

Clinical Roundtable Monograph

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MDS: Practical Treatment Approaches for Physicians and Nurses

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Abstract

The United States Food and Drug Administration approved azacitidine in May 2004 for the treatment of patients with the following subtypes of myelodysplastic syndrome (MDS): refractory anemia; refractory anemia with ringed sideroblasts accompanied by neutropenia or thrombocytopenia requiring transfusions; refractory anemia with excess blasts; refractory anemia with excess blasts in transformation; and chronic myelomonocytic leukemia. Azacitidine, the first drug approved for the treatment of MDS, belongs to the class of compounds called demethylation agents. Azacitidine induces DNA hypomethylation, which may restore normal function to genes that are critical to differentiation and proliferation. It is also directly cytotoxic to abnormal hematopoietic cells in bone marrow, which causes the death of rapidly dividing cells including cancer cells that are no longer responsive to normal growth control mechanisms. This monograph addresses important issues pertaining to the use of azacitidine, including dosing, administration, and the management of side effects. Practical guidelines and suggestions are provided for managing the 7-days-per-week dosing regimen, as well as for determining when to stop therapy and other issues that clinicians are likely to face as they begin to use azacitidine in their practices.

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Overview of the Treatment of Myelodysplastic Syndromes



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Demographics

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal bone marrow stem cell disorders, usually manifest by hypercellular marrows with peripheral blood cytopenias.¹ MDS generally occurs in older individuals—the median age of patients is approximately 70 years—and more rarely in younger people. The incidence of MDS is 5 per 100,000 people, increasing to 22–45 per 100,000 among individuals over age 70.

Presentation and Prognosis

MDS may present with asymptomatic laboratory abnormalities, such as anemia, low white blood cell (WBC) count, or low platelet count. Alternatively, patients may exhibit symptoms associated with these features: fatigue or shortness of breath due to anemia, infection due to low WBC count, or bleeding due to low platelet count. Anemia, fatigue and/or shortness of breath are the most common features of patients presenting with MDS.

The prognosis of a patient diagnosed with MDS is determined by a number of factors.² The French-American-British (FAB) classification system categorizes MDS as follows: refractory anemia (RA; 15–30% of MDS patients), RA with ringed sideroblasts (RARS; 10–15%), RA with excess blasts (RAEB; 25–30%), RAEB in transformation (RAEBt; 20%), and chronic myelomonocytic leukemia (CMML; 10–20%).¹ Prognosis varies according to FAB classification.² RAEB and RAEBt patients generally have a poor prognosis; with a median survival of 5–12 months. RA (<5% blasts) and RARS (>5% blasts plus 15% RS) patients have a longer survival, approximately 3–6 years. Transformation to acute myeloid leukemia (AML) occurs in approximately 40–50% of RAEB and RAEBt patients and 5–15% of RA and RARS patients.

Supportive Care

Currently, the standard treatment for MDS is supportive care, which includes observation, psychosocial support, and quality-of-life assessment.² Red blood cell (RBC) and/or platelet transfusions should be given as needed for anemia and severe thrombocytopenia/thrombocytopenic bleeding, respectively.¹

Current supportive care often includes hematopoietic growth factors, particularly for refractory symptomatic cytopenias.^{2,4} Anemic patients with MDS will sometimes respond to erythropoietin, but in general the response rate is higher among patients with relatively less anemia, a history of nonrefused transfusions, and relatively low baseline erythropoietin levels.

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) do

routinely cause the WBC count to increase; however, there is no convincing evidence that this increase leads to a clinical benefit for MDS patients. Studies have shown that the addition of G-CSF may improve the hematocrit levels in patients who do not respond to erythropoietin alone.^{5–7}

In general, growth factors are reasonably well tolerated. Side effects may include bone pain and, in the case of G-CSF, fevers and chills, but these events are easily managed.

Transplantation

The only known curative treatment for MDS is bone marrow transplantation.⁸ However, recipients must be able to tolerate this fairly toxic therapy. Nonmyeloablative transplants, also known as mini-transplants, are immunosuppressive, rather than myeloablative, and are a promising approach for patients who may not be able to tolerate the more rigorous standard transplantation.⁹

Chemotherapy and Other Treatments for MDS

Beyond transfusions, many therapies, working through a variety of mechanisms of action, have been developed for the treatment of MDS patients. While many of these approaches have shown some benefit in clinical evaluations, others have shown only minimal benefit and are therefore not recommended for routine use.

Historically, steroids and immunosuppressive agents have been used in the treatment of MDS.² A small percentage of patients are candidates for immunosuppressive therapy, particularly younger patients with low platelet counts, hyperplastic marrows, or certain HLA subtypes. Steroids are not commonly used to treat MDS. Antithymocyte globulin (ATG; Atgam, Pfizer) and/or cyclosporine A are more common but must be used cautiously in immunocompromised MDS patients. Non-specific bone marrow stimulants have also been evaluated for the treatment of MDS. Due to side effects and lack of major benefit, these agents are not commonly used.

Several studies have evaluated thalidomide (Thalomid, Celgene) for MDS, both alone and in combination.^{10–13} This agent has shown promising effects in both low- and high-risk MDS, but with problematic toxicity. The subset of patients appropriate for thalidomide therapy needs to be identified; those presenting without excess blasts may be the most likely to benefit.¹⁰

Differentiation agents have also been evaluated in MDS, in order to overcome the presumptive block in hematopoietic maturation. The first such agent to be studied in this setting, low-dose cytarabine, was associated with a fairly low response rate of 15–20%.¹⁴ Because this agent is also myelosuppressive, it is not often used. Retinoic acid showed no clinical benefit versus observation, and therefore this agent is not used in this setting.¹⁵

In preliminary studies, lenalidomide (Revlimid, Celgene), an analog of thalidomide, has shown some activity in indolent MDS. In phase I and II trials, MDS patients with 5q- syndrome have experienced impressive responses to this agent.¹⁶ The results of a recently completed phase II trial are awaited.

The farnesyltransferase inhibitor tipifarnib (Zarnestra, Johnson & Johnson) has shown promising activity in MDS and continues to be evaluated.¹⁷ Also being evaluated for MDS are the histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA) and depsipeptide.¹⁸

Demethylation in the Treatment of MDS

One of the major pathophysiologic problems in MDS is the failure of normal hematopoietic differentiation, meaning that the immature precursor cells are not able to mature to normal, fully functioning cells. Enhancing transcription of genes associated with differentiation can promote this maturation/differentiation.

In normal cells, CpG islands, where transcription of DNA into RNA begins, are protected from methylation.¹⁹ By contrast, cancer cells often exhibit abnormal methylation patterns. When CpG islands are methylated, certain genes, including tumor suppressor genes, become silenced, and transcriptional competency is affected. The *p15* gene is commonly methylated in some hematologic malignancies, including progressive MDS. Other methylation events occur with increasing frequency as MDS increases in severity. Epigenetic changes are reversible, and demethylating agents have been shown to alter the methylation patterns in the promoter regions of genes. Currently, the most active agents for the treatment of MDS are the demethylating agents.

Azacitidine (Vidaza, Pharmion), a demethylating agent, has been approved by the US Food and Drug Administration for the treatment of the following MDS subtypes: RA, RARS (if accompanied by neutropenia or thrombocytopenia requiring transfusion), RAEB, RAEBt, and CMML.²⁰ Silverman et al²¹ reported findings from a phase III clinical trial of azacitidine in which the response rate was 60% (7% complete response [CR] rate, 16% partial response rate, and 37% rate of hematologic improvement). The most common side effects reported in clinical studies have been nausea/vomiting and myelosuppression.^{20,21} These toxicities are typically manageable. A treatment algorithm that includes azacitidine may be considered when deciding on the appropriate therapy for a patient with MDS (Figure 1).

The demethylating agent decitabine (Dacogen, MGI Pharma/SuperGen) is currently in phase III clinical trials.² In studies reported thus far, decitabine was associated with an overall response rate of 49% (64% among high-risk patients).²²

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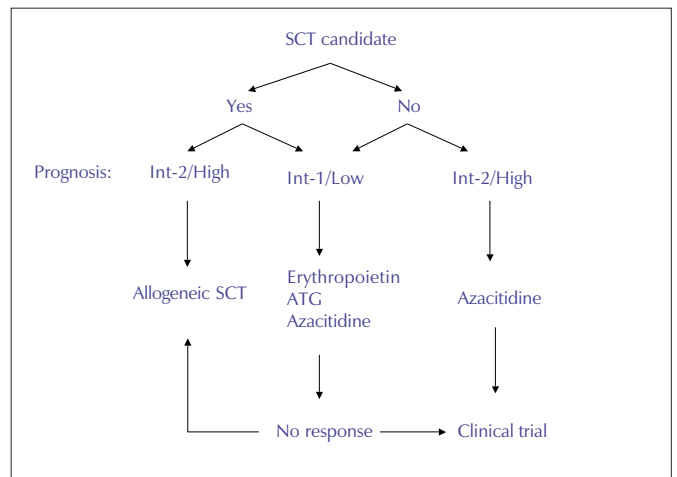


Figure 1. Treatment algorithm for myelodysplastic syndrome. SCT=stem cell transplantation; ATG=antithymocyte globulin.

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Clinical Experience With Azacitidine: A Physician's Perspective



Richard K. Shadduck, MD

Dr. Shadduck, Director of the Western Pennsylvania Cancer Institute, specializes in hematopoietic stem cell transplantation and the diagnosis and management of patients with hematologic malignancies. Dr. Shadduck directs a large clinical trial program with over 100 active protocols and directs a laboratory program evaluating techniques for hematopoietic stem cell expansion.

Overview of Experience

Over the last 5–6 years, more than 140 MDS patients have been evaluated for treatment with azacitidine at the Western Pennsylvania Cancer Institute (WPCI). Experience in the initial 48 patients revealed a substantial improvement in approximately 40% of patients.¹ These results have been confirmed in over 90 patients of all FAB subtypes who received multiple cycles of treatment. Responses were seen with improvements in WBC and platelet counts, or platelet transfusions. A smaller proportion of patients achieved a CR, as defined by International Working Group criteria. However, some patients still revealed dysplastic changes in the marrow. A smaller proportion of patients achieved a CR with loss of dysplastic and chromosomal changes in the marrow.

Interestingly, azacitidine appears to be active in CMML. This condition was recently reclassified into myelodysplastic and myeloproliferative subtypes depending upon the total WBC count. Patients with a monocytosis and WBC count above 12,000, have been termed a “myeloproliferative subtype,” whereas those with low counts are categorized as “myelodysplastic subtypes of CMML.” We found an identical 33% CR rate in both subtypes, with responses occurring within 1–2 cycles of therapy. The rate of transformation to AML was 33% in the MDS group and 22% in the MPS group. The response duration was 13 months in the MDS group, but only half that in the MPS group.

In a recent small study of azacitidine as inductive therapy for newly diagnosed patients with AML, the overall response rate was 53%, with 4 patients achieving a CR.² The most common toxicity, febrile neutropenia, was observed in 4 patients. The study concluded that azacitidine can induce remissions in AML and that further study in this setting is warranted.

Dosing Considerations

The recommended starting dose for azacitidine is 75 mg/m² subcutaneously daily for 7 days, with the cycle repeated every 4 weeks.³ Treatment should be continued for a minimum of 4 cycles, but can be extended for as long as the patient continues to receive benefit. If no benefit is seen after 2 cycles and no toxicity other than nausea and vomiting has occurred, the dose may be increased to 100 mg/m². After the first course, dosing levels can be adjusted based on bone marrow biopsy and the nadir WBC, absolute neutrophil, and platelet counts for a given cycle.³

Time to Response

Among the first 48 patients treated at WPCI, the majority required 3 cycles, and occasionally 4, to respond to treatment. More recently, one patient's hemoglobin levels did not improve

until the sixth cycle, and another patient did not achieve remission until after 8 cycles. At WPCI, we have tried extending azacitidine therapy if a patient is stable (neutrophil count has not worsened, no infection has occurred, patient is not transfusion-dependent and is tolerating the drug well) in order to allow for a late response, with a maximum of 9 cycles given to date.

Special Populations

For patients with severe pre-existing hepatic impairment, azacitidine, which is potentially hepatotoxic, should be used with caution.² Also, because azacitidine and its metabolites are primarily excreted through the kidney, patients with renal impairment should be closely monitored for toxicity. Patients with some degree of renal dysfunction (creatinine levels, 1.5–2.2 mg/dL) do not appear to experience a worsening of creatinine or renal function in association with azacitidine therapy. Generally, a monitoring plan for renally compromised patients includes obtaining the baseline kidney function and then reassessing on a weekly or biweekly basis. Patients should be closely monitored for toxicity.

Use of Growth Factors

Myelosuppression is among the most common side effects associated with azacitidine.⁴ Administration of growth factors may be useful in cases where one cell line or another has not responded to azacitidine therapy. However, WBC and neutrophil counts tend to decrease with each cycle, particularly 7–10 days after therapy, and growth factors are not necessarily required for each patient.

At WPCI, patients with a WBC count of 2,000 and a neutrophil count of 200 are generally given pegfilgrastim (Neulasta, Amgen) and observed for 1–2 days before azacitidine is administered. The goal of this approach is to continue therapy but avoid the fever, infection, and hospital admission that can occur with an extremely low neutrophil count. Epoetin alfa (Procrit, Ortho Biotech) or darbepoetin alfa (Aranesp, Amgen) have been shown to be effective for patients undergoing azacitidine therapy who experience good responses in WBC and platelet counts, but whose hemoglobin is lagging [unpublished data]. At WPCI, patients whose counts drop to zero are routinely given pegfilgrastim throughout their treatment.

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Azacitidine: Dosing and Administration



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Preadministration of Antiemetics

In general, nausea and vomiting are among the most commonly reported side effects occurring in association with the subcutaneous administration of azacitidine, which is a cytotoxic agent. Up to 70% of patients have experienced nausea/vomiting in studies of azacitidine in the treatment of MDS.^{1,2} However, this side effect tends to occur more commonly in the first and second cycles of therapy than in later cycles. In addition, the incidence of nausea/vomiting tends to vary widely among patients, with many patients experiencing only mild, if any, emesis.

Premedication for nausea and vomiting is recommended.² At WPCI, all patients are offered a 5HT₃ antagonist and instructed to take it at the time of their injection or just before. The 5HT₃ antagonist is offered at the first cycle because patients tend to be most anxious and concerned about therapy at treatment initiation. As treatment proceeds, the dose of the 5HT₃ antagonist may be reduced or eliminated.

While the 5HT₃ antagonist is able to stem the nausea and vomiting, some patients are bothered by constipation, a side effect of the antiemetic. These patients may choose to take prochlorperazine or entirely eliminate antiemetic premedication.

Providing 7-Days-per-Week Dosing

Azacitidine is administered in a 7-consecutive-days regimen, which presents a challenge for some oncology offices and clinics. The most conducive setting is an outpatient department that is open on a 7-days-per-week basis. In addition, the office, clinic, or outpatient department should be set up to offer subcutaneous medications, while still being staffed by chemotherapy-certified nurses.

At facilities without an outpatient service open 7 days per week, various approaches for administering azacitidine are being explored. One option is for all patients to receive azacitidine on the same schedule and open the clinic 1 weekend per month to administer azacitidine. In other words, all patients would receive azacitidine therapy for the same 7 consecutive days.

Some clinicians have suggested using an emergency room to administer azacitidine on a weekend. This approach cannot be recommended unless there is certain to be a chemotherapy-certified nurse on duty.

Administration of Subcutaneous Azacitidine

Azacitidine is provided in lyophilized powder form and reconstituted by injecting 4 mL of sterile water slowly into the vial.¹ In order to ensure a homogenous suspension, the vial should

Table 1. Subcutaneous Administration of Azacitidine: Recommended Techniques

- Divide doses of >4 mL equally into 2 or 3 syringes
- Daily rotation of the injection sites is recommended
- Change needle once drug is drawn into syringe, as residual drug on needle may cause skin irritation
- Use a 25-gauge, 5/8-inch needle
- Pinch skin to ensure injection into fatty layer
- Space injection sites by ≥1 inch
- Instruct patients with low platelet counts to apply gentle pressure to injection site for 10–15 min to minimize bleeding into surrounding tissue

be inverted and gently rotated until the resulting suspension, containing 25 mg/mL azacitidine, is consistent.¹ Recommended techniques for administering this subcutaneous agent may help diminish discomfort and ensure the optimal effectiveness of the agent (Table 1). Doses of azacitidine greater than 4 mL should be divided equally into 2 or 3 syringes and injected at separate sites.³

The prepared agent may be held at room temperature for no more than 1 hour. For delayed administration, azacitidine may be refrigerated for up to 8 hours. Upon removal from refrigeration, the agent can be held at room temperature for up to 30 minutes while it equilibrates.

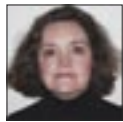
The injection site should be rotated for each injection, and injections should never be given in bruised, tender, red, or hard areas. Injections should be administered to the fatty tissues of the upper arms, thighs, or abdomen, with new injections given at least 1 inch from the previous site.

A 3-mL syringe with a 25-gauge, 5/8-inch needle is recommended for subcutaneous injection. The site should be cleaned with an antimicrobial wipe and allowed to dry. Grasping the fatty tissue between the thumb and forefinger will help ensure that the agent is injected into the subcutaneous tissue and not the muscle. The needle should be inserted at a 45–90° angle.

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Azacitidine: Managing Side Effects



Cheryl Breed, NP, MSN

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Injection-Site Reactions

Individual injection-site reactions occur in approximately 23–35% of patients.¹ These reactions are characterized by redness and swelling, with occasional presence of a hematoma. There may be itching or peeling, and some patients experience pain at the injection site. Injection-site reactions tend to occur with each injection, but appear to diminish in intensity over time. In general, patients who are of small stature and who have minimal subcutaneous fat tend to experience more discomfort in the injection area versus people who have more subcutaneous fat. Patients with very low platelet counts may experience more ecchymoses and swelling at injection sites.

Patients should be informed about this common reaction before the injection is given. Topical heat or ice can be used to treat the reaction, which will diminish in 1–2 days²; however, these should not be applied immediately after the injection because they can delay absorption of the drug. Patients should also be alerted about signs of potential infection.

The site of the injection is often related to the severity of the reaction. It is recommended to avoid injecting medication into any already irritated area or a hard, indurated area. In addition, sites that clothes may rub against should be avoided. Moving the injection site around the body may avoid the discomfort associated with repeated injections at the same site.

At the University of California, San Francisco (UCSF), there is an institutional policy of not injecting more than 3 mL at a single site, so the dose of azacitidine is divided into 2 or more syringes. Changing the needle for each injection will help reduce contamination and decrease the potential for irritation at the injection site.

Other Side Effects

The most common side effect seen with the use of azacitidine is nausea and vomiting, as discussed above.¹ Patients may be given a 5HT₃ antagonist prior to treatment in order to prevent the occurrence of nausea and vomiting.

Another common side effect is diarrhea, usually mild, which tends to occur with the first cycle of azacitidine.¹ This side effect is generally easily managed with loperamide (Imodium, McNeil Consumer) or diphenoxylate/atropine (Lomotil, Searle). At UCSF, azacitidine has never had to be dose-adjusted or discontinued due to diarrhea or nausea/vomiting.

Transfusions and Growth Factors

Hematologic side effects, such as anemia, neutropenia, and thrombocytopenia, are quite common with azacitidine therapy^{1,3}

and sometimes require packed red blood cell and/or platelet transfusions. Patients should be informed of this potential side effect, as worsening blood counts when treatment begins often cause concern. When patients are informed that a transfusion is required, they should be reassured that if azacitidine induces a response, the counts will improve after a few cycles and that the transfusion will address this problem.

In general, growth factors are added after the first or second cycle of azacitidine, and the response to azacitidine is observed. If the patient is becoming transfusion-independent and the hemoglobin and hematocrit levels are increasing but have not quite reached the normal range, growth factors may be given again.

At UCSF, the transfusion threshold is a platelet count of 10,000 or less. Generally, a transfusion is not given if the platelet count is above 10,000, or if the patient is not bleeding and does not have a bleeding history of some kind. In elderly patients, the hematocrit, important for cardiovascular functioning, should be maintained at approximately 30%. In fairly young patients, a transfusion is typically not done unless the hematocrit level is 24–25%. Decisions about whether to use growth factors and whether to administer a transfusion should be based not only on numbers but also on symptoms and how these correlate with laboratory values. Some patients need a slightly higher hematocrit level to feel well and function better.

Use of Azacitidine in the Elderly

In general, elderly patients should not be excluded from treatment with azacitidine. Azacitidine appears to be very safe and well tolerated in elderly patients. More than 60% of the patients included in clinical studies were over 65 years, and 21% were over 75 years.¹ No differences were observed between patients over 65 years and patients under 65 years. In addition, the side effect profile was similar in older and younger (<65 years old) patients.

Because azacitidine and its metabolites are substantially excreted by the kidney, the risk of toxicity may be increased in renally impaired patients. Because renal impairment is more common among older patients, renal function should be carefully monitored in older patients.

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Question and Answer Forum

Richard K. Shadduck, MD, Joan Latsko, MSN, CRNP, OCN, and Cheryl Breed, NP, MSN, discuss their experience treating MDS patients with azacitidine.

Why are response times so variable?

JL Several hematopoietic lines are involved in a response. For some patients, platelet counts recover quickly, but WBC or hemoglobin counts may recover more slowly. While one line may respond quickly, others may take several cycles.

RS Based on this variability, we are now more likely to continue therapy in some cases. If a patient is stable—in other words, has no worsening of neutrophils and platelets, is not experiencing infections or requiring transfusions, and is tolerating the drug well—therapy is continued in order to allow for a late response.

How do you determine whether to give growth factors to MDS patients receiving azacitidine?

RS We know that with each round of therapy there will be a decrease in the WBC and neutrophil counts, particularly 7–10 days into therapy. Growth factors are given fairly routinely to patients whose neutrophil count begins at 200–300 and then decrease to zero. This additional therapy enables the patient to successfully complete azacitidine treatment.

JL The decision of whether or not to administer growth factors often depends on how well the first cycle is tolerated and what other complications may occur.

Do you ever initiate azacitidine therapy at a lower dose than the recommended 75 mg/m²?

JL Some doctors and nurses are cautious about initiating azacitidine therapy at the prescribed starting dose of 75 mg/m². This caution is due to the fact that MDS may involve up to 3 hematologic lineages. Some clinicians may be inclined to start therapy at a lower dose for the first cycle; however, reducing the dose would likely provide suboptimal treatment.

RS The recommended dose of 75 mg/m² is also safe for many patients with comorbid conditions. At WPCI, 2 oxygen-dependent patients, one with chronic pulmonary fibrosis and the other with severe chronic obstructive pulmonary disease, who were treated with azacitidine are now in remission for over 8 months. Both patients are experiencing a functional capacity the same or better than prior to therapy.

How do you decide when to stop azacitidine therapy?

CB Determining the right time to stop therapy can be challenging. At UCSF, several patients are in complete remission and have had 6–7 years of therapy. These patients could be placed on maintenance therapy, or therapy could be stopped altogether, and the patients could be observed to see whether MDS recurs. One patient for whom therapy had to be stopped due to comorbid diabetes and retinopathy is still in remission 2.5 years since

receiving azacitidine and has normal blood counts. Several other patients who were treated at UCSF now receive every-other-month maintenance dosing and have not experienced a loss of remission. However, in some patients who stopped azacitidine after several years of maintenance therapy, relapses occurred and transfusions were necessary.

JL At WPCI, we have given patients treatment breaks, for example, when they wanted to travel and not be worried about injections. Sometimes, patients relapsed before therapy could be restarted. When azacitidine was reinitiated, cytopenia persisted. By contrast, a patient who started azacitidine in 1998 and has received 66 cycles of therapy has had no overt toxicities, and has maintained a normal life through 5.5 years of monthly injections.

What clinical trials of azacitidine are ongoing?

RS An ongoing multicenter, randomized, open-label study is comparing 2 alternative doses of subcutaneous azacitidine plus best supportive care (BSC; Figure 1). In this study, patients will be stratified by FAB classification and randomized to receive either azacitidine 75 mg/m² or 50 mg/m². The primary objective of this study is to determine the hematologic response rate of subcutaneous azacitidine at 2 different dose levels. This study will also evaluate the effect of the different regimens on hematologic status and infections requiring intravenous antibiotics, as well as the safety and efficacy of both dose levels plus BSC. In addition, a randomized, open-label, active control, safety and efficacy study is being conducted globally to determine whether patients with high-risk MDS treated with azacitidine have improved survival compared to conventional care treatments.

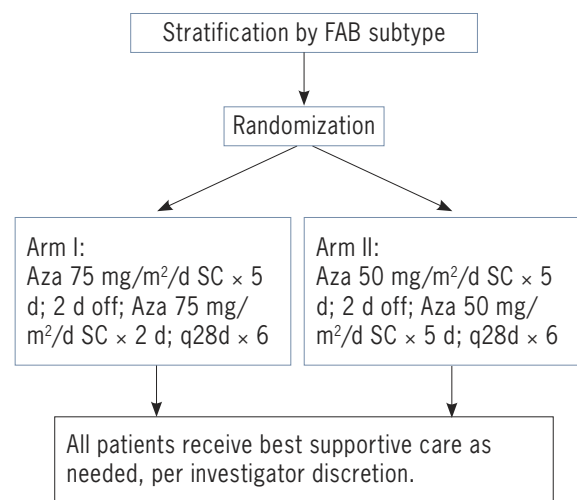


Figure 1. Schema, phase II azacitidine (Aza) dose comparison study. FAB = French-American-British; SC = subcutaneous.

