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Azacitidine
In Myelodysplastic Syndromes

M. Asif A. Siddiqui and *Lesley J. Scott*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

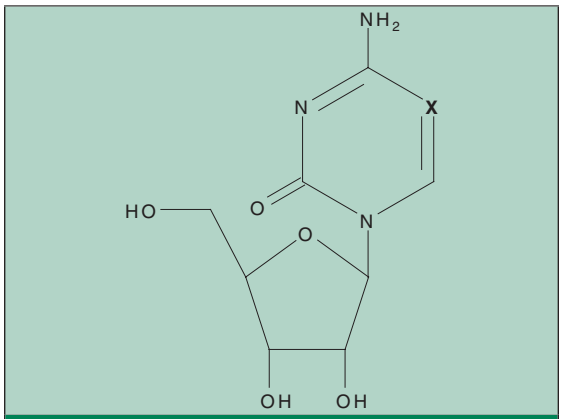
▲ Azacitidine, a pyrimidine analogue, is an antineoplastic agent that acts mainly by causing hypomethylation of cytosine residues in newly replicated DNA and has shown efficacy in the treatment of myelodysplatic syndromes (MDS).

▲ In a randomised controlled trial in patients with MDS (n = 191), subcutaneous azacitidine 75–100 mg/m^2/day in 7-day cycles every 28 days with continuing supportive care produced a significantly higher response rate (including reductions in rate of transformation to acute myeloid leukaemia and transfusion requirements) than that seen with supportive care alone (60% vs 5%; $p < 0.001$). Patients (n = 49) who were switched from supportive care to azacitidine after 4 months also showed a 47% response rate.

▲ The clinical response in patients receiving azacitidine was associated with significant ($p \leq 0.015$) improvements in several measures of health-related quality of life, including those assessing fatigue and physical functioning, compared with those in supportive care recipients.

▲ Given the grim prognosis of MDS patients, azacitidine was generally well tolerated, with common, but transient, myelotoxicity. Adverse events did not increase in severity or frequency during the course of the treatment.

Features and properties of azacitidine (Vidaza™)	
Indication	
Myelodysplastic syndromes (MDS)	
Mechanism of action	
Antineoplastic agent; causes hypomethylation of cytosine residues in newly synthesised DNA by inhibiting DNA methyltransferase	
Pharmacokinetic profile (single dose of subcutaneous azacitidine 75 mg/m^2 in MDS patients)	
Maximum plasma concentration	750 ng/mL
Area under the plasma concentration-time curve from 0 to infinity	960 ng • h/mL
Half-life	41 minutes
Dosage and administration	
Route of administration	Subcutaneous
Dosage	75–100 mg/m^2 in 7-day cycles
Frequency	Every 28 days
Tolerability	
Most common adverse events (≥30%)	Nausea, anaemia, thrombocytopenia, vomiting, pyrexia, leucopenia, diarrhoea, fatigue, injection-site erythema, constipation, neutropenia, ecchymosis and cough



Azacitidine (X = N) and cytidine (X = CH)

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematological disorders, characterised by ineffective haematopoiesis leading to blood cytopenias with generally hypercellular bone marrow and dysplasia of the cellular elements.[1-4] On the basis of morphological criteria derived from bone marrow aspirates, five categories of MDS were described by a French, American and British (FAB) consensus conference of haematologists and haematopathologists: refractory anaemia (RA), RA with ringed sideroblasts (RARS), chronic myelomonocytic leukaemia (CMmL), RA with excessive blasts (RAEB) and RA with excessive blasts in transformation (RAEB-T).[3] A more recent classification of MDS is the WHO classification, a modification of the FAB classification, with more emphasis on cytogenetic analysis and reclassification of some MDS subcategories.[5] In addition, the International Prognosis Scoring System (IPSS) has been developed to provide an improved method for assessing prognosis in MDS. This system incorporates several critical prognostic factors, including cytogenetic abnormalities, percentage of bone marrow myeloblasts and number of cytopenias, along with age and gender, to predict survival and the potential for evolution of the disease to acute myeloid leukaemia (AML).[6]

In the US, approximately five new cases of MDS per 100 000 of general population occur each year.[7] The incidence increases with age, reaching as high as 22–45 cases per 100 000 in individuals aged over 70 years.[7] The prognosis of MDS is poor, with the disease transforming to AML in approximately 35–40% of patients.[4] Furthermore, most patients with MDS are elderly with coexisting medical problems.[7] Death occurs due to bleeding, infection in the setting of neutropenia or therapy-related causes,[1,3,4] with an overall survival of 5–12 months for those with high-risk MDS (FAB subtypes with excess blasts).[7]

The course of disease and the response to therapy are influenced by age and individual clinical and prognostic factors.[7] Therefore, treatment for patients with MDS must be individualised.[7] The treatment of MDS has been unsatisfactory to date. Supportive care, including transfusions to correct anaemia, administration of haematopoeitic growth factors (such as erythropoietin and granulocyte colony-stimulating factor) and antibacterials, remains the mainstay of patient management.[7]

Although high-intensity therapy may produce long-term responses, it is associated with a greater risk of treatment-related morbidity and mortality.[7] Furthermore, benefits of intensive chemotherapy using several different regimens have not been shown in recent comparative trials[7] and allogeneic stem cell transplantation, the other available high-intensity therapy, is a realistic option for only a small proportion of patients.[1]

With the exception of patients with poor performance status (Eastern Cooperative Oncology Group grade 3–4), low-intensity therapy provides a treatment option in almost all cases of MDS. Azacitidine (5-azacytidine, Vidaza™)[1], a pyrimidine analogue, has been recommended as a low-intensity therapy for treating MDS patients, especially those with progressing or relatively high-risk disease.[7] The focus of this review is the use of this drug in the treatment of patients with MDS.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

1. Pharmacodynamic Properties

Azacitidine is a pyrimidine nucleoside (cytidine) analogue with multiple mechanisms involved in its antineoplastic action. There is extensive evidence that RNA metabolism is the primary target of this antimetabolite.[8] Nevertheless, its inhibition of DNA methylation has been proposed as the main effect responsible for its clinical efficacy in MDS.[8]

- DNA methylation is believed to contribute to cancer initiation and progression by inactivation of the expression of genes that are essential for the control of normal cell growth, differentation and apoptosis.[9] Hypermethylation of the calcitonin gene was found in 65% of patients (n = 20) with MDS,[10] and aberrant hypermethylation and the consequent inactivation of the $p15^{INK4b}$ tumor suppression gene were associated with progression of the disease.[11]
- Azacitidine, after incorporation into DNA, acts by noncompetitively inhibiting DNA methyltransferase, the enzyme in mammalian cells responsible for methylating newly synthesised DNA.[8] The resulting hypomethylation of cytosine residues is thought to induce cell differentiation through activation and re-expression of genes silenced by hypermethylation.[8] This inhibition of methylation is not seen in resting nondividing cells and occurs at azacitidine concentrations that do not cause major suppression of DNA synthesis.[8]
- Azacitidine (2–16 μmol/L) induced apoptosis of human promyelocytic HL-60 cells in culture (4–69% apoptotic cells after 4 hours' incubation), with a concentration-dependent mechanism of cytotoxic action.[12] Azacitidine incorporation into RNA predominated at low concentrations (2–8 μmol/L), resulting in the induction of cytotoxicity, mainly in G_1 cells. By contrast, at a high concentration (16 μmol/L), azacitidine affected both DNA replication and RNA metabolism, causing an increase in the proportion of S-phase cells undergoing apoptosis.[12]
- In cell culture, azacitidine appeared to downregulate leukaemia inhibitory factor, oncostatin M, interleukin (IL)-6 and IL-11 release by mononuclear cells of patients with refractory anaemia, but not those of healthy volunteers.[13] These agents have an important role in regulating normal haematopoeisis and also inhibit proliferation of myeloid leukaemic cell lines.[13] Furthermore, azacitidine has been reported to act as a biological response modifier, rendering unresponsive cells sensitive to the effect of cytokines, to restore normal haematopoeisis.[14]

2. Pharmacokinetic Properties

The single-dose pharmacokinetics and bioavailability of subcutaneous and intravenous azacitidine 75 mg/m^2 have been investigated in a randomised, nonblind, crossover study in six patients with MDS.[15] The data in the published report are supplemented by those available from the prescribing information[16] and the azacitidine New Drug Application submitted to the US FDA.[17]

- Azacitidine was rapidly absorbed after subcutaneous administration, with a maximum plasma azacitidine concentration of 750 ng/mL occurring in 0.5 hours; the corresponding area under the plasma concentration-time curve from time 0 to infinity (AUC_∞) was 961 ng • h/mL.[15] Based on the AUC_∞, the bioavailability of subcutaneous azacitidine relative to intravenous azacitidine was approximately 89%.[15]
- Azacitidine is widely distributed throughout the body, with a mean volume of distribution of 76L after intravenous administration.[15] The drug may be metabolised in the liver and undergoes deamination by cytidine deaminase.[17] Azacitidine metabolites in humans have not yet been characterised.[17]
- Following subcutaneous administration, the mean apparent systemic clearance of azacitidine was 167 L/h, with a mean half-life of 41 minutes.[15] Azacitidine and its metabolites are primarily excreted in urine.[16,17] Mean excretion of radioactivity in urine following subcutaneous administration (50%) of radiolabeled azacitidine was substantially lower than that after intravenous administration (up to 98%) in cancer patients.[17] Faecal excretion accounted for <1% of administered radioactivity.[16,17] Total radioactivity (azacitidine and its metabolites) was eliminated with similar plasma half-lives after

intravenous and subcutaneous administrations (approximately 4 hours).[16,17]

- Drug interaction studies with azacitidine have not been conducted. Azacitidine 1.0–100 μmol/L did not induce cytochrome 1A2, 2C19 or 3A4/5 in human cultured hepatocytes.[16,17]

3. Therapeutic Trials

The efficacy of azacitidine has been evaluated in a randomised, controlled, multicentre phase III trial in 191 patients with all subtypes (FAB classification) of MDS.[18] In addition to fulfilling the FAB classification criteria for MDS, patients with RA or RARS were also required to meet criteria of significant marrow dysfunction: required RBC transfusions for ≥3 months before study entry; had ≥2 platelet counts of $\leq 50 \times 10^9$/L or required platelet transfusions; or had an absolute neutrophil count of $<1 \times 10^9$/L with an infection requiring intravenous antibacterials.

Patients, stratified by FAB subtype, were randomised to receive standard supportive care alone (n = 92) or along with subcutaneous azacitidine 75 mg/m^2/day (n = 99) administered in 7-day cycles beginning on days 1, 29, 57 and 85. In the absence of any significant toxicity (other than nausea or vomiting), azacitidine dosage was increased by 33% if a beneficial effect was not observed by day 57. The dosage of azacitidine showing benefit was continued unless toxicity developed.[18]

Patients were assessed after the fourth treatment cycle.[18] In patients showing a favourable response (figure 1) at this assessment, azacitidine treatment was continued for three more cycles (for complete responders) or until either complete response or relapse was seen (for partial responders and improved patients). Patients were classified as treatment failures (figure 1) and removed from treatment if their disease progressed during the induction phase or remained stable at day 113. Patients whose disease was worsening after a minimum of 4 months of supportive care were permitted to crossover to azacitidine treatment. The treatment in these patients was identical to that in patients initially randomised to azacitidine.[18]

In addition to the above trial, several uncontrolled studies have demonstrated the efficacy of subcutaneous azacitidine in the treatment of patients with MDS.[19-24] In a phase II study (n = 68) employing the same dosage schedule for subcutaneous azacitidine and response criteria as described above, the response rate was 53% (complete response 12%, partial response 15%, improvement 27%).[19] Overall, more than 500 patients with MDS have been treated with azacitidine, with response rates of 49–61%.[2]

Clinical Response

- Patients receiving azacitidine showed a significantly higher overall response rate (complete plus partial plus improvement) than those receiving supportive care (60% vs 5%; $p < 0.001$).[18] All responses in the supportive care arm were improvements only. A comparison of complete response rate (7% vs 0%; $p = 0.01$) and complete plus partial response rates (23% vs 0%; $p < 0.0001$) also showed significant differences between azacitidine and supportive care recipients. The overall response rate in patients who crossed over from supportive care to azacitidine (n = 49) was 47% (complete response 10%, partial response 4%, improvement 33%).[18]
- The response to azacitidine was independent of the type of MDS; overall response rates in patients with RA and RARS were similar to those in patients with the more advanced subtypes (59% vs 61%).[18] Initial and best responses occurred in a median of 64 and 93 days, with a median duration of response of 15 months.[18]
- In addition to the 23% of patients achieving complete or partial response, which by definition did not require RBC or platelet transfusion (figure 1), 22% of those showing improvement (n = 37) had an elimination of all RBC transfusion requirements; a further 51% experienced restitution in the RBC deficit, or a decrease in RBC transfusions, of ≥50%.[18]
- The median time to treatment failure was significantly longer in azacitidine than in supportive care recipients (9.1 vs 3.8 months; $p < 0.001$).[18] Similarly, there were significant differences between azaci-

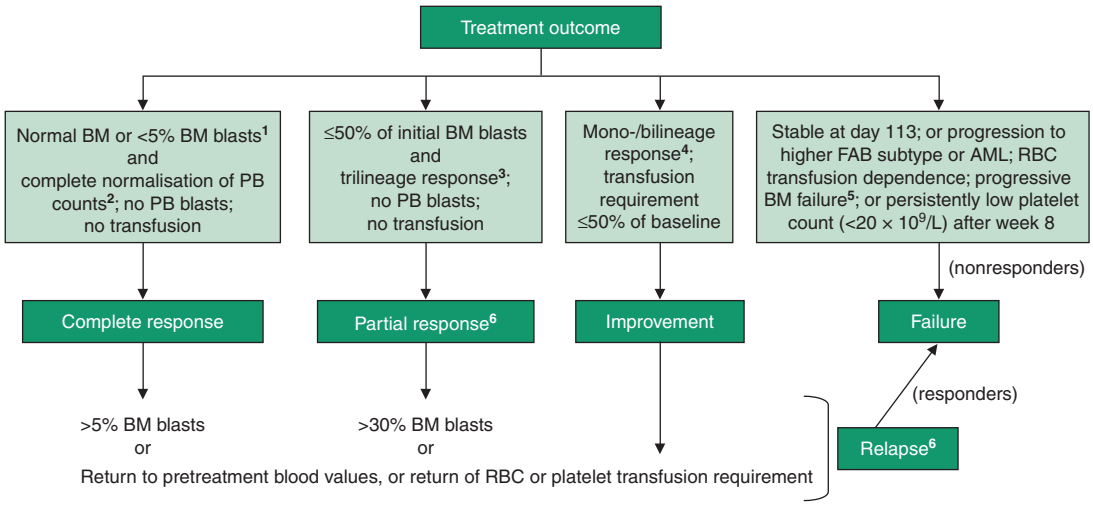


Fig. 1. Definitions of treatment outcomes in patients with MDS in a randomised, controlled, multicentre phase III trial. Patients received supportive care alone or in conjunction with subcutaneous azacitidine 75–100 mg/m^2/day in 7-day cycles every 28 days.[18] **1** Some dyshaematopoietic features may persist; **2** haemoglobin ≥133 (males) or ≥117 (females) g/L, WBC ≥4.4 × 10^9/L, ANC ≥1.8 × 10^9/L, platelets ≥140 × 10^9/L; **3** ≥50% restitution of the initial deficit from normal in all three PB cell counts and elimination of all blood transfusion requirements; **4** ≥50% restitution of the initial deficit from normal in one or two PB cell counts; **5** confirmed fall in cell count from baseline of >25% (trilineage), >50% (bilineage) or >75% (monolineage), or development of RBC transfusion requirement; **6** partial response and relapse in patients with RA or RARS were defined in terms of PB criteria alone. **AML** = acute myeloid leukaemia; **ANC** = absolute neutrophil count; **BM** = bone marrow; **FAB** = French, American and British classification; **MDS** = myelodysplastic syndromes; **PB** = peripheral blood; **RA** = refractory anaemia; **RARS** = RA with ringed sideroblasts; **RBC** = red blood cells; **WBC** = white blood cells.

tidine and supportive care groups in the median time to transformation to AML or death for all patients (21 vs 12 months; p = 0.007) and for patients with high-risk FAB subtypes (RAEB, RAEB-T or CMmL) [19 vs 8 months; p = 0.004]. A landmark analysis at 12 months indicated that the median additional duration of survival of patients who had already transformed to AML was significantly shorter than that of patients who had not yet transformed to AML (3 vs 18 months after the 12-month landmark; p < 0.001).[18]

- Azacitidine recipients had significantly (p = 0.03) longer median overall survival duration than supportive care recipients who crossed over late (after 6 months) or never (18 vs 11 months, additional to the initial 6 months at which a landmark analysis was conducted to eliminate the confounding effect of crossover).[18] Nevertheless, the trial was not powered to detect differences in survival between the two groups.

Health-Related Quality of Life Measures

Health-related quality of life (HR-QOL) assessments were performed during standard telephone interviews before randomisation, and on days 50, 106 and 182 (corresponding to completion of two cycles and 6 days before a bone marrow response evaluation, completion of four cycles and 7 days before re-evaluation and approximately 6 months after study entry, respectively).[25] Patient-assessed measures of physical symptoms and functioning, psychological state, social functioning and sociodemographic characteristics were used to evaluate effects of treatment on the HR-QOL. The 30-item EORTC (European Organization for Research and Treatment of Cancer) QOL Questionnaires-C30 (assessing general physical symptoms, physical functioning, fatigue/malaise and social and emotional functioning) and the 38-item MHI (Mental Health Inventory; comprising the subscales of anxiety, depression, positive affect, emotional ties and loss of

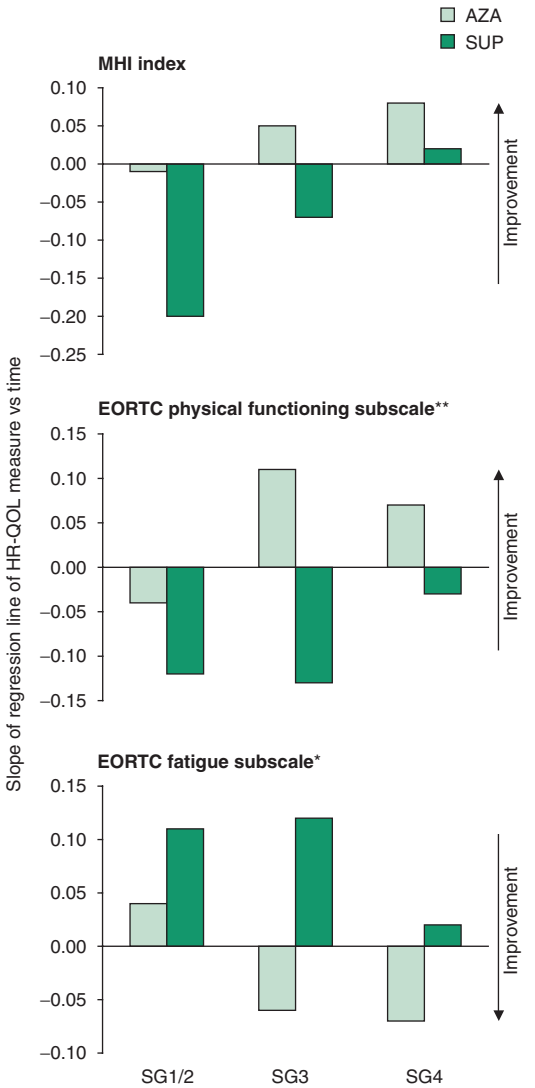


Fig. 2. Effect of azacitidine (AZA) and supportive care (SUP) on health-related quality of life (HR-QOL) measures in patients with myelodysplastic syndromes. The slopes obtained after linear regression analysis of changes in HR-QOL scores with time observed in patients randomised to receive SUP alone (n = 92) or in conjunction with subcutaneous AZA 75–100 mg/m^2/day in 7-day cycles every 28 days (n = 99) in a multicentre, phase III trial.[25] Assessments were performed before randomisation, and on days 50, 106 and 182. Patients were divided into four subgroups (SG) 1–4 based on time of their last HR-QOL assessment (see text for definitions of these subgroups). Because of the small number of patients in subgroups 1 and 2, and assuming similar treatment differences, these groups were combined for statistical analysis (SG1/2). **EORTC** = European Organization for Research and Treatment of Cancer; **MHI** = Mental Health Inventory; * p = 0.001, ** p = 0.0002 for comparison between the two treatments over time.

behavioural and emotional control) were administered at each assessment.[25]

A linear random coefficient model of regression analysis was used to test the effect of treatment arm and time on patients' HR-QOL.[25] Patients were divided into four subgroups based on the time of their last HR-QOL assessment: subgroup 1, patients at study entry within 39 days after randomisation (including a few patients with two assessments within this time interval); subgroup 2, last assessment occurring between days 40 and 82 (most patients with two assessments); subgroup 3, last assessment between days 83 and 159 (most patients with three assessments); and subgroup 4, last assessment between days 160 and 259 (most patients with four assessments). In each arm of the study, the slopes of regression lines for the various subgroups represented the individual rate of change in HR-QOL measure (EORTC or MHI) with time.[25] The primary HR-QOL endpoints were changes in the EORTC fatigue and physical functioning subscales and MHI index, with the significance level set at 0.017.[25]

- A comparison of the slopes of regression lines for the individual subgroups generally showed significantly greater rates of improvements in HR-QOL measures in azacitidine recipients than in those receiving supportive care.[25] Among the primary HR-QOL endpoints, both EORTC subscales (fatigue and physical functioning) were significantly improved with time in azacitidine recipients compared with those in supportive care recipients, while the difference with respect to rate of change of MHI index did not reach the prespecified significance level of 0.017 (figure 2). There were also significantly greater improvements with time in EORTC dyspnoea (p = 0.0014), EORTC overall HR-QOL (p = 0.0001), MHI positive affect (p = 0.0077) and MHI psychological distress (p = 0.015) subscales in the azacitidine than in the supportive care group.[25]

- These improvements were generally maintained after adjusting for differences in RBC transfusions between the two groups.[25] Importantly, no significant placebo or Hawthorne (i.e. an improvement due

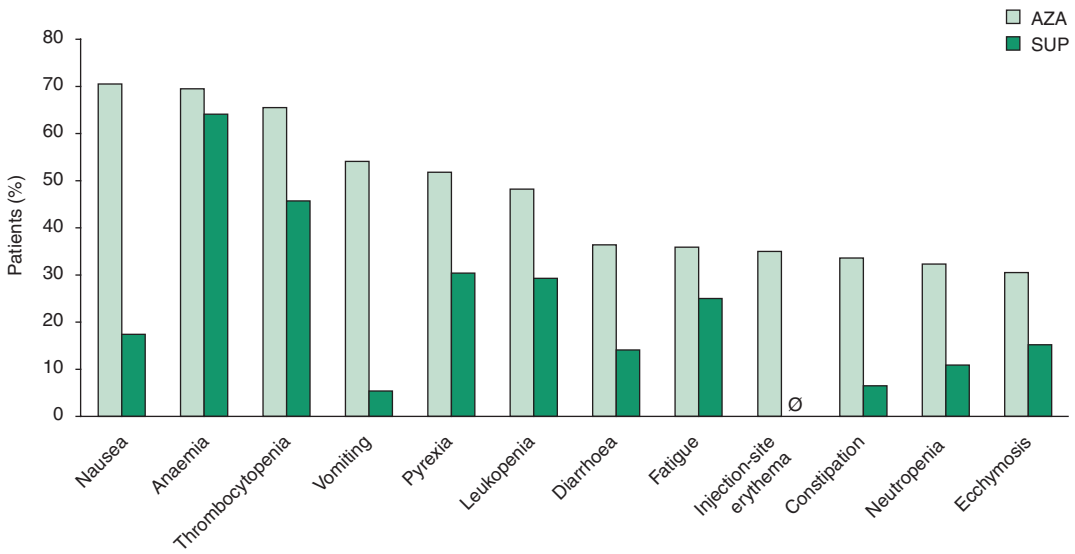


Fig. 3. Tolerability profile of azacitidine (AZA) in patients with myelodysplastic syndromes. The combined incidence of the most common adverse events (≥30% in AZA recipients) with AZA (n = 220; mean treatment duration 11.4 months) or supportive care (SUP) [n = 92; observation time 6.1 months], whether or not considered treatment-related, as reported in the US prescribing information.[16] Patients received at least one dose of subcutaneous AZA 50–100 mg/m^2/day in 7-day cycles every 28 days in phase II and phase III trials.

to the extra attention received) effects were evident in these analyses.[25]

- In general, patients who crossed over from supportive care to azacitidine (n = 38; with ≥1 HR-QOL assessment after crossover) had significantly ($p \leq 0.016$) improved HR-QOL measures with time, which were comparable to those observed in the original azacitidine group.[25]

4. Tolerability

- Figure 3 summarises all adverse events that occurred in ≥30% of patients with MDS who received at least one dose of subcutaneous azacitidine 50–100 mg/m^2 (including crossover patients), and those reported in patients receiving supportive care alone, in phase II and III trials, as reported in the US prescribing information.[16] There was a trend of an increase in the incidence of gastrointestinal adverse events (nausea/vomiting [incidence in the phase III trial 4%],[18] diarrhoea and constipation) with increasing doses of azacitidine.[16] However, the frequency and severity of adverse events generally decreased or remained stable with repeated cycles over the course of treatment.[16]

- As expected, the most common toxicity in patients with MDS receiving subcutaenous azacitidine was myelosuppression in the pivotal phase III trial discussed in section 3.[18] However, toxicity was transient, with patients generally recovering in time for the next treatment cycle. The criteria for haematological toxicity assessment were modified in this trial, with relative decreases from study entry in peripheral blood counts of 50–74% and ≥75% designated as grade 3 or grade 4 toxicities.[18] In azacitidine recipients, the incidences of grade 3 or 4 granulocytopenia, thrombocytopenia and leukopenia were 58%, 52% and 43%, respectively.[18] According to the US prescribing information of azacitidine, these were the adverse reactions that most frequently resulted in a clinical intervention (discontinuation, dose interruption or dose reduction) during clinical trials.[16]

- Treatment-related infection occurred in 20% of patients in the phase III trial.[18] There was one treatment-related death.[18]

5. Dosage and Administration

In the treatment of MDS, the recommended starting dose of subcutaneous azacitidine for the first cycle is 75 mg/m^2/day for 7 days (all patients, regardless of baseline haematology laboratory values).[16]

Treatment cycles should be repeated every 4 weeks.[16] The dose may be increased to 100 mg/m^2/day if no beneficial effect is seen after two treatment cycles and if no toxicity other than nausea and vomiting has occurred. The treatment should be given for a minimum of four cycles, although longer treatment may be required for a complete or partial response to be achieved.[16]

For comprehensive dosage and administration guidelines, the manufacturer's prescribing information should be consulted.

6. Azacitidine: Current Status

Azacitidine has been approved in the US for the treatment of all subtypes of MDS (FAB classification). In a randomised, controlled trial in patients with MDS, recipients of subcutaenous azacitidine 75–100 mg/m^2/day in conjunction with supportive care experienced a significantly higher overall response rate and greater improvements in HR-QOL than those seen in supportive care recipients. The drug was generally well tolerated in the context of its use in this highly morbid disease.

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Correspondence: *M. Asif A. Siddiqui*, Adis International Limited, 41 Centorian Drive, Mairangi Bay, Private Bag 65901, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz