Poor Outcome of Patients With Myelodysplastic Syndrome After Azacitidine Treatment Failure

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Abstract

For patients with higher-risk myelodysplastic syndrome (MDS), treatment with azacitidine yields a meaningful survival benefit. However, most responders experience disease progression within 2 years. In our retrospective review of 59 patients in whom azacitidine therapy had failed, outcome was poor. Subsequent treatment with intensive chemotherapy or decitabine resulted in disappointing response rates, emphasizing the importance of prioritizing consideration for clinical trials.

Background: Limited data have been reported describing the outcome and prognosis of patients with MDS in whom treatment with azanucleosides has failed. We report our single-institutional experience of patients with higher-risk MDS in whom therapy with azacitidine has failed. **Patients and Methods:** This was a retrospective study of MDS patients treated at the Moffitt Cancer Center in whom azacitidine treatment regimens had failed. Patients were identified through the Moffitt database, and clinical data were extracted. Azacitidine failure was defined as failure to achieve hematologic improvement or better after at least 4 cycles of therapy, loss of response, or disease progression during therapy. The objectives were to characterize response to salvage therapies after azacitidine failure and to estimate the overall survival. All responses were defined according to the International Working Group 2006 criteria, and survival was estimated using the Kaplan-Meier method. **Results:** A total of 59 patients in whom azacitidine treatment had failed were identified. The median age at treatment failure was 68 years, and most were Caucasian male patients. Thirteen patients received intensive chemotherapy with an overall response rate of 31%. Six patients were treated with decitabine, and none responded. Median overall survival of the entire cohort after azacitidine failure was 5.8 months (95% confidence interval, 1.3-10.3 months), with an estimated 12-month survival of 17%. **Conclusion:** Patients with higher-risk MDS in whom azacitidine treatment has failed have a poor prognosis and low probability of response to salvage treatments. The standard of care after azanucleoside failure should be enrollment in clinical trials.

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Introduction

The myelodysplastic syndromes (MDS) encompass a group of heterogeneous hematopoietic stem cell malignancies characterized by ineffective hematopoiesis, peripheral blood cytopenias, cytologic atypia, and a variable risk of progression to acute myeloid leukemia (AML).[1] Median survival for patients with de novo disease ranges from more than 10 years to approximately 6 months in those with the highest-risk disease.[2-4] Within the past decade, the azanucleoside analogues, azacitidine and decitabine, were shown to have clinical activity, leading to their approval by the US Food and Drug Administration (FDA). These agents are nucleoside analogues that have dual mechanisms of action that include genomic hypomethylation-restoring expression of silenced genes and direct cytotoxicity.

Azacitidine and decitabine are generally well tolerated and are widely used in the treatment of MDS. In phase III studies, decitabine was associated with complete remission rates of 9% to 13%, with partial response rates of 6% to 8% and a trend toward improved survival, especially in higher-risk patients.[5,6] Azacitidine

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Table 1 Patient Characteristics

Characteristic	Value
Total Patients, n	59
Median Age, Years (Range)	68 (46-85)
Sex, n (%)	
Male	39 (66)
Female	18 (34)
Caucasian Race, n (%)	50 (88)
Median Number of Azacitidine Cycles (Range)	5 (2-26)
Best Response to Azacitidine, n (%)	
CR	8 (14)
Marrow CR	2 (3)
Partial response	0
Hematologic improvement	12 (20)
Stable disease	16 (27)
Progressive disease	19 (32)
Not evaluable	2 (3)

Abbreviation: CR = complete response.

treatment demonstrated complete remission rates of 7% to 17% and partial response rates of 12% to 16% in phase III studies.[7,8] Furthermore, the landmark AZA-001 study demonstrated an overall survival (OS) benefit of 24.5 months compared with 15.0 months in patients with intermediate-2 or high-risk disease according to the International Prognostic Scoring System (IPSS) who were treated with conventional-care regimens.[8] As a result, azacitidine and decitabine have become the standard of care for higher-risk MDS patients. Although the azanucleosides mark a clear advancement in the management of MDS, treatment is not curative. Most responders experience disease progression within 2 years of initial response.[8] For patients who fail to respond, lose their response, or progress during therapy, treatment options are limited to clinical trials and best supportive care, with only a minority of patients eligible for induction chemotherapy or allogeneic stem cell transplant.

Limited data are available in the literature regarding azanucleoside failure, survival, and response expectations with salvage treatments. The M.D. Anderson Cancer Center group reported a median survival of 4.3 months in 87 MDS and chronic myelomonocytic leukemia (CMML) patients after decitabine failure and a 1-year survival rate of 28%. At treatment failure, 22 (25%) patients had already progressed to AML.[9] Prébet et al recently reported a median OS of 5.6 months and a 1-year survival of 29% after azacitidine failure in patients treated in 3 large clinical trials and the French compassionate use program.[10] In this report, we describe our institutional experience and outcomes of MDS patients in whom treatment with standard doses of azacitidine alone had failed, and their response to subsequent salvage treatment.

Patients and Methods

This was a retrospective review of patients who were treated with azacitidine at the H. Lee Moffitt Cancer Center and Research Institute. Patients were identified through the Moffitt MDS database, individual charts were reviewed, and clinical data were extracted. Patients with MDS of all risk categories, CMML, or AML with less than 30% blasts were included, and patients could have received any previous therapy for MDS. All patients were treated with at least 1 cycle of azacitidine at a dose of 75 mg/m^2 subcutaneously or intravenously for 7 days every 4 weeks. Azacitidine failure was defined as a loss of response, failure to achieve hematologic improvement or better after at least 4 cycles, or

Table 2 Classification and Risk Stratification at the Start of Azacitidine and at Treatment Failure

Classification	At Start of Azacitidine	At Failure of Azacitidine
WHO		
RA	1 (1.7)	0
RARS	1 (1.7)	1 (1.7)
RCMD	17 (28.8)	5 (8.5)
RAEB I	8 (13.6)	8 (13.6)
RAEB II	17 (28.8)	12 (20.3)
CMML	8 (13.6)	3 (5.1)
MDS/MPN-U	4 (6.8)	0
AML	2 (3.4)	12 (20.3)
Unknown	1 (1.7)	18 (30.5)
FAB		
RA	16 (27.1)	5 (8.5)
RARS	3 (5.1)	1 (1.7)
RAEB	23 (39)	14 (23.7)
RAEBT	4 (6.8)	16 (27.1)
CMML	8 (13.6)	3 (5.1)
Unknown	5 (8.5)	18 (30.5)
IPSS		
Low	1 (1.7)	1 (1.7)
Intermediate-1	20 (33.9)	13 (22)
Intermediate-2	23 (39)	9 (15.3)
High	11 (18.6)	15 (25.4)
Unknown	4 (6.8)	21 (35.6)
WPSS		
Low	1 (1.7)	1 (1.7)
Intermediate	9 (15.3)	4 (6.8)
High	17 (28.8)	10 (16.9)
Very high	15 (25.4)	13 (22)
Unknown	17 (28.8)	31 (52.5)
MDAS		
Low	1 (1.7)	1 (1.7)
Intermediate-1	12 (20.3)	2 (3.4)
Intermediate-2	14 (23.7)	11 (18.6)
High	29 (49.2)	24 (40.7)
Unknown	3 (5.1)	21 (35.6)

Data are presented as n (%).
Abbreviations: AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; FAB = French-American-British, scoring systems; IPSS = International Prognostic Scoring System; MDAS = M.D. Anderson Scoring System; MDS/MPN-U = myelodysplastic syndrome/myeloproliferative neoplasms-unclassifiable; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEBT = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; Unknown = data missing; WHO = World Health Organization; WPSS = WHO Prognostic Scoring System.