aggravated | 5.5 | 5.4 |
| Loose stools | 5.5 | 0 |
| Nasal congestion | 5.5 | 1.1 |

| | | |
|---|---|---|
| Atelectasis | 5.0 | 2.2 |
| Chest wall pain | 5.0 | 0 |
| Dry skin | 5.0 | 1.1 |
| Dysphagia | 5.0 | 2.2 |
| Injection site granuloma | 5.0 | 0 |
| Injection site pigmentation changes | 5.0 | 0 |
| Injection site swelling | 5.0 | 0 |
| Mouth hemorrhage | 5.0 | 1.1 |
| Tongue ulceration | 5.0 | 2.2 |

*Nausea, vomiting, diarrhea, and constipation are dose related

Nausea, vomiting, injection site erythema, constipation, rigors, petechiae, injection site pain, dizziness, injection site bruising, anxiety, hypokalemia, insomnia, epistaxis, and rales tend to be more pronounced during the first 1-2 cycles. There were no cumulative adverse events.

**Serious Adverse Events Resulting in Clinical Intervention**

Discontinuation: leukopenia, thrombocytopenia, neutropenia

Dose Held: leukopenia, neutropenia, febrile neutropenia

Dose Reduced: leukopenia, neutropenia, thrombocytopenia

**Common Adverse Events (Subcutaneous route)**

Nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site reaction, constipation, neutropenia, ecchymosis

**Other Serious Adverse Events (<5%)**

Blood: agranulocytosis, bone marrow depression, splenomegaly
Cardiac: atrial fibrillation, cardiac failure, congestive failure, cardio-respiratory arrest, congestive cardiomyopathy
GI: diverticulitis, GI hemorrhage, melena, perirectal abscess
General: catheter site hemorrhage, general physical deterioration, systemic inflammatory response syndrome
Hepatobiliary: cholecystitis
Immune: anaphylactic shock, hypersensitivity
Infection: limb abscess, bacterial infection, blastomycosis, injection site infection, Klebsiella sepsis, streptococcal pharyngitis, Klebsiella pneumonia, sepsis, Staph bacteremia, Staph infection , toxoplasmosis
Metabolism: dehydration
Musculoskeletal: aggravated bone pain, muscle weakness, neck pain
Neoplasms: leukemia cutis
Nervous system: convulsions, intracranial hemorrhage
Psychiatric: confusion
Renal: hematuria, loin pain, renal failure
Respiratory: hemoptysis, lung infiltration, pneumonitis, respiratory distress
Skin: pyoderma gangrenosum, pruritic rash, skin induration
Vascular: orthostatic hypotension

**Tolerability**

Of the patients originally assigned to the azacitidine arm, 56% remained on active treatment by day 182 (6 months). At that time, 16% had died, and 22% had terminated therapy because of treatment failure, toxicity, or transformation to acute leukemia.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 14).

## Precautions/Contraindications

**Precautions**

1. Blood counts should be performed periodically to monitor hematologic toxicity. At a minimum, counts should be performed before each dosing cycle. Dosing after the first cycle should be reduced or delayed based on nadir counts and hematologic toxicity if needed.

2. Safety and efficacy in patients with renal or hepatic insufficiency has not been studied.

3. Azacitidine is potentially hepatotoxic in patients with pre-existing severe hepatic impairment. Patients with extensive hepatic tumor burden have rarely experienced progression to hepatic coma and death during azacitidine therapy. This has occurred especially in patients with baseline serum albumins of <30g/dL. (See Contraindications)

4. Abnormalities ranging from increased serum creatinine to renal failure and death have rarely been reported in patients treated with IV azacitidine in combination with chemotherapy. Additional, renal tubular acidosis (a fall in serum bicarbonate to <20mEq/L with alkaline urine and hypokalemia) has been described in 5 patients with CML treated with azacitidine and etoposide. The dose of azacitidine should be reduced or held of unexplained reductions in serum bicarbonate to <20mEq/L or elevations in BUN or serum creatinine occur.

5. Since azacitidine and its metabolites are primarily excreted from the kidney, patients with renal impairment should be monitored closely. This includes geriatric patients who are more likely to have decreased renal function.

**Use in Pregnancy:** Pregnancy Category D

**Use in Males:** Men should be advised not to father a child during azacitidine therapy. In animal studies, azacitidine caused decreased fertility and loss of offspring during embryonic and postnatal development.

**Contraindications**

1. Patients with known hypersensitivity reactions to azacitidine or mannitol
2. Patients with advanced malignant hepatic tumors

## Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name azacitidine: cimetidine, famotidine, ranitidine, azathioprine, azulfidine, capecitabine, zalcitabine

Severity Category: minor-moderate

LA/SA for trade name Vidaza: Videx, Vitrase, Viadur

Severity Category: minor-moderate

## Drug Interactions

**Drug-Drug Interactions**

No formal assessments have been conducted.

In vitro studies indicate azacitidine may be metabolized in the liver. The effect of hepatic enzyme inducers and inhibitors is unknown.

In vitro studies found that azacitidine does not induce CYP 1A2, 2C19, or 3A4/5.

## Acquisition Costs

**Table #10 Azacitidine Costs**

| Drug | Dose | Cost/Day/Cycle/patient ($) | Cost/Year/patient ($) |
|---|---|---|---|
| Azacitidine | 75mg/m$^{2/}$/day for 7 days | 555.92/3891.44 | 46,697.28 |

Azacitidine 100mg vials FSS $277.96

## Pharmacoeconomic Analysis

There are no pharmacoeconomic studies of azacitidine in MDS.

## Conclusions

Clinical Efficacy: Azacitidine produces response rates, measured using strict response criteria, in first line treatment of MDS that are statistically superior to best supportive care. In addition, a significant number of patients who did not meet the PR requirements were categorized as "improved", with mono- or bilineage response in blood counts or ≥50% decrease in transfusion requirements from baseline. In the area of timed events, azacitidine patients had a statistically significant delay in time to treatment failure, time to AML transformation, and time to death. In fact, this is the first drug used in MDS to delay and decrease transformation to AML. Overall survival showed a trend that favored azacitidine but was not statistically significant. This is confounded by the patients in the best supportive care arm who crossed over to azacitidine. In a landmark analysis of survival, patients initiated on the azacitidine arm had a statistically longer survival after the landmark date than patients who never crossed over or crossed over after the landmark date.

By definition, patients who achieved a CR or PR had an elimination of transfusion requirements for RBC's and platelets. Patients in the improved category also had improvement in transfusion requirements: 22% had elimination of all RBC transfusions, and 16% had a decrease of ≥50% in RBC transfusion requirements. In total, 45% of patients who were transfusion dependent at study entry had elimination of all transfusions and an additional 9% had a 50% reduction in transfusion requirements.

Quality of Life was measured on three scales assessing physical functioning, psychological well being, and patient's perception of well being. Azacitidine patients showed statistically significant improvement in fatigue, physical functioning, dyspnea, psychosocial distress, and positive affect. QoL scores were compared to performance status scores over time to test for clinical significance of improvement in QoL scores. In patients who completed the most QoL assessments (3 or 4 over 6 months), as QoL scores improved so did performance status scores.

There are questions about the study design. Although strict criteria were utilized to define complete and partial responses, the majority of the responses fell into the less strictly defined "improved" category. An analysis of only patients who met the CR or PR criteria was not performed. The second issue is the availability of crossover to azacitidine, especially once the phase II trial results were shown to be positive. It reduces the capacity to see significant differences in survival. Other randomization strategies may be needed in the future. The question of whether survival it the ultimate treatment endpoint in this and other cancers is still being debated. Although the studied regimen is active, other doses and schedules, as well as combination with cytokines and other signal modulators are areas of exploration.

Drug stability issues will make administration over 7 consecutive days in the ambulatory care arena difficult for some sites.

Clinical Safety: The most common adverse events were GI (nausea, vomiting, diarrhea) and myelosuppression. In early trials, the incidence of nausea and vomiting was the most common adverse events; in the majority of cases it was mild to moderate. In the registration trial, nausea and vomiting was reported in only 4% of patients, possibly due to better antiemetic regimens. Diarrhea is generally mild to moderate and controlled with standard antidiarrheals (loperamide). Myelosuppression is difficult to assess with standard criteria because MDS already causes profound cytopenias. In patients with profound baseline cytopenias it may be useful to assess relative changes in blood counts (e.g. a percent decrease from baseline values). Leukopenia, thrombocytopenia, and anemia were the most common reasons for discontinuation in therapy, dose reductions, and held doses. Blood counts should be monitored during therapy, at a minimum before the start of each cycle.

Azacitidine is potentially hepatotoxic in patients with severe pre-existing liver disease and in patients with significant metastatic disease to the liver. Hepatic transaminase elevations have been reported.

Injection site reactions were not reported in the registration trial, but were reported in another CALGB trial. They are generally mild and do not require further intervention in most cases.

Renal impairment may decrease excretion of azacitidine and its metabolites. Since geriatric patients are at risk for decreased renal function, they should be monitored carefully. A small number of cases of renal tubular acidosis have been reported.

Azacitidine can cause impairment of fertility and may cause fetal harm.

Most treatment related deaths were due to infection. The majority of deaths were due to disease transformation or progression.

## Recommendations

Place in Therapy:
Myelodysplastic syndromes are a group of disorders of the bone marrow in which mature blood cells are produced from an abnormal clone cell. These abnormal clones eventually predominate in the bone marrow, which is less able to produce normal cells. It is characterized by bone marrow hyperproliferation and peripheral cytopenias, with signs and symptoms of fatigue, weakness, bleeding, infections, and anemia. Transformation to acute myelogenous leukemia occurs in 35-40% and it is often refractory to standard therapy. A number of chemotherapy drugs and cytokines have been studied in MDS, but none have altered the natural history of the disease. The standard of care is best supportive care with antibiotics and transfusions. The number of required RBC transfusions eventually leads to iron overload and the need for iron chelation therapy. Allogeneic bone marrow transplant is the only potentially curative approach, but is not a realistic option for the majority of patients.

Azacitidine is the first drug to provide clinical benefits to patients with MDS across a number of parameters when compared to best supportive care: increased response rate, delayed time to transformation to AML, decreased incidence of transformation to AML, decreased transfusion requirements, increased QoL, and a trend towards increased survival although not statistically significant.

Criteria for use should follow those in the phase III trial:
1. Patients with MDS. Those with RA or RARS in addition should have one of the following: symptomatic anemia requiring transfusions for at least the past 3 months, or thrombocytopenia with a platelet count ≤50 x $10^9$/L or significant clinical hemorrhage requiring platelet transfusion, or neutropenia with an ANC< 1 x $10^9$/L requiring IV antibiotics.
2. Performance Status ≤2
3. Total bilirubin ≤1.5 X ULN

4. AST/ALT ≤1.5 X ULN
5. Serum creatinine ≤1.5 X ULN
6. Serum bicarbonate ≥19mEq/L
7. No previous treatment for MDS with chemotherapy drugs or cytokines within 7 days except epoetin.
8. No history of leukemia
9. No pregnancy or uncontrolled CHF

As the only treatment besides best supportive care for MDS, recommend adding azacitidine to the national formulary.

**Prepared Mo/Yr. Contact person: Name, Title(s)**

Mark C. Geraci, Pharm.D., BCOP
Clinical Specialist, VHA Pharmacy Benefits Management Strategic Healthcare Group
April 2005

## References

[1] Product Package Insert. Vidaza™. Pharmion Corporation, Boulder, Colorado. May 2004.

[2] Kaminskas E, Farrell AT, Wang YC, Sridhara R, Pazdur R. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza™) for injectable suspension. The Oncologist 2005;10:176-182.

[3] Marcucci G, Silverman L, Eller M, Lintz L, Beach CL. Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. J Clin Pharamcol 2005;45:597-602.

[4] Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002; 20:2429-2440.

[5] Kornblith AB, Herndon JE, Lilverman LR, Demakos EP, Odchimar-Reissig R, et al. Impact of azacitidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a cancer and leukemia group B study. J Clin Oncol 2002;20:2441-2452.

## Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to April 2005) using the search term azacitidine. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

**Appendix Table: Azacitidine clinical trials**

| Citation<br>Design<br>Analysis type<br>Setting | Eligibility Criteria | Interventions | Patient Population Profile | Efficacy Results | Safety Results |
|---|---|---|---|---|---|
| Silverman 2002<br>CALGB 9221<br>Phase III | Inclusion criteria<br>1. FAB classification criteria for MDS<br>2. For RA or RARS additional criteria: at least 1 of the following: symptomatic anemia requiring transfusions for at least 3 months, thrombocytopenia with 2 or more counts ≤50 x $10^9$/L with clinical hemorrhage requiring transfusion, or neutropenia and infection requiring IV antibiotics<br>3. PS ≤2<br>4. T.bili ≤1.5 x ULN<br>5. AST/ALT≤2 x ULN<br>6. S. creatinine ≤1.5 x ULN<br>7. S. $CO_2$ ≥19 mEq/L<br>8. No previous treatment for MDS with Aza C. GCSF, GMCSF, or other cytokines except epoetin<br>9. No epoetin, | A.. Azacitidine 75mg/$m^2$ subcutaneously daily for 7 days, repeat every 28 days + best supportive care (transfusions, antibiotics, hospitalizations)<br><br>B. Best Supportive Care (BSC) (crossover to azacitidine allowed after a minimum of 4 months) | N=191<br><br>AzaC N=99 / BSC N=92<br>FAB<br>RA 17 / 20<br>RARS 5 / 3<br>RAEB 32 / 34<br>RAEBT 27 / 18<br>CMMoL 7 / 7<br>Other 11 / 10<br>Age 69 / 67<br>Male 72 / 73<br>Bleeding 16 / 18<br>Platelet Transfusion 18 / 10<br>RBC transfusion 68 / 56 | Result: AzaC / BSC / Cross-over N=49<br>CR 7%* / 0% / 10%<br>PR 16* / 0 / 4<br>Improved 37* / 5† / 33<br>Total 60* / 5 / 47<br>Trilineage Response 23 / 0 / 14<br>Response to AzaC was independent of MDS classification<br>† all 5 patients had improved counts while transforming to AML<br>*differences in arms in CR rate (P=0.01), CR+PR (P<0.0001), CR+PR+improvement (P<0.0001)<br><br>Timed Analyses (median)<br>Event: AzaC / BSC<br>TT initial response 64 days / -<br>TT best response 93 days / -<br>Duration of response 15 months / -<br>TTF 9.1 mos* / 3.8 mos<br>TT AML or death 21 mos** / 12 mos<br>AML as first event 15%† / 38%<br>Overall survival 20 mos‡ / 14mos<br>*P<0.0001, **P=0.007, †P=0.001 ‡P=0.1 | Most common: myelosuppression<br>Difficult to assess using standard criteria because the disease causes severe cytopenias<br><br>Grade 3 or 4 Hematologic Toxicity<br>Cytopenia: Standard Criteria / Relative Criteria<br>Leukopenia 59% / 43%<br>Granulocytopenia 81% / 58%<br>Thrombocytopenia 70% / 52%<br>Toxicity was transient and usually recovered by the next cycle<br><br>Treatment-related infection in 20%<br><br>Nausea or vomiting in 4%.<br><br>1 treatment related death |

<table>
<tr><th>Citation<br>Design<br>Analysis type<br>Setting</th><th>Eligibility Criteria</th><th>Interventions</th><th>Patient Population Profile</th><th>Efficacy Results</th><th>Safety Results</th></tr>
<tr><td></td><td>corticosteroids, interferon, or retinoids w/l 1 month<br>10. No history of leukemia<br>11. No pregnancy or uncontrolled CHF</td><td></td><td></td><td>Landmark survival analysis<br>(6 month landmark date)<br><table><tr><td>Subgroup</td><td>Survival</td></tr><tr><td>BSC patients who never crossed over or crossed over after 6 months</td><td>11 months</td></tr><tr><td>BSC patients who crossed over before 6 months</td><td>14 months</td></tr><tr><td>Patients initially randomized to Azacitidine</td><td>18 months (p=0.03 compared to group who never crossed over or crossed over late)</td></tr></table><br>Landmark AML transformation analysis<br>(12 month Landmark date)<br><table><tr><td>Subgroup</td><td>Additional Survival</td></tr><tr><td>Transformed to AML before landmark date N=13</td><td>3 months (95%CI 1-11)</td></tr><tr><td>Had not yet transformed to AML by landmark date N=93</td><td>18 months (95%CI 14-26) p<0.001</td></tr></table><br>Effect on RBC’s and platelets<br><table><tr><td>Effect</td><td>AzaC</td></tr><tr><td>RBC lineage response</td><td>51%</td></tr><tr><td>Elimination of RBC transfusion</td><td>45%</td></tr></table></td><td></td></tr>
</table>

| Citation Design Analysis type Setting | Eligibility Criteria | Interventions | Patient Population Profile | Efficacy Results | Safety Results |
|---|---|---|---|---|---|

| | |
|---|---|
| Reduce RBC transfusion by 50% | 9% |
| Platelet response | 47% |
| WBC response | 40% |

Quality of Life Analysis AzaC vs BSC

| QoL Parameter | P value |
|---|---|
| Fatigue | 0.001 |
| Dyspnea | 0.0014 |
| Physical function | 0.002 |
| Positive affect | 0.0077 |
| Psychological distress | 0.015 |

FAB=French-American-British; MDS=myelodyplastic syndrome; RA=refractory anemia; RARS=refractory anemia with ringed sideroblasts; PS=performance status' T. bili= total bilirubin; ULN=upper limits of normal; AzaC=azacitidine; RAEB=refractory anemia excessive blasts; RAEB-T=refractory anemia excessive blasts in transformation to leukemia; CMMoL=chronic myelomonocytic leukemia; CR=complete response; PR=partial response; RBC=red blood cell, TT initial response=time to initial response; TT best response=time to best response; TTF=time to treatment failure; Amlm=acute myelogenous leukemia; WBC=white blood cell