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# Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*

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## Abstract

**Objective—**Myelodysplastic syndrome (MDS) treatment can initially worsen patients' clinical condition and they may discontinue therapy before achieving benefit. We present previously unpublished data from two large phase III trials describing common adverse events (AEs) associated with azacitidine and methods to manage them.

**Methods—**In the Cancer and Leukemia Group B (CALGB) 9221 study, patients with any French-American-British (FAB) subtype of MDS were randomized to azacitidine or best supportive care (BSC). After 56 d, patients randomized to BSC with disease progression could cross over to receive azacitidine. In the AZA-001 study, patients with higher-risk MDS (FAB-defined refractory anemia with excess blasts (RAEB), RAEB in transformation, or chronic myelomonocitic leukaemia and IPSS int-2 or high) were randomized to azacitidine or to conventional care regimens (CCR), which included low-dose ara-C, BSC, or intensive

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chemotherapy. In both studies, azacitidine dose was 75 mg/m$^2$/d SC for 7 d every 28 d. AEs were graded per National Cancer Institute's Common Toxicity Criteria version 2.0 (AZA-001) or CALGB Expanded CTC (CALGB 9221).

**Results—**In safety-evaluable patients in AZA-001 (*N* = 175) or CALGB 9221 (*N* = 150), the most common AEs with azacitidine included hematologic (eg, cytopenias) and non-hematologic administration-related events (eg, injection-site reactions and gastrointestinal disorders). Most AEs were transient and resolved during ongoing therapy (> 83%). Hematologic AEs, most frequently observed during early treatment cycles, decreased during subsequent cycles and were usually managed with dosing delays (23–29%). Gastrointestinal symptoms were primarily managed with anti-emetics and laxatives.

**Conclusion—**Hematologic and non-hematologic AEs with azacitidine decreased in frequency as treatment continued. Awareness of the onset, duration and management of AEs can facilitate treatment, permitting patients to continue therapy for maximum benefit.

## Keywords

azacitidine; safety; disease management; myelodysplastic syndromes; adverse drug event

Many patients with myelodysplastic syndromes (MDS), particularly the elderly and those with comorbidities, receive only palliative or best supportive care (BSC) rather than specific disease-targeted therapy (1). Exacerbation of cytopenias and myelosuppression-related complications, most notably bleeding and infections, are potential adverse events (AEs) of active MDS treatments that may lead to initial deterioration of the clinical condition of these typically frail patients. For many years, these sequelae have often resulted in withholding active treatment. Thus, to be appropriate for use and achieve clinical benefit in a majority of patients with MDS, a treatment should ideally have a good safety profile and be reasonably well tolerated.

Azacitidine (Vidaza®, Celgene Corporation, Summit, NJ, USA), a cytidine analog with hypomethylating activity, is indicated for treatment of all French-American-British (FAB) subtypes of MDS in the United States and for treatment of intermediate-2 and high-risk MDS [by IPSS criteria (2)], chronic myelomonocitic leukaemia (CMML) with 10–29% marrow blasts, and WHO-defined acute myeloid leukemia (AML; 20% to 30% marrow blasts) in the European Union. The phase III CALGB 9221 study established that azacitidine can alter the natural history of MDS (3). In that study, azacitidine prolonged time to transformation to AML, induced red blood cell (RBC) transfusion-independence and hematologic responses and improvement, was associated with enhanced quality of life, and showed a trend for prolonged overall survival (OS) compared with BSC (3, 4). More recently, the phase III AZA-001 trial demonstrated that azacitidine is the first MDS treatment to significantly prolong OS in patients with intermediate-2 and high-risk MDS or WHO-AML with low blast count compared with conventional care regimens (CCR) (5). Hematologic response to azacitidine may be achieved in early treatment cycles (median three cycles) (6); however, in the AZA-001 study, it took 9 months of therapy to induce the maximal number of patients to respond (7), and the OS benefit with azacitidine was manifest in patients who had received a median of nine azacitidine treatment cycles (range 1 to 39)

(5). To facilitate the success of therapy and provide longer-term administration for maximum benefit (8), clinicians should be aware of potential AEs associated with azacitidine and effective ways to manage or resolve them. The most common AEs with azacitidine can be broadly categorized as those related to the pharmacologic actions of the drug (e.g, myelosuppression) and those associated with the administration of the drug (e.g, injection-site reactions, nausea, constipation).

This manuscript reports previously unpublished azacitidine safety data from the phase III AZA-001 and CALGB 9221 trials, to provide more thorough and comprehensive analyses than were possible to include in the primary publication for either study (3, 5). Additionally, this article describes effective ways to manage common AEs associated with azacitidine pharmacology and administration.

## Methods

The CALGB 9221 and AZA-001 studies had similar, but not identical, study designs, as reported in detail elsewhere (3, 5). CALGB 9221 was a phase III randomized, multicenter US study conducted from February 1994 to October 2002 comparing azacitidine with BSC and allowing crossover from BSC to azacitidine. AZA-001 was a phase III, randomized multicenter international study conducted from November 2003 to July 2007 comparing azacitidine with CCR. In both studies, pathology was centralized, with standardized central review of cytogenetic data.

### Patients

CALGB 9221 enrolled patients ≥ 15 yr of age who fulfilled any of the five FAB subgroup classification criteria for MDS, had a Cancer and Leukemia Group B (CALGB) performance score (PS) of 0–2 (scale 0–4), and life expectancy of ≥ 2 months. Patients with therapy-related MDS were eligible if they had been cancer-free for at least 3 yr and had not received radiation or chemotherapy for 6 months. No erythropoietin was allowed within 1 month of study entry. AZA-001 patients were ≥ 18 yr of age with higher-risk MDS (FAB-defined refractory anemia with excess blasts, RAEB in transformation, or CMML and IPSS int-2 or high), with an ECOG PS of 0–2, and had life expectancy of ≥ 3 months. Patients with therapy-related MDS or who were planned to receive hematopoietic stem cell transplantation were excluded.

### Study designs

Both studies employed the azacitidine dose regimen of 75 mg/m$^2$/d for 7 consecutive days every 28 d. In CALGB 9221, if a beneficial effect was not demonstrated by day 57 and no significant toxicity occurred, the azacitidine dose was increased by 33%. Once benefit was manifest on any dosage, azacitidine was continued at that dose unless unacceptable toxicity developed. Patients who achieved complete remission (CR) continued on azacitidine for three more cycles; patients with partial remission (PR) or protocol defined ‘improvement’ continued azacitidine until either CR or disease progression occurred. Patients who manifested disease progression and those with stable disease at 16 wk were classified as treatment failures, and azacitidine treatment was discontinued. In AZA-001, patients were to

receive a minimum of six azacitidine treatment cycles, with treatment to continue until study end or until disease progression or unacceptable toxicity. In both studies, anti-emetics were recommended before (AZA-001) or after (CALGB 9221) SC administration of azacitidine.

The 28-d interval between azacitidine treatments allowed most patients to reach nadir values for hemoglobin, platelets, RBC, and absolute neutrophil count (ANC) and to achieve hematologic recovery prior to the next treatment cycle. In both AZA-001 and CALGB 9221, azacitidine-dosing cycles could be delayed and/or modified because of hematologic toxicity by 7–14 d, as needed, until hematologic recovery. For patients with baseline counts of WBC $\geq 3 \times 10^9$/L and ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L, dose modification or delay could occur if ANC nadir was $\leq 1 \times 10^9$/L ($\leq 1.5 \times 10^9$/L in CALGB 9221) and/or platelet nadir was $< 50 \times 10^9$/L. For patients with baseline counts of WBC $< 3 \times 10^9$/L or ANC $< 1.5 \times 10^9$/L or platelets $< 75 \times 10^9$/L, dose modification or delay could occur if WBC, ANC, or platelet nadir decreased ≥ 50% from baseline. In CALGB 9221, dose modification or delay was also contingent on bone marrow cellularity at the time of nadir WBC or platelet counts.

Prophylactic IV antibiotic treatment was not allowed, but in the CALGB 9221 study, oral antibiotics for prophylaxis against infection in subjects with ANC ≤ 150/$\mu$L (0.15 G/L) were allowed. Granulocyte colony-stimulating factors (G-CSF) and erythropoietic stimulating agents were also not allowed; however, in AZA-001, myeloid growth factors were permitted for infections in patients with neutropenia.

### Differences in study designs and data reporting

While similar in many respects, there are also important differences in study design between CALGB 9221 and AZA-001. As part of the prospective study design of CALGB 9221, patients randomized to BSC were eligible to crossover to azacitidine treatment after study day 56 if criteria supporting disease progression were met. Crossover patients were monitored and treated identically to patients initially randomized to azacitidine.

As part of the study design of AZA-001, after enrollment but before randomization, patients were preselected by investigators, based on age, ECOG, comorbidities, and regional consensus guidelines (9, 10) to receive one of three CCR: BSC; low-dose ara-C (LDAC) 20 mg/m$^2$/d SC for 14 d for at least four cycles; or intensive chemotherapy (7 + 3 regimen) for up to three cycles. Subsequently, patients were randomized to receive azacitidine or were randomized to CCR, in which case, patients received their preselected treatment.

Clinical findings from the AZA-001 study were based on prospective analyses, while clinical findings reported for CALGB 9221 are based on a retrospective collection/reverification of clinical data to reflect more current classification and response criteria (6). AE severity in AZA-001 was assessed using the National Cancer Institute's Common Toxicity Criteria version 2.0. AE severity in CALGB 9221 was assessed using the CALGB Expanded CTC (four-point scale: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening). However, for both studies, preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 10.0.

### Safety assessments

Safety outcomes are reported for the safety-evaluable azacitidine arms of both studies. Patients who received at least one azacitidine dose and had at least one safety assessment comprised the safety-evaluable population in each study. Rates of bleeding and infection are also reported for the BSC arm of the two studies. In CALGB 9221, rates in patients who received any azacitidine ($n$ = 150) are compared with rates in patients randomized to BSC ($n$ = 92). For patients who crossed-over from BSC to active treatment in CALGB 9221, events that occurred during BSC-only treatment were counted for the BSC arm and those that occurred post cross-over are counted in the azacitidine arm, as reported previously (6). For AZA-001, the comparison includes patients preselected for BSC who then were randomized to and received ≥ 1 azacitidine dose ($n$ = 114) vs. patients randomized to receive BSC with ≤ 1 study visit ($n$ = 102). These 216 patients can be assumed to have comparable baseline clinical status because physicians' selection of CCR assignment preceded randomization.

In AZA-001, azacitidine exposure was the time from the first dose to the last dose plus 42 d, and for BSC patients, exposure was the time from randomization until last study visit. In CALGB 9221, total azacitidine exposure was the time from the first dose to 30 d after the last dose, and for BSC was the time from randomization to withdrawal from the study or to the day before crossover to azacitidine.

Safety assessments included clinical laboratory measurements (hematology and serum chemistry); bone marrow aspirate and biopsy results (for evaluation of toxicity); and evaluation of any medically significant changes from baseline in physical examinations, which were performed before every treatment cycle. All abnormal changes from baseline measures were reported as AEs.

The most common AEs were defined as those that occurred in ≥ 20% of patients who received azacitidine in the AZA-001 study. Proportions of patients experiencing AEs and frequency of AEs are reported descriptively. The severity, median duration, and outcome of the most common AEs are summarized. Additionally, the occurrence of these AEs by azacitidine treatment cycle in both studies is reported. To investigate the potential for selection bias (i.e, AEs decrease with subsequent cycles because patient numbers also decrease) in both studies, the frequency per cycle of the most common AEs during cycles 1–6 was recalculated for the subgroup of patients who completed ≥ 6 azacitidine cycles.

The most commonly reported infections and bleeding events and rates per pt-year of exposure in azacitidine-treated patients relative to rates in patients in the BSC arms for both studies are described. Relative risk (RR) was calculated as the ratio of the rate with azacitidine to the rate with BSC. $P$ values for testing that the common RR is 1, and the corresponding 95% exact confidence intervals (CI) were computed using StatXact software (Cytel Inc., Cambridge, MA, USA). Management and/or treatment of individual AEs are described for both studies.

## Results

In CALGB 9221, 191 patients were enrolled, 99 patients were randomized to azacitidine, and 92 patients to BSC. In all, 150 patients comprised the safety cohort; including the 99 patients randomized to azacitidine and 51 (55%) patients originally randomized to BSC who crossed-over to azacitidine because of disease progression. Mean duration of azacitidine exposure in all azacitidine-treated patients was 12.0 months, and overall exposure to azacitidine for all 150 treated patients was 138.2 pt-yrs.

Of 358 patients in the AZA-001 study, 179 were randomized to azacitidine of whom, 175 patients comprised the safety population. Patient characteristics at baseline are shown in Table 1. Azacitidine was administered for a median of nine cycles (range 1–39), and total treatment exposure to azacitidine reached 169.2 pt-yrs.

### Most common AEs

Common AEs were broadly categorized as those events associated with azacitidine pharmacology (e.g, cytopenias, fatigue, pyrexia) and events generally related to azacitidine administration (injection-site reactions, gastrointestinal symptoms) (Table 2). The majority of AEs were considered ‘expected’ based on observations in previous studies (6, 11) and were usually transient, with resolution during the studies (Table 3). AEs observed in later cycles were similar to but less frequent than those in early treatment cycles. There were no cumulative toxicities. Based on estimated serum creatinine clearance, azacitidine had no detrimental effects on renal function in either study.

In both studies, most AEs occurred during the first two cycles and tended to decrease in frequency with subsequent cycles (Table 4). In the subgroups of patients in AZA-001 and CALGB 9221 who completed ≥ 6 treatment cycles, a similar pattern of reduced frequencies of AEs with each successive treatment was observed. For example, in these patients in CALGB 9221, anemia was reported in 53% (39/74) of azacitidine-treated patients during cycle 1 and in 26% (19/74) during cycle 6. In comparable patients in AZA-001, anemia was reported in 19% (22/119) of patients during cycle 1 and 8% (9/119) during cycle 6.

### AEs associated with azacitidine pharmacology

**Cytopenias—**In many cases, patients in both trials had underlying cytopenias at study entry (Table 5). Hematologic events during treatment were consistent with underlying MDS and previous reports of azacitidine treatment (6, 11). In AZA-001 and CALGB 9221, proportionately more patients experienced anemia, thrombocytopenia, neutropenia, and/or other hematologic events during the first 1–2 azacitidine treatment cycles compared with later cycles (Table 4).

Across all dosing cycles, nadir values for hematologic parameters (hemoglobin, platelets, and ANC) occurred at a median of 15–16 d in CALGB 9221 (6) and 14–15 d in AZA-001. In AZA-001, median nadir values for hemoglobin and platelets, but not neutrophils, tended to increase with continued dosing. Median durations of anemia, neutropenia, and thrombocytopenia ranged from 14–16 d in AZA-001 and 8–9 d in CALGB 9221 (Table 3). The majority (> 86%) of these events resolved during each study. Overall, in AZA-001 and

CALGB 9221, 78% and 89% of patients, respectively, had anemia, thrombocytopenia, neutropenia, and/or other hematologic AEs assessed as Grade 3 or 4.

**Fatigue and pyrexia—**Ten patients in AZA-001 (5.7%) and 19 patients in CALGB 9221 (12.7%) experienced pyrexia that was considered serious. The median durations of pyrexia were 5 and 7 d. The worsening of fatigue or a report of fatigue not previously observed was associated with median durations of 8 and 33 d in AZA-001 and CALGB 9221, respectively (Table 3).

### Infections and bleeding events

Infections and bleeding events were not among the most common AEs, nevertheless, they are symptoms of underlying disease and can be exacerbated by MDS treatment. In the group of patients preselected to receive BSC in AZA-001 who were then randomized to and received azacitidine ($n$ = 114), overall infection rates per pt-year (any grade) were not statistically different from those of patients who received BSC ($n$ = 102) (RR = 1.00 [95%CI: 0.81, 1.22], $P$ = 1.00). Similarly, in BSC preselected patients, risk of bleeding events was not significantly different between azacitidine and BSC (RR = 1.11 [95%CI: 0.87, 1.42], $P$ = 0.43). Numbers and rates per pt-year of selected Grade 3 or 4 infections in azacitidine-treated patients and BSC-treated patients in both studies are shown in Table 6, and selected Grade 3 or 4 bleeding events are shown in Table 7.

### Azacitidine administration-related events

Events typically associated with azacitidine administration, including nausea, vomiting, constipation, and injection-site erythema/reaction, generally occurred within the first week of the treatment cycle and coincided with the days of drug administration. These events were usually of Grade 1 or 2 severity (Table 2).

**Gastrointestinal events—**Approximately 95% of gastrointestinal events in azacitidine-treated patients were transient and resolved during the studies (Table 3). Constipation was the most frequently reported gastrointestinal event in AZA-001 (50.3%, Table 2), with most occurrences reported during cycles 1 and 2. As administration of azacitidine in the majority of patients were accompanied by anti-emetic therapy, before and sometimes after subcutaneous injection, we hypothesized that constipation could be induced by anti-emetic drugs, such as ondansetron or tropisetron. The median duration of constipation was 8 d in AZA-001, corresponding to the 7-d treatment period. The median duration of constipation in CALGB 9221 was longer (17 d). Nausea was the most frequently reported gastrointestinal event in CALGB 9221. Grade 3 or 4 gastrointestinal events were reported in < 6% of azacitidine-treated patients in either study. *Injection-site reactions*. The majority of injection-site reactions involved erythema, were transient, and resolved during the studies (Table 3).

### Study discontinuation

In CALGB 9221, commonly reported reasons for discontinuing azacitidine therapy (there was no specific ‘study end’) were development of AML ($n$ = 20, 13%), lack of response ($n$ = 30, 20%), patient request ($n$ = 25, 17%), and investigator discretion ($n$ = 18, 12%).

Treatment-emergent AEs that resulted in discontinuation of study medication occurred in 27 azacitidine-treated patients (18.0%), with comparable frequencies in the azacitidine only (19.2%; 19/99) and azacitidine after BSC (15.7%; 8/51) groups. These AEs were mainly hematologic abnormalities, most commonly leukopenia or neutropenia.

In AZA-001, 68 patients (38.9%) discontinued azacitidine treatment before study end. The most common reason was disease progression, which occurred in 23 patients (13.1%). Eighteen patients (10.3%) discontinued because of an AE, 10 of which were considered treatment-related (febrile neutropenia $n = 2$, and 1 each because of neutropenia, *Clostridium difficile* infection, cerebral hemorrhage, development of bone marrow fibrosis, pulmonary fibrosis, bone marrow failure, sepsis, bronchopulmonary aspergillosis).

In CALGB 9221, 13 patients (9%) died during the study (within 30 d of the last azacitidine dose). Proportionately more patients in the BSC-only cohort (6/41, 15%) died during the study. Causes of death appeared to be related to underlying MDS, possibly exacerbated by azacitidine treatment in some cases, or concomitant diseases: infection ($n = 3$), hemorrhagic event ($n = 2$), progressive disease ($n = 2$), cardiac arrest ($n = 1$), cardiopulmonary arrest ($n = 2$), coronary artery disease ($n = 1$), pneumonia ($n = 1$), respiratory failure ($n = 1$). In the AZA-001 study, 21 azacitidine-treated patients (12.0% of the safety population) died during the treatment period. More than half (13/21) of the on-treatment deaths occurred during the first two cycles. Except for one patient who died because of a myocardial infarction during cycle 1, all other causes of death during the first two cycles were considered probably related to underlying disease and included infection, hemorrhage, and respiratory failure. Of the eight deaths after cycle 2, the investigator assessed the cause of death as possibly related to azacitidine in one patient (cardiac failure) who had a prior history of myocardial infarction, chronic obstructive pulmonary disease, thrombosis, and smoking.

## Management of AEs

Strategies used during both studies to manage the anemia, thrombocytopenia, neutropenia, and other hematologic AEs associated with azacitidine treatment included delaying the next dosing cycle, dose reduction, and administering blood product transfusions.

In AZA-001, 86% of patients receiving azacitidine received the 75 $mg/m^2/d$ dose throughout the study with no dose adjustments. Median cycle length was 28 d. In all, 29% of hematologic AEs (anemia, thrombocytopenia, or neutropenia, any grade) were managed by azacitidine dose delay and 9% by dose reductions. Anemia and thrombocytopenia were managed by transfusions in 87% and 29% of cases, respectively. In 15% of cases, febrile neutropenia was managed with antibiotics (e.g, levofloxacin, ciprofloxacin) and, when severe neutropenia was present, with the addition of a brief G-CSF course. In CALGB 9221, AEs resulted in interruption of azacitidine dosing in 23% of patients and in dose reductions in 11%. The most common AEs resulting in therapy interruptions or dose reductions were hematologic and included neutropenia or febrile neutropenia, leukopenia, thrombocytopenia, and pyrexia. The median azacitidine treatment cycle length across all cycles was 34.3 d (range 8.0–72.5 d). Fatigue and pyrexia were managed by dose delays in approximately 5% and 6% of total fatigue and pyrexia events reported, respectively.

In AZA-001, nausea, vomiting, constipation, and diarrhea were frequently managed with concomitant medications including anti-emetics (e.g, ondansetron, metoclopramide, domperidone), laxatives or stool softeners (e.g, lactulose, coloxyl with senna), and anti-diarrheals (e.g, loperamide). A minority (< 12%) of injection-site reactions required treatment with concomitant medications, which were typically corticosteroids (e.g, betamethasone, hydrocortisone) and/or antihistamines (e.g, clemastine). Little benefit was observed with topical medications; rather, most injection-site reactions were self-resolving.

Some sites reported that changing the needle used to load the syringe to a clean needle (i.e, a needle with no azacitidine residue) before injection reduced the incidence of injection-site reactions. Additionally, use of warm compresses postinjection may alleviate symptoms.

**Commonly used concomitant medications—**In AZA-001, 99% (177/179) of azacitidine-treated patients received concomitant medications. The most common were paracetamol (43%, 153/358), furosemide (36%, 128/358), ondansetron (36%, 127/358), allopurinol (28%, 101/358), and levofloxacin (28%, 100/358). The most common IV antibiotics used to treat infections were vancomycin, piperacillin/tazobactam, and gentamicin. Concomitant use of G-CSF in AZA-001, which was allowed only in the case of neutropenic infection, occurred in 13% of azacitidine-treated patients.

In CALGB 9221, the most frequent AEs requiring treatment with concomitant medications in the azacitidine group were gastrointestinal symptoms, e.g, nausea, vomiting, and constipation, and pyrexia. The most common concomitant medications were anti-emetics and anti-nauseants. Other common medications used in the azacitidine and BSC groups included analgesics (76% and 60%, respectively), systemic antibacterials (76% and 59%), and systemic antihistamines (64% and 40%). Use of G-CSF was prohibited in CALGB 9221.

## Discussion

The majority of AEs reported in the AZA-001 and CALGB 9221 studies were transient and consistent with those observed in other studies and were managed by either supportive care measures, dose delays, or less commonly, dose reductions. AEs were reported most often in cycles 1 and 2 and decreased in frequency thereafter, as also has been demonstrated in other azacitidine studies (11). Within cycles, administration-associated AEs (constipation, nausea, vomiting, injection-site erythema/pain) occurred most often during the drug-administration week and were usually Grade 1 or 2. AEs related to myelosuppression typically occurred in the third week of the treatment cycle. The occurrences of AEs by cycle and within cycles suggest AEs with azacitidine attenuate over time with no cumulative toxicity. Nadir values of hemoglobin and platelets (but not so neutrophils) improve with continued azacitidine treatment cycles, even while the majority of patients continued to receive the initial dosing regimen of 75 mg/m$^2$/d × 7 d with no dose delays. Improvements in these indices are consistent with observed attainment of hematologic improvement and decreased transfusion requirements reported for azacitidine in AZA-001, CALGB 9221, and other studies (3, 5, 6, 11). Decreases (or lack of increases) in ANC values with azacitidine were evidently not associated with increased risk of infection compared with BSC. Similarly, while rates of

thrombocytopenia were higher with azacitidine than with BSC, azacitidine treatment did not increase the risk of bleeding events compared with BSC in either phase III study. These findings could reflect improved function of the neutrophils and platelets that remain, as well as general clinical improvement. It is well known that in patients with MDS, bleeding and infection rates may be higher than would be expected based on neutrophil and platelet counts only, because of functional defects of these cells.

In AZA-001, investigator preselection of treatment was overwhelmingly weighted toward BSC, which was apparently still considered by the majority of hematologists involved in the study to be the most appropriate treatment (because of lack of toxicity) for elderly patients with higher-risk MDS. Toxicity and poor efficacy weighed against the use of LDAC and IC. As reported by Fenaux *et al*., rates of thrombocytopenia (71%), neutropenia (69%), and anemia (66%) based on laboratory values in patients who received BSC in AZA-001 demonstrate the severity of the underlying disease in these patients (5). Clearly, a drug such as azacitidine that can alter the natural history of MDS (3) is preferable to palliative care, and tolerability is a crucial issue in patients with advanced disease. Results of these two large phase III studies show that azacitidine is generally well tolerated. Most AEs with azacitidine resolved during the studies and were amenable to treatment with concomitant medications, transfusions, or by delaying the next azacitidine treatment cycle.

In some cases in clinical practice, MDS (and AML) treatment is often discontinued if or when the patient achieves a response. Recent data show that after patients begin to respond to azacitidine, 48% of patients who continue treatment subsequently achieve an improved hematological response (at a median of four additional cycles following the onset of an initial response) (7). In the AZA-001 study, azacitidine treatment was to continue until intolerable toxicity or disease progression. The median of nine cycles observed in the AZA-001 study, and its association with a significant OS advantage compared with CCR suggests this treatment duration might be optimal (5). Accordingly, it has not been shown that shorter median treatment durations are associated with a similar survival benefit.

There may also be additional benefits derived from continued azacitidine therapy. Quality of life was assessed during the CALGB 9221 study and was found to be significantly improved with azacitidine compared with BSC, as shown by decreased fatigue and dyspnea and improved physical functioning and positive affect (4). Importantly, however, these improvements were statistically significant only in patients who remained on azacitidine therapy for four cycles or more.

Results from these two phase III studies challenge an established MDS treatment paradigm, in which CR is considered necessary for prolongation of OS. Data from AZA-001 and CALGB 9221 studies suggest that CR is not an obligate endpoint associated with the achievement of prolonged survival. CR rates were modest in both trials, and in AZA-001, survival was extended in patients with PR or hematological improvement as their best response (12). Additionally, a first response may improve to a better quality of response with continued treatment (7). Clinicians should be alert to the onset, duration and management of AEs so that they can be treated promptly, thereby allowing patients to continue therapy.

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**Table 1**

Baseline characteristics: azacitidine safety-evaluable populations

| | AZA-001 | | | | CALGB 9221 | |
|---|---|---|---|---|---|---|
| | Overall | | Investigator preselection for BSC (*N* = 216) | | | |
| | Azacitidine | CCR | Azacitidine | BSC | Azacitidine | BSC |
| | *N* = 175 | *N* = 165 | *N* = 114 | *n* = 102 | *N* = 150 | *n* = 92 |
| Age, yr | | | | | | |
| Median | 69.0 | 70.0 | 68.9 | 69.8 | 68.0 | 67.0 |
| Min, max | 42, 83 | 38, 87 | 52, 83 | 50, 87 | 31, 92 | 35, 88 |
| ≤ 64 yr, *n* (%) | 56 (32.0) | 41 (24.8) | 33 (29.0) | 24 (23.6) | 53 (35) | 33 (36) |
| ≥ 65 yr, *n* (%) | 119(68.0) | 124 (75.2) | 81 (71.1) | 78 (76.5) | 97 (65) | 58 (63) |
| Sex, *n* (%) | | | | | | |
| Male | 130(74.3) | 110 (66.7) | 80 (70.2) | 66 (64.7) | 103 (69) | 60 (65) |
| FAB classification, *n* (%) | | | | | | |
| RAEB | 102 (58.3) | 97 (58.8) | 67 (58.8) | 67 (65.7) | 67 (45) | 44 (46) |
| RAEB-t | 59 (33.7) | 55 (33.3) | 37 (32.5) | 28 (27.5) | 29(19) | 17(19) |
| Other | 14(8.0) | 13 (7.8) | 10 (8.8) | 7 (6.8) | 54 (36) | 31 (34) |
| PSS, *n* (%) | | | | | | |
| Intermediate-1 | 5 (2.9) | 12 (7.3) | 4 (3.5) | 9 (8.8) | Not determined | |
| Intermediate-2 | 74 (42.3) | 69 (41.8) | 47 (41.2) | 46(45.1) | | |
| High | 80 (45.7) | 74 (44.8) | 55 (48.2) | 43 (42.2) | | |
| Performance status[1] *n* (%) | | | | | | |
| 0 | 78 (44.6) | 72 (43.6) | 47 (41.2) | 35 (34.3) | 48 (32) | 26 (28) |
| 1 | 83 (47.4) | 80 (48.5) | 56 (49.1) | 57 (55.9) | 58 (39) | 39 (42) |
| 2 | 12 (6.9) | 10 (6.1) | 11 (9.6) | 8 (7.8) | 10(7) | 6(7) |
| 3 | 0 | 0 | 0 | 0 | 1 (1) | 0 |
| Missing | 2 (1.1) | 3 (1.8) | 0 | 2 (2.0) | 33 (22) | 21 (23) |

CCR, conventional care regimen; BSC, best supportive care.

[1] ECOG performance status used in AZA-001 and NCI performance status used in CALGB 9221.

## Table 2

Most common[1] adverse events (AEs) with azacitidine

| Adverse event[2] | Percent of patients | | | |
|---|---|---|---|---|
| | AZA-001 (*n* = 175) | | CALGB 9221 (*n* = 150) | |
| | Any grade | Grade 3/4 | Any grade | Grade 3/4 |
| Patients with at least 1 individual AE occurring in ≥ 20% of patients in the azacitidine group in AZA-001 | 97.7 | 80.0 | 100.0 | 92.7 |
| Anemia | 51.4 | 13.7 | 74.0 | 60.7 |
| Neutropenia | 65.7 | 61.1 | 34.0 | 24.0 |
| Thrombocytopenia | 69.7 | 58.3 | 68.7 | 56.0 |
| Constipation | 50.3 | 1.1 | 39.3 | 3.3 |
| Diarrhea | 21.7 | 0.6 | 40.0 | 3.3 |
| Nausea | 48.0 | 1.7 | 67.3 | 5.3 |
| Vomiting | 26.9 | 0 | 48.0 | 2.7 |
| Fatigue | 24.0 | 3.4 | 47.3 | 5.3 |
| Injection-site erythema | 42.9 | 0 | 33.3 | 0.7 |
| Injection-site reaction | 29.1 | 0.6 | 3.3 | 0 |
| Pyrexia | 30.3 | 4.6 | 51.3 | 2.0 |

[1] Greater than or equal to 20% of azacitidine-treated patients in AZA-001.

[2] Multiple reports of the same preferred term for a patient are counted only once.

**Table 3**

Median durations of common adverse events[1] with azacitidine

| | AZA-001 (*N* = 175) | | | CALGB 9221 (*n* = 150) | | |
|---|---|---|---|---|---|---|
| **Adverse event** | **Percent (%) of patients** | **Percent (%) of events resolved[2]** | **Median duration (d)** | **Percent (%) of patients** | **Percent (%) of events resolved[2]** | **Median duration (d)** |
| Anemia | 51.4 | 88.2 | 14 | 71.3 | 97.8 | 8 |
| Neutropenia | 65.7 | 88.3 | 16 | 34.0 | 98.4 | 9 |
| Thrombocytopenia | 69.7 | 86.5 | 15 | 68.0 | 96.0 | 8 |
| Constipation | 50.3 | 91.9 | 8 | 38.7 | 83.3 | 17 |
| Diarrhea | 21.7 | 95.8 | 3 | 36.0 | 93.5 | 8 |
| Nausea | 48.0 | 95.0 | 4 | 66.7 | 93.8 | 10 |
| Vomiting | 26.9 | 97.9 | 1 | 48.0 | 98.2 | 5 |
| Fatigue | 24.0 | 85.9 | 8 | 38.7 | 83.1 | 33 |
| njection-site erythema | 42.9 | 97.0 | 12 | 32.7 | 84.9 | 30 |
| njection-site reaction | 29.1 | 97.9 | 12 | 13.3 | 83.3 | 18 |
| Pyrexia | 30.3 | 91.9 | 5 | 51.3 | 93.0 | 7 |

[1] Greater than or equal to 20% of azacitidine-treated patients in AZA-001.

[2] Multiple reports of the same preferred term for a patient are counted, and percentages are based on the total number of events.

**Table 4**

Common adverse events[1] with azacitidine by cycle

| | Percent of patients by cycles | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AZA-001 | | | | | CALGB 9221 | | | |
| System organ class preferred term[2] | Cycles 1–2 (*N* = 175) | Cycles 3–4 (*N* = 147) | Cycles 5–6 (*N* = 130) | Cycles 7–8 (*N* = 107) | Cycles 9–10 (*n* = 89) | Cycles 1–2 (*N* = 150) | Cycles 3–4 (*N* = 122) | Cycles 5–6 (*n* = 83) | Cycles 7–12[3] (*n* = 66) |
| Anemia | 32.6 | 18.4 | 13.8 | 11.2 | 13.5 | 66.7 | 52.5 | 34.9 | 28.8 |
| Neutropenia | 50.3 | 31.3 | 27.7 | 18.7 | 20.2 | 26.7 | 24.6 | 21.7 | 22.7 |
| Thrombocytopenia | 54.3 | 29.9 | 25.4 | 19.6 | 21.3 | 58.0 | 44.3 | 30.1 | 40.9 |
| Constipation | 35.4 | 19.7 | 13.1 | 9.3 | 16.9 | 22.0 | 9.0 | 3.6 | 16.7 |
| Diarrhea | 12.0 | 7.5 | 3.8 | 4.7 | 4.5 | 21.3 | 13.9 | 10.8 | 10.6 |
| Nausea | 36.0 | 19.0 | 11.5 | 14.0 | 11.2 | 44.7 | 21.3 | 21.7 | 24.2 |
| Vomiting | 17.7 | 10.9 | 5.4 | 7.5 | 5.6 | 32.7 | 8.2 | 9.6 | 9.1 |
| Fatigue | 12.6 | 9.5 | 3.1 | 5.6 | 3.4 | 27.3 | 15.6 | 15.7 | 22.7 |
| njection-site erythema | 34.9 | 21.1 | 17.7 | 15.9 | 11.2 | 23.3 | 11.5 | 6.0 | 9.1 |
| njection-site reaction | 20.6 | 12.9 | 9.2 | 9.3 | 9.0 | 2.7 | 0 | 1.2 | 0 |
| Pyrexia | 16.0 | 6.1 | 3.8 | 5.6 | 6.7 | 24.7 | 21.3 | 14.5 | 25.8 |

[1] Greater than or equal to 20% of azacitidine-treated patients in AZA-001.

[2] Multiple reports of the same preferred term during a cycle are counted once.

[3] CALGB 9221 data were not reported in the same cycle groupings as AZA-001 after cycles 5–6.

**Table 5**

Cytopenias at baseline

| Adverse event grade at baseline | Number of Azacitidine-treated patients (%) | |
|---|---|---|
| | **AZA-001 (*N* = 175)** | **CALGB 9221 (*N* = 150)** |
| Hemoglobin (g/dL) | | |
| Grade 0–2 | 156 (89.1) | 107 (71.3) |
| Grade 3 | 16 (9.1) | 30 (20.0) |
| Grade 4 | 0 | 10 (7.3) |
| Platelets ($10^9$/L) | | |
| Grade 0–2 | 97 (55.4) | 80 (53.3) |
| Grade 3 | 62 (35.4) | 57 (38.0) |
| Grade 4 | 5 (2.9) | 6 (4.0) |
| ANC ($10^9$/L) | | |
| Grade 0–2 | 80 (45.7) | 40 (26.7) |
| Grade 3 | 48 (27.4) | 22 (14.7) |
| Grade 4 | 38 (21.7) | 23 (15.3) |

ANC, absolute neutrophil count.

## Table 6

Selected infection rates (Grade 3 or 4)

| | Number of events (Rate per patient-year of exposure) | | | |
|---|---|---|---|---|
| | AZA-001[1] | | CALGB 9221 | |
| | **Azacitidine *N* = 114** | **BSC *N* = 102** | **Azacitidine *N* = 150** | **BSC *N* = 92** |
| Infections – total[2] | 55(0.51) | 24 (0.41) | 29(0.21) | 16 (0.37) |
| Bacteremia | 1 (0.01) | 0 | 0 | 0 |
| Bronchitis | 0 | 0 | 1 (0.01) | 0 |
| Cellulitis | 2 (0.02) | 3 (0.05) | 1 (0.01) | 1 (0.02) |
| *Clostridium Difficile* colitis | 3 (0.03) | 0 | 0 | 0 |
| Lower respiratory tract infection | 2 (0.02) | 0 | 0 | 0 |
| Neutropenic sepsis | 3 (0.03) | 0 | 0 | 0 |
| Pneumonia | 14(0.13) | 8 (0.14) | 7 (0.05) | 4 (0.09) |
| Sepsis | 6 (0.06) | 3 (0.05) | 2 (0.01) | 4 (0.09) |
| Urinary tract infection | 3 (0.03) | 0 | 0 | 1 (0.02) |

BSC, best supportive care.

[1] Includes patients preselected to BSC in AZA-001 who were then randomized to and received azacitidine (*n* = 114) or BSC (*n* = 102).

[2] Includes events not listed here.

## Table 7

Selected bleeding event rates (Grade 3 or 4)

| | Number of events (Rate per patient-year of exposure) | | | |
|---|---|---|---|---|
| | AZA-001[1] | | CALGB 9221 | |
| | Azacitidine *N* = 114 | BSC *N* = 102 | Azacitidine *N* = 150 | BSC *N* = 92 |
| Bleeding events – total[2] | 37 (0.34) | 27 (0.46) | 20 (0.14) | 7 (0.16) |
| Gastrointestina hemorrhage | 1 (0.01) | 1 (0.02) | 0 | 0 |
| Gingival bleeding | 3 (0.03) | 0 | 3 (0.02) | 0 |
| Hemorrhoidal bleeding | 1 (0.01) | 0 | 0 | 0 |
| Melena | 0 | 3 (0.05) | 1 (0.01) | 0 |
| Mouth hemorrhage | 2 (0.02) | 1 (0.02) | 1 (0.01) | 0 |
| Rectal hemorrhage | 2 (0.02) | 1 (0.02) | 2 (0.01) | 0 |
| Cerebral hemorrhage | 3 (0.03) | 4 (0.07) | 0 | 0 |
| Hematuria | 2 (0.02) | 1 (0.02) | 0 | 3 (0.07) |
| Epistaxis | 10(0.09) | 10 (0.17) | 7 (0.05) | 0 |

BSC, best supportive care.

[1] Includes patients preselected to BSC in AZA-001 who were then randomized to and received azacitidine (*n* = 114) or BSC (*n* = 102).

[2] Includes events not listed here.