e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(2); 22-27

Review Article

Use of Azacitidine in the Myelodysplastic Syndromes/Acute Myeloid Leukaemia

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Received: 06-01-2023 / Revised: 20-01-2023 / Accepted: 03-02-2023
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Conflict of interest: Nil

Abstract

Acute myeloid leukaemia risk and increasing cytopenias are characteristics of myelodysplastic syndromes (MDS). Since the majority of patients with MDS are not candidates for more intense chemotherapy, supportive care including transfusions, antibiotics, and hematopoietic growth factors has long been the cornerstone of MDS treatment. The first chemotherapy drug to be licenced by the U.S. Food and Drug Administration for the treatment of MDS was the hypomethylating agent 5-azacitidine (AZA), which marked a significant advancement in the treatment of the condition. In comparison to supportive care alone, azacitidine showed a greater response rate and a longer overall survival in Phase III trials. It is also a well-tolerated medication that can be administered IV or SC according to different outpatient schedules. Future research is anticipated to compare the efficacy of azacitidine and decitabine and to assess the activity of AZA when combined with other epigenetic modifiers. This study explicitly discusses the function of azacitidine in the therapy of MDS and provides a summary of the current MDS treatment landscape.

Keywords: Azacitidine, Myelodysplastic Syndromes, Disease Management.

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Introduction

The MDSs are a wide range of haematological disorders in which the production of mature blood cells is insufficient due to abnormal bone marrow function. MDS can affect red blood cells (RBCs), white blood cells (WBCs), and platelets, which can cause anaemia, an increased risk of bleeding, and infections. Due to debilitating symptoms including exhaustion and dyspnea, treatment regimens requiring hospitalisation with intravenous drug infusions and blood transfusions, and consequences like severe infections, MDS has an impact on patients' quality of life.[1]

The French-American-British (FAB) and World Health Organization (WHO) categorization systems,[2] as well as the International Prognostic Scoring System (IPSS), are used to further categorise myelodysplastic syndromes (Table -1). The IPSS categorises outcomes as low-risk, intermediate-I risk, intermediate-II risk, or high-risk depending on the percentage of leukemic cells (or "blasts"), the presence of

chromosome 7 abnormalities, and the presence of blood cytopenia. The intermediate-II and high-risk MDS subgroups are thought to make up about 22% and 7%, respectively, of the overall MDS population.

Table 1: WHO classification of MDS

Type	Peripheral blood findings	Bone marrow findings
RA,	Anemia, no blasts or rare blasts	Erythroid dysplasia, <5% blasts, <15% ringed sideroblasts
RARS	Anemia, no blasts	Erythroid dysplasia, <5% blasts, <15% ringed sideroblasts
Refractory Cytopenia with Multilineage Dysplasia (RCMD)	Bicytopenia or Pancytopenia, no blasts or rare blasts, no Auer rods, monocytes <1000/uL	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines, no Auer rods, <5% blasts, <15% ringed sideroblasts
Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts (RCMD-RS)	Bicytopenia or Pancytopenia, no blasts or rare blasts, no Auer rods, monocytes <1000/uL	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines, no Auer rods, <5% blasts, ≥15% ringed sideroblasts
RAEB-1	Cytopenias, <5% blasts, no Auer rods, monocytes <1000/uL	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
RAEB-2	Cytopenias, 5%–19% blasts, +/- Auer rods, monocytes <1000/uL	Unilineage or multilineage dysplasia, 10%–19% blasts, +/- Auer rods
MDS-Unclassified (MDS-U)	Cytopenias, no blasts or rare blasts, no Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes, no Auer rods, <5% blasts
MDS with del (5q)	Anemia, <5% blasts, platelets normal or increased	Normal to increased megakaryocytes with hypolobulated nuclei, no Auer rods, <5% blasts. Isolated del(5q)

Myelodysplastic syndromes are linked to a higher risk of developing into AML. AML is a kind of MDS that progresses and is characterised by a blood and bone marrow cancer that is growing quickly. About 30% of MDS patients will eventually develop AML. In England, there were 1993 new cases of MDS in 2004, with more than 90% of patients being over 60 at the time of diagnosis. The median survival for MDS patients is about 20 months, but for high-risk subgroups, it can be as low as 6 months. It is crucial to confirm the existence of chromosome 7 abnormalities because they are linked to AML's quick development. Best supportive care (BSC), which includes transfusions, growth factors, and antibiotics to manage the symptoms of bone marrow loss, as well as low-dose conventional chemotherapy for some patients, is the cornerstone of treatment for MDS. Most patients cannot receive a stem cell transplant because of their advanced age and/or other comorbid conditions.[3]

According to the AZA-001 study, MDS patients who received Aza had a median survival that was approximately 9 months longer than those who received CCR, a slower rate of progression to AML, less need for blood transfusions, and a marginally higher response rate. Due to its open-label design, this study was susceptible to bias, and concerns about loss to follow-up may have led to an overestimation of the survival benefit of Aza. The claim that "azacitidine results in a marked improvement in patient well-being" has been made. Aza reduces the need for transfusion and intravenous antibiotic administration. There is no direct research evidence about the patient population of interest in this STA, and it is obvious that more research is needed to determine the quality of life for MDS patients.[4-5]

A pyrimidine nucleoside analogue of cytidine is azacitidine. DNA hypomethylation and a cytotoxic effect on abnormal haematopoietic cells in the bone marrow are the causes of its antineoplastic activity. Azacitidine is quickly absorbed under the skin and has an 89% absolute bioavailability. Azacitidine is metabolised by cytidine deaminase-mediated deamination and spontaneous hydrolysis. The majority of azacitidine and/or its metabolites are eliminated in the urine, with a mean elimination half-life of 41 minutes.[6-7]

AZA-001, a randomised, open-label, multicenter trial, assessed the effectiveness of subcutaneous azacitidine in patients with higher-risk MDS.[8] Patients had higherrisk MDS (i.e., IPSS intermediate-2-risk or highrisk classification), were 18 years old, had refractory anaemia with excess blasts as defined by FAB, refractory anaemia with excess blasts in transformation, or had CMML with 10% bone marrow blasts and a white blood cell count of 13 109 cells/L. They also had an Eastern Cooperative Oncology Group performance status of 0-2 and an MDS associated with therapy, azacitidine use in the past, and allogeneic HSCT are all exclusion criteria.

After a median follow-up period of 21.1 months, patients with higher-risk MDS who received azacitidine outlived those receiving standard care by 9.4 months (hazard ratio (HR) 0.58; 95% confidence interval (CI) 0.43, 0.77) (Table 2). Kaplan-Meier survival curves separated after >3 months of treatment, indicating that the survival benefit associated with azacitidine was visible early in the course of treatment (at which time approximately three-quarters of azacitidine recipients had completed three cycles of therapy). The estimated 2-year survival rates for azacitidine recipients were 50.8%, compared to 26.2% for patients receiving standard care (p 0.0001).

Additionally, azacitidine recipients' median time to AML transformation was significantly longer than that of those receiving standard care (table 2) [HR 0.50; 95% CI 0.35, 0.70]. [27] Additionally, azacitidine significantly outperformed standard care in terms of rates of total remission, partial remission, any haematological improvement, significant erythroid improvement, and significant platelet improvement (table 2). There was no discernible difference in the rates of stable disease or significant neutrophil improvement between the groups (table 2). Significantly (p 0.0001) more azacitidine receivers (50 of 111 [45%]) than conventional care recipients (13 of 114 [11%]) achieved transfusion independence in the patients who required RBC transfusions at baseline.

Azacitidine had an acceptable tolerability profile in patients with higher-risk MDS. In the AZA-

001 trial, the most commonly occurring grade 3 or 4 adverse events in patients receiving

either azacitidine or conventional care were neutropenia, thrombocytopenia and anaemia (figure 1).[8]

Table 2: Efficacy of subcutaneous azacitidine (AZA) in patients (pts) with higher-risk myelodysplastic syndromes (MDS). Results of a randomized, open-label, multicentre trial in which pts with higher-risk MDS received subcutaneous AZA 75mg/m^2/day for 7 days every 28 days for at least six cycles or conventional care (comprising best supportive care, low-dose cytarabine or intensive chemotherapy)[8]

Treatment [no. of pts]	Median overall survival (mo)	Median time to AML transformation (mo)	Haematological response (% of pts)			Haematological improvement (% of pts)			
			complete remission	partial remission	stable disease	any	major erythroid	major platelet	major neutrophil
AZA [179]	24.5	17.8	17	12	42	49	40	33	19
Conventional care [179]	15	11.5	8	4	36	29	11	14	18

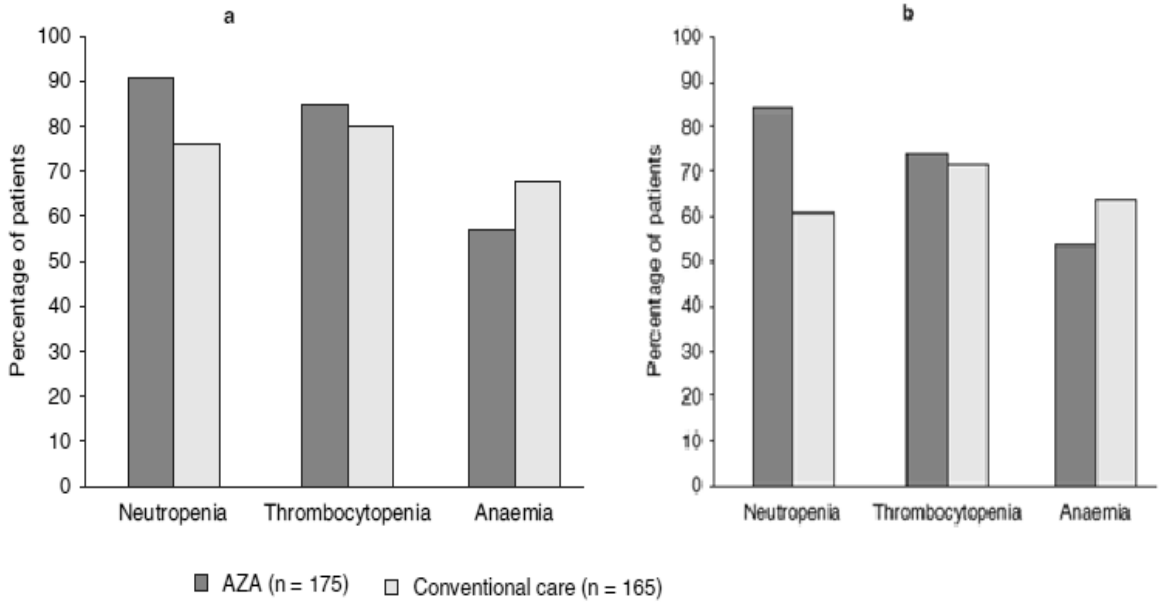

Figure 1: Haematological toxicity in patients with higher-risk myelodysplastic syndromes receiving subcutaneous azacitidine (AZA). Proportion of patients with (a) grade 3 or 4 haematological toxicity or (b) grade 0–2 haematological toxicity at baseline that progressed to grade 3 or 4 during treatment. In this randomized, open-label, multicentre trial, patients received subcutaneous AZA 75mg/m2/day for 7 days every 28 days for at least six cycles or conventional care comprising best supportive care, low-dose cytarabine or intensive chemotherapy.

The recommended azacitidine regimen is 75 mg/m^2/day administered subcutaneously for 7 consecutive days, followed by a 21-day rest period; azacitidine should be administered for at least six cycles and treatment should be continued for as long as patient benefit is seen or until disease progression.[9] In some HSCT patients, azacitidine may be helpful. For instance, patients with higher-risk MDS who are candidates for HSCT and are waiting for a donor who is a good match, or whose marrow blast count needs to be reduced, or whose performance status needs to be improved, before HSCT, may benefit from azacitidine as a bridging therapy. Studies looking at the administration of azacitidine before allogeneic HSCT in patients with high-risk MDS are currently being conducted.[10] Treatment of MDS may also involve combining the administration of azacitidine with additional medications. As the suppression of histone deacetylation may further decrease the activity of DNA methyltransferase, histone deacetylase inhibitors are an intelligent choice for concurrent administration with azacitidine. In fact, a phase I/II study in patients with MDS or AML showed promising early outcomes when azacitidine and the histone deacetylase inhibitor vorinostat were combined. Other combination therapies for MDS have also been studied, such as azacitidine combined with the histone deacetylase inhibitor valproic acid (with or without tretinoin),[11] azacitidine combined with hydroxycarbamide and gemtuzumab ozogamicin, and azacitidine combined with lenalidomide.[12-13]

Conclusion

In comparison to standard therapy, subcutaneous administration of the pyrimidine analogue azacitidine dramatically increases survival in individuals with higher-risk MDS or WHO-defined AML. Additionally, azacitidine is linked to higher rates of total remission, partial remission, haematological improvement, and independence from RBC transfusion as well as a lower risk of AML progression. The most frequent adverse event associated with azacitidine is peripheral cytopenias, which has a tolerable safety profile. As a result, azacitidine is a beneficial option for patients with MDS/AML who are at higher risk.

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