

A Comprehensive Overview of the Role of Azacitidine in the Management of Myelodysplastic Syndromes and Acute Myeloid Leukaemia

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Abstract

Myelodysplastic syndromes (MDS) are a heterogeneous group of haematological disorders marked by progressive cytopenias and risk of transformation to acute myeloid leukaemia (AML). Best supportive care (BSC) remains the mainstay of therapy. The pyrimidine analogue azacitidine was the first drug to demonstrate that a change in the natural history of MDS is possible and was the first chemotherapeutic agent approved by the US Food and Drug Administration for the treatment of MDS. Azacitidine, a hypomethylating agent, has shown to reduce proliferation and induce apoptosis of dysplastic cells. The Cancer and Leukemia Group B (CALGB) 9221 and AZA-001 trials demonstrated superiority of azacitidine over BSC and conventional care regimen, respectively. Various studies have demonstrated that azacitidine has better tolerability with comparable efficacy in terms of conventional therapy in older AML patients. Azacitidine is well tolerated even in the elderly patients. Cytopenias were the most commonly occurring haematological adverse events. Gastrointestinal adverse events (AEs) (e.g. nausea, vomiting and diarrhoea) and injection-site reactions were the most commonly occurring non-haematological AEs. The review summarises the current role of azacitidine in the management of MDS and AML.

Keywords

Myelodysplastic syndrome, acute myeloid leukaemia, azacitidine, CALGB 9221 trials, AZA-001 trials

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The myelodysplastic syndromes (MDS) are a heterogeneous group of haematological disorders characterised by ineffective haematopoiesis with associated cytopenias and a hypercellular bone marrow (BM) with dysplastic changes.¹ Patients with MDS have a variable reduction in the production of normal red blood cells (RBCs), platelets, and mature granulocytes. This often results in a variety of systemic consequences including anaemia, bleeding and an increased risk of infection.^{2,3}

The incidence of MDS in the US has been estimated as 4.1/100,000 population. The incidence rises with increasing age: 4.9 for people aged 50 to 70 years and 22.8 for people older than 70 years.⁴

There are two systems to classify MDS: the older French-American-British (FAB) classification⁵ and the more recent World Health Organization (WHO) classification.⁶ The FAB system classified MDS into five main subtypes:

- Refractory anaemia (RA) (<5 % marrow blasts);
- RA with ring sideroblasts (RARS) (<5 % marrow blasts);
- RA with excess blasts (RAEB) (5–20 % marrow blasts);
- RAEB in transformation (RAEB-T) (21–30 % marrow blasts); and
- Chronic myelomonocytic leukaemia (CMML) (5–20 % marrow blasts).

The 2008 WHO system further subdivided MDS, based on factors such as the presence or absence of multilineage dysplasia and the

percentage of BM blasts, into the following subtypes:

- Refractory cytopenia with unilineage dysplasia (including refractory anaemia, refractory neutropenia and refractory thrombocytopenia) (<5 % marrow blasts);
- RARS (<5 % marrow blasts);
- Refractory cytopenia with multilineage dysplasia (<5 % marrow blasts);
- RAEB-1 (5–9 % marrow blasts);
- RAEB-2 (10–19 % marrow blasts);
- MDS, unclassified (<5 % marrow blasts); and
- MDS associated with isolated del(5q) (<5 % marrow blasts).

In addition, ≥30 % marrow blasts are required for a diagnosis of acute myeloid leukaemia (AML) using the FAB system, whereas only ≥20 % marrow blasts are required for an AML diagnosis using the WHO system. *Table 1* gives an overview of comparison of the FAB and WHO classifications for MDS.

Prognosis of the MDS is evaluated by the Revised International Prognostic Scoring System (IPSS-R).⁷ Based on prognostic factors such as cytogenetic status (very good, good, intermediate, poor and very poor), BM blast percentage, haemoglobin (Hb) (g/dl), platelets (cells/μl) and absolute neutrophil count (cells/μl) patients are classified as very low, low, intermediate, high or very high risk of evolution to

Table 1: Overview of Comparison of the FAB and WHO Classifications for MDS

FAB (1982)	WHO (2008)
	Myelodysplastic Syndromes
Refractory anaemia	Refractory anaemia Refractory cytopenia with multilineage dysplasia Refractory cytopenia with unilineage dysplasia
Refractory anaemia with ring sideroblasts	Refractory anaemia with ring sideroblasts
Refractory anaemia with excess blasts	Refractory anaemia with excess blasts -1 and -2 Myelodysplastic syndrome, unclassifiable Myelodysplastic syndrome associated with del(5q)
Refractory anaemia with excess blasts in transformation	<i>Reclassified from MDS to:</i> Acute myeloid leukaemia identified as AML with multilineage dysplasia following a myelodysplastic syndrome
Chronic myelomonocytic leukaemia	Myelodysplastic and myeloproliferative diseases

AML = acute myeloid leukaemia; FAB = French-American-British classification scheme; MDS = myelodysplastic syndromes; WHO = World Health Organization.

AML, with an estimated median survival duration of 8.8, 5.3, 3.0, 1.6 and 0.8 years, respectively.⁸ The International Prognostic Scoring System (IPSS), the WHO Prognostic Scoring System (WPSS) and the MD Anderson Cancer Centre (MDACC) MDS Model⁹ are the other prognostic models used.

Existing Treatment Options of Myelodysplastic Syndromes

The main treatment option for MDS has been best supportive care (BSC), which aims to alleviate the negative effects of cytopenia and to increase quality of life (QOL). BSC remains the backbone of MDS therapy for all patients despite the emergence of novel drugs. This includes RBC transfusions to alleviate symptoms of anaemia, adequate iron chelation therapy to reduce haemosiderosis, platelet transfusions to decrease risk of haemorrhage in thrombocytopenic patients and control of infections by the use of antibiotics and granulocyte-colony stimulating factor (G-CSF).¹⁰ The only proved curative approach for MDS is allogeneic stem cell transplant (ASCT),¹¹ but its use has been limited by donor availability, advanced age of most patients with this disorder and higher costs. SCT-related mortality is in the range of 30 % to 40 % in most studies.¹² Given these limitations ASCT is not an adequate option for most patients with higher-risk MDS. Other less-intensive treatment options include non-intensive chemotherapy (non-IC), immunomodulatory agents or immunosuppressive therapy. These approaches do not offer significant survival benefit in higher-risk MDS patients.

Demethylating agents such as azacitidine and 5-aza-deoxycytidine (decitabine) have recently emerged as effective drugs for the treatment of MDS. Azacitidine was approved for the treatment of patients with MDS of all subtypes in 2004 by the US Food and Drug Administration (FDA) and for higher-risk MDS, CMML and AML with 20 % to 30 % blasts and multi-lineage dysplasia by the European Medicines Agency (EMA) in 2009. Azacitidine was approved by Drug Controller General of India (DCGI) for the treatment of adult patients with all subtypes of MDS on 15 May 2014. This article reviews the basic pharmacology, clinical efficacy, tolerability and its placement in the management of AML and MDS.

Pharmacodynamic Properties

Azacitidine is a pyrimidine nucleoside analogue of cytidine that is phosphorylated intracellularly to its active form, azacitidine triphosphate. The azacitidine molecule exerts its antineoplastic activity by hypomethylation of the DNA and a cytotoxic effect on abnormal haematopoietic cells in the BM.¹³

Following cellular uptake, azacitidine gets converted into azacitidine triphosphate, which is incorporated into the RNA. About 10–20 % is converted to 5-aza-2-deoxycytidine triphosphate via the enzyme ribonucleotide reductase and gets incorporated into the DNA. This results in the formation of adducts between the DNA and DNA methyltransferase 1 (DNMT-1). At high doses, the DNA is not able to recover and cell death occurs. However, at lower doses the formed adducts are degraded by the proteasome, after which the DNA is restored. DNA synthesis is then resumed in the absence of DNMT-1. As a consequence the aberrant DNA methylation pattern can no longer be reproduced toward the daughter strands.¹⁴ In this way, a low dose of azacitidine is able to induce re-expression of previously silenced genes. Reactivation of cell cycle-regulating genes that were initially silenced due to hypermethylation may induce cell differentiation, reduce proliferation and/or increase apoptosis of the daughter cells.¹⁵

Pharmacokinetic Properties

Absorption

Absorption of azacitidine is rapid after subcutaneous (SC) administration. A maximum plasma concentration of 750 ± 403 ng/ml is attained within 30 minutes of administration of a standard dose of 75 mg/m² subcutaneously. The SC administration attains a bioavailability of approximately 89 % in comparison with intravenous (IV) infusion.¹⁴

Distribution

For azacitidine the mean volume of distribution after IV administration was about 76 l.¹⁴

Metabolism

Intracellular phosphorylation is a pivotal step for azacitidine to become active. Azacitidine is metabolised principally in the liver. Other sites of metabolism include granulocytes, intestinal epithelium and whole blood. It undergoes spontaneous hydrolysis followed by cytidine deaminase mediated deamination. As azacitidine metabolism is not mediated by cytochrome P450 (CYP 450) isoenzymes no clinically significant drug interactions are seen with CYP 450 substrates, inducers or inhibitors.

Elimination

Azacitidine and its metabolites are primarily excreted in urine. It is cleared rapidly from plasma with mean elimination half-life of 41 minutes after a standard SC dose of 75 mg/m², where as the mean elimination half-life after IV administration is 22 minutes. The systemic clearance of azacitidine is 147 ± 47 l/hour.¹⁴

Alterations in Special Populations

Caution is required in patients with renal impairment because azacitidine and its metabolites are primarily excreted by the kidneys. Prior estimation of liver function tests and serum creatinine before starting each treatment cycle should be performed. Renal insufficiency prior to starting treatment does not require dose modification. However, close monitoring of the patients for toxicity is necessary and dose reductions should be implemented if necessary.¹⁶ A retrospective study examined the feasibility of therapy with azacitidine or decitabine in patients with renal insufficiency (creatinine clearance ≤ 59 ml/minute).¹⁷ Toxicity rates were comparable to previous reports in patients with adequate renal function. Standard doses of hypomethylating agents were tolerated by most patients. However, dose reductions and treatment interruptions were required for patients with severe renal insufficiency (i.e., creatinine clearance ≤ 30 ml/minute). This group experienced more treatment-related toxicities, mainly myelosuppression and worsening of the renal function.¹⁷

There have been no studies on the effects of age and gender on azacitidine pharmacokinetics. The pharmacokinetics of azacitidine in Japanese patients with MDS were similar to those in Caucasian patients with MDS.¹

Therapeutic Efficacy in Myelodysplastic Syndromes – Landmark Studies

The Cancer and Leukemia Group B Trials

Two early Cancer and Leukemia Group B (CALGB) trials by Silverman et al.¹⁸ (CALGB 8421 and CALGB 8921) demonstrated the potential of SC or IV azacitidine in the treatment of patients with MDS. *Table 2* gives response rates of these phase II studies. Median duration of response (complete response [CR] + partial response [PR]) was 14.7 and 17.3 months for patients treated with IV versus SC azacitidine, respectively. Mild degree of nausea and vomiting were more frequent with SC azacitidine. Myelosuppression was seen in only 25 % of patients. The activity of azacitidine administered IV or SC was comparable at the dose and schedule tested.

The randomised, multicentre, phase III, CALGB 9221 trial,¹⁹ compared the efficacy of SC azacitidine 75 mg/m²/day subcutaneously for 7 days every 28 days with that of supportive care alone in patients with MDS fulfilling FAB classification criteria (RA, RARS, RAEB, RAEB-T or CMML).

In the CALGB 9221 trial, patients with MDS who received azacitidine had a significantly higher overall response rate than those receiving supportive care alone (60 % versus 5 %) (see *Table 3*).

The CR rate and the CR plus PR rate were also significantly higher with azacitidine than with supportive care alone.

The median time to treatment failure (21 versus 12 months) and to AML transformation or death (9.1 versus 3.8 months) were significantly longer in patients receiving azacitidine than in those receiving supportive care (see *Table 3*).

There was no significant difference in the median duration of overall survival (OS) between patients receiving azacitidine and those receiving supportive care (20 versus 14 months) (see *Table 3*), although these results were confounded by the 49 supportive care recipients who crossed over to azacitidine during the course of the trial. In a landmark analysis designed to eliminate this confounding effect, the median duration of OS was significantly longer in patients initially randomised

Table 2: Azacitidine in MDS-CALGB 8421 and 8921

	CALGB 8421	CALGB 8921
Number of patients	48	72
Study drug	Azacitidine 75 mg/m ²	Azacitidine 75 mg/m ²
Dosage administration	Continuous intravenous infusion for 7 days on a 28-day cycle	Subcutaneous daily for 7 days on a 28-day cycle
Number of cycles	Minimum 4	Minimum 4
Overall response	49 %	53 %
Complete response	12 %	12 %
Partial response	25 %	15 %
Improved	12 %	27 %

CALGB = Cancer and Leukemia Group B.

to azacitidine than in patients initially randomised to supportive care who never crossed over to azacitidine or only crossed over after 6 months had elapsed (18 versus 11 months; $p=0.03$) (see *Table 3*).

Patients who achieved a complete or PR by definition did not require any RBC or platelet transfusion requirements. Among patients experiencing improvement, 22 % had elimination of RBC transfusion requirements, 16 % had a ≥ 50 % decrease in RBC transfusions and 35 % had ≥ 50 % restitution in the RBC deficit.

Certain health-related QOL (HR-QOL) measures such as fatigue, physical functioning, dyspnoea, psychosocial distress and positive effect improved to a significantly greater extent in patients receiving azacitidine than in those receiving supportive care.¹⁹

Haematological response data from the CALGB 9221 trial (and the CALGB 8421 and CALGB 8921 trials) were retrospectively reanalysed in 2006 using International Working Group (IWG) 2000 criteria. Among 99 patients who received azacitidine and 41 patients who received supportive care (without subsequently crossing over to azacitidine), the overall response rate (CR plus PR plus haematological improvement) was 47 % versus 17 %, with CR rates of 10 % versus 0 %, partial remission rates of 1 % versus 0 % and haematological improvement rates of 36 % versus 17 %.²⁰

The AZA-001 Trial

The AZA-001 trial was a randomised, open-label, multicentre, phase III trial that examined the efficacy of SC azacitidine 75 mg/m² per day for 7 days every 28 days in adults with higher-risk (i.e. IPSS intermediate-2-risk or high-risk classification) MDS/AML.²¹ Patients were randomised to receive azacitidine ($n=179$) or the preselected conventional care regimen (CCR) ($n=179$). CCRs were given as follows: BSC only; low-dose cytarabine (LDAC), 20 mg/m² per day subcutaneously for 14 days, every 28 days for at least four cycles; or IC (induction with cytarabine 100–200 mg/m² per day by continuous IV infusion for 7 days, plus 3 days of either IV daunorubicin [45–60 mg/m² per day], idarubicin [9–12 mg/m² per day] or mitoxantrone [8–12 mg/m² per day]).

Azacitidine was effective in the treatment of patients with higher-risk MDS/AML. Median OS was significantly better with azacitidine than with conventional care (see *Table 4*) (24.5 versus 15 months). When OS was analysed according to the preselected conventional care strategy, median OS was significantly longer with azacitidine than with BSC (21.1 versus 11.5 months; $p=0.0045$) and with azacitidine versus LDAC (24.5 versus 15.3 months; $p=0.0006$), with no significant difference

Table 3: Details of Phase III Randomised Controlled Trial (CALGB 9221) in MDS to Compare Azacitidine with Supportive Care

Parameter	Silverman et al. (CALGB 9221)	
	AZA (n=99) ^a	Supportive Care (n=92)
FAB Classification at Baseline (% of Patients)		
RA	17	22
RARS	5	3
RAEB	32	37
RAEB-T	27	20
CMML	7	8
Other AML	11	11
IPSS Risk Group at Baseline (% of Patients)		
Low	5	12
Intermediate-1	54	38
Intermediate-2	23	31
High	18	19
Main inclusion criteria	MDS fulfilling FAB classification criteria; age >15 y; life expectancy ≥2 mo; NCI performance status ≤2	
Selected exclusion criteria	Prior treatment for MDS with AZA, G-CSF, GM-CSF or other haematopoietic cytokines; erythropoietin, corticosteroids, interferon or retinoids within 1 mo before study; prior history of leukaemia; pregnancy; uncontrolled heart failure	
Primary endpoints	Haematological response rate	
Results		
Response Rates^b (%)	AZA (n=99)	Supportive Care (n=92)
Complete response	7**	0
Partial response	16*	0
Improved	37****	5
Total	60****	5
Other Endpoints	AZA (n=99)	Supportive Care (n=92)
Main Analysis		
Median time to AML transformation or death (mo)	21**	12
Median time to treatment failure (mo)	9.1****	3.8
Median overall survival (mo)	20	14
Eliminating Confounding Effect of Cross-over^c		
Median overall survival (mo)	18*	11
High-risk Patients		
Median time to AML transformation or death (mo)	16.9***	4.5
Median overall survival (mo)	19.4*	9.6

a. Subcutaneous (SC) azacitidine (AZA) 75 mg/m²/day for 7 consecutive days (d) every 4 weeks (i.e. starting on days 1, 29, 57 and 85). b. Haematological response definitions were based on Cancer and Leukemia Group B (CALGB) criteria. c. The 36 patients who died before the 6 month landmark date were excluded. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; FAB = French-American-British; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony stimulating factor; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; mo = months; NCI = National Cancer Institute; RA = refractory anaemia; RAEB = RA with excess blasts; RAEB-T = RAEB in transformation; RARS = RA with ring sideroblasts; y = year.

between azacitidine and IC (25.1 versus 15.7 months). Further analysis of patients preselected to receive LDAC (n=94) revealed a 2-year OS rate of 54 % with azacitidine and 27 % with LDAC.²²

The median time to AML transformation was significantly longer in patients receiving azacitidine than in those receiving conventional care (17.8 versus 11.5) (see Table 4). When analysed according to

the preselected conventional care strategy, the median time to AML transformation was significantly longer with azacitidine than with BSC (15.0 versus 10.1 months; p<0.0001), with no significant difference between azacitidine and LDAC (15.0 versus 14.5 months) or between azacitidine and IC (23.1 versus 10.7 months). Among patients who were RBC transfusion dependent at baseline, significantly more azacitidine than conventional care recipients achieved RBC transfusion independence (see Table 4).

Rates of any remission (29 % versus 12 %), CR (17 % versus 14 %) or PR (12 % to 8 %) and rates of any (49 % versus 29 %), major erythroid (40 % versus 11 %) or major platelet (33 % versus 14 %) improvement were significantly higher in patients receiving azacitidine than in those receiving conventional care (see Table 4).

Therapeutic Efficacy in Acute Myeloid Leukaemia – Landmark Studies

AML is associated with poor prognosis in elderly patients with 2-year OS rates of approximately 10 %. There is lack of adequate treatments for AML patients. IC is generally limited to only 30 % to 60 % of older AML patients due to poor performance status, significant comorbidities, adverse tumour cytogenetics and poor treatment tolerability, leading to treatment-related mortality rates of 10 % to 25 %. Therefore, new treatment options are needed for these patients.²³

Fenaux et al. conducted a phase III trial in which azacitidine demonstrated significantly prolonged OS compared with CCRs in patients with International Prognostic Scoring System–classified intermediate-2- and high-risk MDS.²¹ A subgroup analysis was further conducted²⁴ that compared the relative efficacy and safety of azacitidine versus CCR in patients with refractory anaemia with excess blasts in transformation (RAEB-t; 20 % to 30 % BM blasts), which were diagnosed as AML according to the new WHO 2008 classification. Patients were randomly assigned to receive SC azacitidine 75 mg/m²/d or CCR (BSC only, LDAC), or IC. At a median follow-up of 20.1 months, median OS for azacitidine-treated patients was 24.5 months compared with 16.0 months for CCR-treated patients (hazard ratio [HR] 0.47, 95 % confidence interval [CI], 0.28 to 0.79; p=0.005), and 2-year OS rates were 50 % and 16 %, respectively (p=0.001). Number of days spent in hospital was fewer in the azacitidine group (0.5 versus 56; p<0.001), and needed fewer RBC and platelet transfusions (2.7 versus 7; p<0.001 and 0.3 versus 5; < 0.001) in the first 3 months.

Maurillo et al.²⁵ analysed 82 patients with AML who were diagnosed according to WHO criteria. The overall response rate to azacitidine was 32 % (26 of 82 patients) and included 12 (15 %) CRs, four (5 %) CRs with incomplete blood count recovery (CRI) and 10 (12 %) PRs. Patients with white blood cell counts <10 × 10⁹/l had a significantly higher response rate (p=0.006). The median overall response duration was 13 months, and the 1-year and 2-years OS rates were 58 % and 24 %, respectively, for untreated patients who achieved a response. These results indicated that azacitidine promises to be an effective therapy for elderly patients with untreated AML and with white blood cell counts <10 × 10⁹/l.

Van der helm et al. collected data of 227 consecutive AML patients (≥60 years) who were treated with azacitidine (n=26), IC (n=90) or BSC (n=97) to compare the effectiveness of azacitidine with conventional therapy. OS was similar (1-year OS 57 % versus 56 %; p=0.93; 2-year OS 35 % versus 35 %; p=0.92) with azacitidine and conventional therapy. Azacitidine-treated patients spent fewer days in the hospital (median

Table 4: Details of a Randomised, Multicentre, Phase III Trial AZA-001 and Comparing the Efficacy of Azacitidine with Conventional Care in Patients of Myelodysplastic Syndromes

Parameter	Fenaux et al. (AZA-001) AZA (n=179) ^a	Conventional Care ^b (n=179)
FAB Classification at Baseline (% of Patients)		
RA	-	-
RARS	-	-
RAEB	58	58
RAEB-T	34	35
CMML	3	3
Other/AML	1	1
WHO Classification at Baseline (% of Patients)		
RA	-	-
RCMD	-	-
RCMD-RS	-	-
RAEB-1	8	10
RAEB-2	55	53
CMML-1	1	0
CMML-2	6	3
del(5q)	-	-
AML	31	32
IPSS Risk Group at Baseline (% of Patients)		
Low	-	-
Intermediate-1	3	7
Intermediate-2	43	39
High	46	48
Main inclusion criteria	Higher-risk MDS (i.e. IPSS intermediate-2-risk or high-risk classification); FAB-defined RAEB, RAEB-T or CMML with $\geq 10\%$ bone marrow blasts and a white blood cell count of $<13 \times 10^9/l$; age ≥ 18 y; ECOG performance status of 0–2; estimated life expectancy of ≥ 3 months	
Selected exclusion criteria	Therapy-related MDS; previous treatment with AZA; planned allogeneic HSCT	
Primary endpoints	Overall survival	
Other endpoints	Time to transformation to AML; haematological response or improvement ^c ; independence from RBC transfusion for ≥ 56 consecutive days	
Results		
Endpoint	AZA (n=179)	Conventional Care (n=179)
Median overall survival (months)	24.5****	15
Overall survival at 2 years (%)	50.8****	26.2
Median time to AML	17.8****	11.5
RBC transfusion independence (%)	45****	11
Haematological Response (%)	AZA (n=179)	Conventional Care (n=179)
Any remission	29 %****	12 %
Complete remission	17 %*	14 %
Partial remission	12 %**	7 %
Stable disease	75 %	65 %
Haematological Improvement (%)	AZA (n=179)	Conventional Care (n=179)
Any improvement	49 %****	29 %
Major erythroid Improvement	40 %****	11 %
Major platelet Improvement	33 %***	14 %
Major neutrophil Improvement	19 %	18 %

a. Subcutaneous (SC) azacitidine (AZA) 75 mg/m²/day was administered for 7 consecutive days every 28 days for at least six cycles. b. Conventional care comprised best supportive care, low-dose cytarabine or intensive chemotherapy. c. Definitions for haematological response and improvement were based on International Working Group 2000 criteria for MDS. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ versus supportive care. AML = acute myeloid leukaemia; CMML = chronic myelomonocytic leukaemia; ECOG = Eastern Co-operative Oncology Group; FAB = French-American-British; HSCT = haematopoietic stem cell transplantation; IPSS = International Prognostic Scoring System; IV = intravenous; MDS = myelodysplastic syndromes; RA = refractory anaemia; RAEB = RA with excess blasts; RAEB-T = RAEB in transformation; RARS = RA with ring sideroblasts; RBC = red blood cell; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = RCMD with ring sideroblasts; WHO = World Health Organization.

in first 3 months 0.5 versus 56; $p < 0.001$). Azacitidine-treated patients required fewer RBC and platelet transfusions (median per month 2.7 versus 7; $p < 0.001$ and 50.3 versus 5; $p < 0.001$) in the first 3 months.²⁶

Thepot et al. collected data of 149 previously untreated AML patients considered ineligible for IC, who were treated with azacitidine. Response rate was 33 %. Median OS was 9.4 months. Fifty-one per cent of responders survived beyond 2 years whereas only 10 % of non-responders survived this period ($p < 0.0001$).²⁷

Dombret et al. conducted a phase III trial to compare effects of azacitidine versus CCR in 488 patients aged ≥ 65 years (median age 75 years, 59 % male) with newly diagnosed *de novo* or secondary AML ($>30\%$ BM blasts), ineligible for ASCT. The results demonstrated a significant benefit with azacitidine in terms of greater median OS (12.1 versus 6.9 months; $p = 0.019$) and 1-year survival (47 % versus 34 %) compared with CCR.²⁸

Thus, from the available data it can be concluded that azacitidine treatment is associated with a comparable OS but higher tolerability,

reduced transfusion dependence and decreased duration of hospital stay in older AML patients compared with conventional therapy.

Hypomethylating Agents – Azacitidine versus Decitabine

In an adjusted indirect meta-analysis by Kumar et al. to assess the efficacy of azacitidine compared with decitabine in MDS patients, 5-azacitidine demonstrated a statistically significant benefit for the outcome of OS. The HR for OS was 0.63 (95 % CI 0.46–0.85; $p=0.003$). However, 5-azacitidine and decitabine lacked any statistically significant difference for time to AML transformation or death (HR 0.85, 95 % CI 0.59–1.23; $p=0.406$), response rate (risk ratio 0.716, 95 % CI 0.372–1.375; $p=0.315$, using the number of non-responders) or treatment-related mortality (risk ratio 1.026, 95 % CI 0.01–102.118; $p=0.991$).²⁹

A meta-analysis was performed by Xie et al. to compare the efficacy, toxicity and survival advantage of decitabine and azacitidine in patients with MDS. Eleven trials with a total of 1,392 patients with MDS (decitabine $n=768$; azacitidine $n=624$) were included for analysis. Azacitidine had significantly higher PR, haematological improvement and overall response rates than for decitabine. CR, RBC transfusion-independent rates and grade 3 or 4 haematological toxicity were similar with both drugs. Azacitidine was significantly superior to BSC in improving OS (HR 0.69, 95% CI 0.54–0.87) and time to AML transformation (HR 0.51, 95 % CI 0.35–0.74). The decitabine group did not show such superiority. Azacitidine was a favourable factor in patients with higher risk (IPSS value of 3) or older than 75 years, treatment with azacitidine was a favourable factor.³⁰

A retrospective analysis by Smith et al.³¹ in AML patients initiating treatment with decitabine or azacitidine demonstrated a significantly higher OS (10.1 versus 6.9 months, respectively; $p=0.007$) and longer time to death (adjusted HR 0.721; $p=0.008$) in the azacitidine-treated cohort than in the decitabine-treated cohort. Overall hospitalisation rates were lower in the azacitidine-treated cohort compared with the decitabine-treated cohort (2.90 vs. 3.42 per person-year). Patients in the azacitidine-treated cohort also had a significantly longer median time to first hospitalisation compared with decitabine-treated patients (1.9 versus 1.4 months respectively, $p=0.015$) and an overall lower risk of hospitalisation (adjusted HR 0.787; $p=0.02$).

Adverse Events Associated with Azacitidine

Haematological toxicity was the most commonly occurring adverse event (AE) in azacitidine recipients.

In the CALGB 9221 trial, grade 3–4 leukopenia, granulocytopenia and thrombocytopenia occurred in 43 %, 58 % and 52 % of azacitidine recipients, respectively. They were managed by interruption of azacitidine dosing in 23 % patients and azacitidine dose reduction in 11 % of patients.³²

Among azacitidine recipients, nadir haemoglobin levels, platelet counts and absolute neutrophil counts occurred in a median of 14–15 days in the AZA-001 trial and a median of 15–16 days in the CALGB 9221 trial.

In the AZA-001 trial, anaemia and thrombocytopenia were managed by blood transfusions in 87 % and 29 %, respectively. Infections were treated with antibiotics (levofloxacin, ciprofloxacin). Neutropenia was treated with G-CSF in 13 % of patients.

The most common non-haematological AEs were gastrointestinal (GI) and injection-site reactions. Anti-emetics (ondansetron, metoclopramide,

domperidone), stool softeners (lactulose) and anti-diarrhoeal (loperamide) were used to manage GI adverse effects in the CALGB and AZA-001 trials.³² Haematological and non-haematological AEs with azacitidine decreased in frequency as treatment continued.³²

In the AZA-001 trial, the rate of infections requiring IV antimicrobials was significantly lower in patients receiving azacitidine than in those receiving conventional care (0.60 versus 0.92 per patient-year; $p=0.0032$) in adults with higher-risk (i.e. IPSS intermediate-2-risk or high-risk classification) MDS/AML.²¹ The rate of hospitalisations was also significantly ($p<0.0001$) lower in azacitidine recipients than in patients receiving conventional care (29 % versus 39 % per patient-year).

The majority of AEs reported in the AZA-001 and CALGB 9221 studies were transient and were managed by either supportive care measures, dose delays or, less commonly, dose reductions. Early detection and prompt management of AEs would allow patients to continue therapy and offer maximum benefit of azacitidine therapy.

Summary and Place of Azacitidine in the Management of Myelodysplastic Syndromes/ Acute Myeloid Leukaemia

Patients with MDS are at risk of symptomatic anaemia, infection and bleeding, as well as progression to AML. The main goal of treatment in patients with lower-risk MDS is to achieve transfusion independence, while the goals of therapy in patients with higher-risk MDS include increasing survival and suppressing leukaemic transformation.

The pyrimidine analogue azacitidine was the first drug to demonstrate that a change in the natural history of MDS is possible. According to guidelines from the US National Comprehensive Cancer Network (NCCN),²³ although the major candidates for treatment with the hypomethylating agents are patients with higher-risk MDS (i.e. IPSS intermediate-2-risk or high-risk classification), their use is also recommended in lower-risk MDS (i.e. IPSS low-risk or intermediate-1-risk classification) with clinically relevant thrombocytopenia or neutropenia, and in those with symptomatic anaemia, no del(5q) (with or without other cytogenetic abnormalities), a serum erythropoietin level of >500 mU/ml and a poor probability of responding to immunosuppressive therapy.

Patients diagnosed with MDS treated with azacitidine demonstrated a significantly higher response rate, higher OS and longer median time-to-AML transformation than BSC and CCR. Azacitidine also provided relief from repetitive transfusions, limiting hospitalisations.²⁹

Azacitidine is a considerable treatment option for AML and offers comparable OS but better tolerability in older patients compared with IC. In older adult patients with low BM blast count (20 % to 30 %) WHO-defined AML, azacitidine significantly prolongs OS and significantly improves several patient morbidity measures compared with conventional care.

Azacitidine was generally well tolerated in patients with MDS, including in the elderly. Cytopenias were the most commonly occurring AE in azacitidine recipients, with GI AEs (e.g. nausea, vomiting and diarrhoea) and injection-site reactions among the most commonly occurring non-haematological AEs. However, most of these are transient and can be managed by supportive care measures or delay in dosing.

In conclusion, azacitidine is an important agent for use in the treatment of patients with MDS/AML. ■

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