

Off-label uses included in the table represent only those uses that have been submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI).

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
<p>Acute Myelogenous Leukemia (AML) with multilineage dysplasia (previously RAEB-t).</p> <p>Untreated Acute Myelogenous Leukemia (AML) in elderly patients (> 60 years old) who are not considered eligible to receive conventional induction therapy, as defined by a poor performance status or evidence of a clinically important comorbidity.</p>	<p>Azacitidine 75 mg/m² as a subcutaneous injection days 1-7</p>	<p>Low Quality; ORR and OS</p>	<p>Reasonable Choice (Accepted)</p>	<p>Committee members disclosed no conflict of interests for this particular matter review. A consultant, who was used to provide expert commentary, disclosed consultant activities with Pharmion and Celgene, Speaker's Bureau activities with MGI and Celgene, and having equity interests in Celgene; however, the consultant did not participate or vote on the final determination.</p>	<p>April 2008</p>

Clinical Trial Summary:

Newly Diagnosed Acute Myelogenous Leukemia (AML) with Multilineage Dysplasia (previously classified as refractory anemia with excessive blasts in transformation [RAEB-t])

- Objective response rates (ORR) of 36–60% reported in 3 retrospective analyzes (n=158) for patients with RAEB-t/WHO-AML^a with complete response (CR) rates ranging from 9-20%.^{1,2,3}
- Improved survival in responding patients (i.e., achieving either a partial [PR] or complete response) compared to non-responders (15+ months versus 2.5 months).²
- Improved survival reported in a phase III, randomized study (n = 358) with high-risk myelodysplastic syndrome (MDS) patients, including patients with RAEB-t/WHO-AML (34%), who received azacitidine or conventional care – characterized as best supportive care (e.g., transfusions, antibiotics, and filgrastim) or treatment including either low-dose cytarabine or an anthracycline–cytarabine induction/consolidation regimen.⁴
 - Median overall survival (Kaplan-Meier estimate) was 24.4 and 15 months, respectively for azacitidine versus conventional care. The 2-year survival was reported as 51 and 26% (p= <0.0001) for azacitidine and conventional care, respectively. Improved survival rates across all International Prognostic Staging System (IPSS) groups, including patients with intermediate and poor risk cytogenetics, were reported with azacitidine (intermediate: 26.3 versus 17 months; poor: 17.2 versus 6.0 months, for azacitidine and conventional care, respectively). Improvements in median overall survival for azacitidine, based on Kaplan Meier estimates, were reported as 12.9 months, 9.1 months, and 8.7 months when compared with best supportive care, low-dose cytarabine, and standard induction therapy, respectively.
 - Results from a subsequent analysis, which included those patients who failed to achieve a CR (as determined by IWG^b response criteria), revealed an improved survival rate at 1 year for azacitidine compared with conventional care (68.2 and 55.6% [p=0.015; HR 0.65]).⁵
 - A subset analysis performed on patients with the 7q deletion, a poor risk karyotype, revealed improved responses (CR +PR) and improved survival with azacitidine when compared with conventional care therapy (CR+ PR: 43 and 4%; overall survival 13.1 and 4.6 months, respectively).⁶

Untreated Acute Myelogenous Leukemia in elderly (> 60 years old) who are not eligible to receive standard induction therapy

- Ineligibility defined as a poor performance status or the presence of a clinically important comorbidity
- Overall response rates of 49–60% with complete response rates of 13–35% reported in a case series with a mean age of 75 years and 68 years.^{7,8,9} Survival duration reported as 5 months (secondary AML) and 9 months (de novo AML) in a heterogeneous population (mean age 75 years);⁷ an improved survival of 13 months versus 9 months reported in another series comparing azacitidine with cytarabine/idarubicin (mean age 68 years).⁹

^a WHO AML: Reflects the newer World Health Organization classification for both MDS and AML. Previously, RAEB-T was classified as a high-risk myelodysplastic (MDS) subtype in the French-American-British (FAB) system; it is now classified as AML (with multilineage dysplasia) in the WHO system.

^b IWG: International Working Group.

- Improved survival and favorable ORR reported for patients with good-risk cytogenetics; ^{7,9} recommended for patients with normal to favorable karyotypes.
- Variable responses and poor survival outcomes reported in patients with poor-risk or complex cytogenetics; ^{7,9} therefore, use in these patients is considered inconclusive.
- Variable responses reported for relapsed and refractory patients; ^{7,8} therefore, use in these patients is considered inconclusive.

Discussion:

Based on improved response rates, including hematologic improvements (i.e., decreased transfusion requirements), and improved survival, azacitidine represents a reasonable treatment option for patients diagnosed as AML with multilineage dysplasia (previously characterized as the high risk myelodysplastic syndrome, RAEB-t), including those with poor-risk cytogenetics.^{1,2,3,4,5} Results from the phase III trial comparing azacitidine with conventional therapy (i.e., best supportive care or chemotherapy), demonstrated improved responses and survival, suggesting that azacitidine may be a preferred regimen for patients with high risk MDS, including WHO AML. Achievement of a CR after conventional induction AML treatment predicts for improved survival; however, a higher 1-year survival rate was reported for high risk MDS/WHO AML patients who failed to achieve a CR (i.e., those with partial responses, stable disease, and a hematologic improvement) with azacitidine, suggesting a survival benefit without the requirement for a complete remission. Improved survival seen with azacitidine in patients with the chromosome 7q deletion suggests that azacitidine has enhanced activity and appears to overcome this poor prognostic risk feature, compared with standard chemotherapeutic agents (e.g., cytarabine or an anthracycline/cytarabine-containing regimen).

Although efficacy has not been evaluated consistently and reported in a sufficient number of AML patients with classic French-American-British (FAB)-defined AML (e.g., marrow blast counts > 30 %), azacitidine may represent a treatment option for some elderly patients, especially those with poor host-related features (i.e., compromised performance status or the presence of clinically important comorbidities) who are not likely to tolerate standard induction therapy. Advantages of azacitidine include ease of administration in the outpatient setting with potentially reduced morbidity (i.e., hematologic and infectious complications). However, based on the lack of prospective, controlled studies with adequate sample sizes, additional data are needed to define the response rate, survival benefit, tolerability, and relevance of prognostic characteristics (e.g., host status, cytogenetic-risk features, and the history of an antecedent hematologic disease) in patients receiving azacitidine or other DNA-methyltransferase inhibitors (DMITs), either as monotherapy or in combination with other targeted agents. Prophylactic antibiotic and antifungal therapy may be considered for AML patients receiving azacitidine.¹⁰

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