

# Clinical Roundtable Monograph

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## Recent Advances in Low- and Intermediate-1-Risk Myelodysplastic Syndrome: Developing a Consensus for Optimal Therapy

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### Abstract

Myelodysplastic syndrome (MDS) is relatively common, with an incidence estimated as high as 50 cases per 100,000 people per year. This cancer mainly affects older ( $\geq 60$  years) patients. MDS refers to a collection of hematologic malignancies that share an ineffective production, or hematopoiesis, of normal bone marrow or myeloid cells. As progressive bone marrow failure occurs, patients generally display gradually worsening cytopenias specific to the type of bone marrow cell affected, such as thrombocytopenia or neutropenia. MDS patients often develop disease-related anemia requiring chronic blood transfusion; this can lead to complications including iron overload. As MDS progresses and the number of bone marrow blasts increases, the disease transforms into acute myelogenous leukemia (AML). Several classification systems have been developed to identify and differentiate particular types of MDS. Proper identification is essential, allowing the oncologist to determine prognosis, as well as the optimal therapeutic strategy. Several agents have been developed or are under investigation for the treatment of MDS, with the therapeutic goal of increasing survival and decreasing the rate of AML transformation. Currently, 3 agents are FDA-approved: azacitidine, decitabine, and lenalidomide. This clinical roundtable will discuss the optimal management of patients with each of these approved therapies, as well as the various classification systems used to differentiate MDS subtypes for treatment.

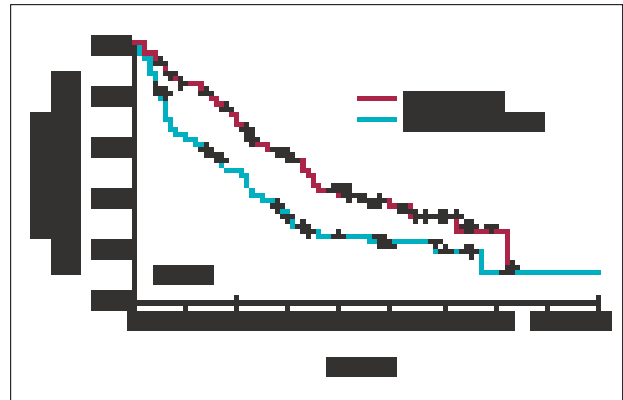
# Duration of Therapy and Patient Management With Azacitidine

Richard Stone, MD

**A**zacitidine is a pyrimidine nucleoside analogue that displays antineoplastic activity. Its mechanism of action is attributed to a reversible inhibition of the DNA methyltransferase enzyme, leading to DNA hypomethylation. Some studies have shown that this inhibition may then relieve methylation-induced silencing of tumor suppressor genes.<sup>1-3</sup> Additionally, clinical response has also been attributed to azacitidine-mediated tumor cell apoptosis.<sup>4</sup>

Azacitidine was the first drug to receive approval from the Food and Drug Administration for the treatment of myelodysplastic syndrome (MDS).<sup>5</sup> Currently, azacitidine is approved for the treatment of patients with all 5 subtypes of MDS, including refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), if accompanied by neutropenia or thrombocytopenia or requiring transfusions, refractory anemia with excess blasts (RAEB), RAEB in transformation to leukemia (RAEB-T), and chronic myelomonocytic leukemia (CMML).

These approvals were based on results from the Cancer and Leukemia Group B (CALGB) trial 9221, a phase III randomized trial that was initiated to determine the clinical efficacy of azacitidine.<sup>6</sup> A total of 191 patients with a median age of 68 years (range, 31–92 years) were included in this trial, with all 5 MDS subtypes represented. Patients were randomized to receive either azacitidine (75 mg/m<sup>2</sup> for 7 days, every 28 days; n=99) or best supportive care (n=92). After 4 months, those in the supportive care arm could switch to azacitidine if their disease had progressed or if they required a transfusion. Patients in the azacitidine arm showed a superior rate of response compared to patients in the supportive care arm: In the azacitidine arm, 7% achieved a complete response (CR) and 16% a partial response (PR), whereas no patient in the supportive care arm achieved such a level of response. Of the 49 patients who switched to azacitidine therapy, 10% had a CR and 4% had a PR.



**Figure 1.** Time to acute myelogenous leukemia transformation or death.

Adapted from Silverman, et al. *J Clin Oncol.* 2002;20(10):2429-2440.

The response to azacitidine treatment occurred irrespective of MDS classification.

Azacitidine treatment significantly prolonged the time to an event (either transformation to acute myelogenous leukemia [AML] or death) compared to supportive care (12 vs 21 months,  $P=.007$ ; Figure 1). During the first 6 months of therapy, significantly fewer patients in the azacitidine arm experienced AML transformation compared with the supportive care arm (3% vs 24%,  $P<.0001$ ).

Because azacitidine is myelosuppressive, it is not uncommon for blood counts to worsen during treatment. Therefore, patients in the azacitidine arm actually experienced an increase in the mean number of red blood cell (RBC) transfusions during the first month of treatment, but declined thereafter. A total of 45% of patients receiving RBC transfusions at study entry became transfusion-independent. The median time to initial response was 64 days,

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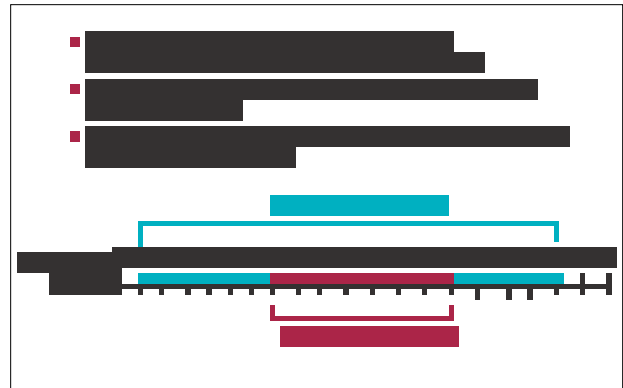
suggesting that those patients who responded to azacitidine showed early signs of that response with improved blood cell counts after 2 cycles. The median time to best response was 93 days. Therefore, it is important to stay on the drug until either disease progression or an intolerable adverse effect precludes its use, and for at least 4 treatment cycles. The median number of cycles required to achieve a CR was 8 and to achieve a PR was 7 (Figure 2).

A quality of life (QOL) assessment was also performed in the patient population from the CALGB 9221 trial.<sup>7</sup> Over the course of the study period, several QOL parameters were significantly improved in the azacitidine arm compared to the supportive care arm, including fatigue ( $P=.001$ ), physical functioning ( $P=.0002$ ), dyspnea ( $P=.0014$ ), positive affect ( $P=.0077$ ), and psychological distress ( $P=.015$ ). These differences remained significant even after controlling the number of RBC transfusions.

AZA-001 was a second pivotal trial showing the efficacy of azacitidine for the treatment of MDS. Preliminary data from this trial were presented at the 2007 American Society of Hematology and the 2008 American Society of Clinical Oncologists annual meetings.<sup>8,9</sup> AZA-001 was an international, multi-center phase III study which randomized 358 patients to receive either azacitidine (75 mg/m<sup>2</sup> for 7 days, every 28 days; n=179) or conventional care based on physician choice (best supportive care, low-dose cytarabine, or standard chemotherapy; n=179). Patient enrollment was restricted to those having higher risk MDS, defined as an International Prognostic Scoring System (IPSS) category of intermediate-2 or high risk, along with excess (10–29%) blasts.<sup>10</sup> The MDS subtypes included were RAEB, RAEB-T, or CMML.

Patients in the azacitidine arm received a median of 9 treatment cycles, compared with 7 (28 day) cycles of best supportive care, 4.5 cycles of low-dose cytarabine, or 1 cycle of standard chemotherapy. Results showed that the primary study objective, median overall survival (OS), was significantly longer in the azacitidine arm compared with the conventional care arm (24.5 vs 15 months,  $P=.0001$ ; Figure 3). This benefit in OS was apparent in all MDS subtypes. Additionally, the time to either AML transformation or death was significantly longer in the azacitidine arm (13 vs 7.6 months,  $P=.003$ ). More patients became transfusion-independent in the azacitidine arm compared with the conventional care arm (45% vs 11%,  $P<.0001$ ). The rate of overall response (OR [CR+PR]) was also significantly superior in the azacitidine treatment group compared with the conventional care group (29% vs 12%,  $P=.0001$ ). A higher rate of CR (17% vs 8%,  $P=.02$ ) and PR (12% vs 4%,  $P=.009$ ) were apparent in patients receiving azacitidine.

A recent combined analysis of 3 CALGB trials (8421, 8921, and 9221) further elaborated on the efficacy of azacitidine in patients with high-risk MDS.<sup>11</sup> This re-



**Figure 2.** Study 9221: Maximizing response with azacitidine.

\*The median number of cycles needed to achieve a PR was 7.

†The median number of cycles needed to achieve a CR was 8.

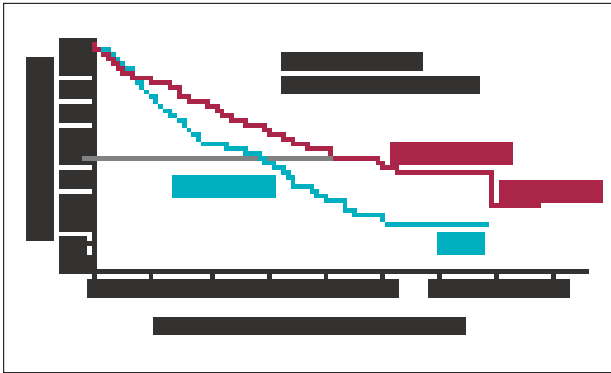
CR=complete response; PR=partial response.

Data courtesy of Celgene Corporation.

analysis applied the World Health Organization (WHO) classification for disease categorization and the International Working Group (IWG) criteria for response assessment. Together, these 3 trials included 309 patients and administered azacitidine (75 mg/m<sup>2</sup> for 7 days, every 28 days) either intravenously or subcutaneously. The rate of CR in these 3 trials was 10–17%; 23–36% of patients receiving azacitidine exhibited hematologic improvement. The first response was noted after a median of 3 cycles, and 90% of all responses were observed by the sixth cycle.

According to the most recent Practice Guidelines from the National Comprehensive Cancer Network (NCCN), azacitidine therapy should be considered for the treatment of MDS patients with progressing or relatively high-risk disease (IPSS intermediate-2 or high risk) who are not candidates for high-intensity therapy.<sup>12</sup> Additionally, the NCCN recommends that azacitidine may be used as a bridging therapy to stem cell transplantation in patients who require a decrease in their high blast counts prior to the transplant procedure.

The results from all of these trials together suggest that azacitidine should be considered an agent employed to chronically suppress MDS. In addition, a retrospective analysis found that a median of 4 azacitidine cycles led to significantly superior rates of response and survival.<sup>13</sup> Furthermore, oncologists optimally should administer the drug and wait at least 4 cycles, if not longer, before judging a lack of response. The NCCN guidelines recommend that a minimum of 4–6 courses should be attempted before considering azacitidine treatment a failure.<sup>12</sup> This approach is quite different from conventional chemotherapy, whose cytotoxic adverse effects often preclude its long-term continued use with no clinical benefit. This long duration of



**Figure 3.** AZA-001 trial: Azacitidine significantly improves overall survival.

CI=confidence interval; CCR=conventional care regimen; HR=hazard ratio.

therapy may be necessary because of the mechanism of action of azacitidine, namely relief of tumor suppressor gene methylation. The best responses with azacitidine may be the result of prolonged DNA hypomethylation.

The 7-day dosing schedule of azacitidine may be relatively inconvenient for both patients and doctors, due to the necessity of weekend administration. Therefore, studies are underway to determine the optimal dosing for therapy. One study of 151 patients evaluated 3 different azacitidine dosage schedules: 5, 7, or 10 days without weekend injection.<sup>14</sup> Preliminary results of this trial showed that all 3 schedules resulted in similar rates of transfusion independence and hematologic response, and all displayed similar safety profiles. However, the conventional 7-day regimen was not included as a control, and therefore the optimal dosing regimen has not been established. The only regimen shown to have a survival benefit in a randomized trial is the subcutaneous 75 mg/m<sup>2</sup>/day 3 7 days schedule.

Aside from initial myelosuppression, nausea and vomiting are the main adverse effects associated with azacitidine. Because of its relatively good safety profile, if no beneficial effect is observed after the first 2 treatment cycles, the usual dose of 75 mg/m<sup>2</sup> may be increased to 100 mg/m<sup>2</sup> in the absence of adverse effects.<sup>15</sup>

Based on its positive results in the treatment of MDS, current studies are investigating the efficacy of a combined treatment strategy using azacitidine. Several of these trials combine azacitidine with histone deacetylase (HDAC) inhibitors—another class of epigenetic treatment options for MDS. It is possible that sequential administration of a DNA methyltransferase inhibitor with an HDAC inhibitor may potentiate the reactivation of tumor suppressor gene expression.<sup>15</sup> A small phase I study evaluating the combination of azacitidine with the HDAC inhibitor SNDX-275 found that

7 of 13 patients with MDS exhibited a response. Although adverse effects were noted, the study authors determined it to be clinically tolerated.<sup>16</sup> In addition, a separate phase I/II trial showed that azacitidine combined with the HDAC inhibitor MGCSD0103 elicited some clinical response.<sup>17</sup> Importantly, this study population included patients with relapsed/refractory MDS. Other agents potentially usable in combination with azacitidine, such as lenalidomide and etanercept, are under investigation.

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# Duration of Therapy and Patient Management With Lenalidomide

Mikkael Sekeres, MD, MS

Lenalidomide is indicated for the treatment of low or intermediate-1-risk MDS patients with transfusion-dependent anemia and a 5q chromosomal deletion (del[5q]), with or without additional cytogenetic abnormalities.<sup>1</sup> Currently, this is the only agent approved specifically for lower risk (low or intermediate-1) MDS.

Approximately 65% of recently diagnosed patients and 80% of established patients with MDS are classified as having lower risk disease, and most of these patients go on to develop transfusion-dependent anemia.<sup>2-4</sup> Additionally, up to 15% of MDS patients exhibit a del(5q) karyotype.<sup>5,6</sup> This group is comprised of 3 karyotypically defined subsets: isolated del(5q), which includes patients with the “5q-syndrome”; del(5q) with 1 additional chromosome abnormality; and del(5q) with 2 or more cytogenetic abnormalities (ie, complex karyotype). Increasing cytogenetic complexity is correlated with a decrease in OS.<sup>6</sup> Unlike most other MDS subtypes, MDS with del(5q) may be associated with a constellation of characteristics including severe anemia, a normal platelet count or thrombocytosis, and a favorable outcome.<sup>7</sup>

The primary mechanism of action of lenalidomide in MDS involves direct anti-proliferative effects on the del(5q) malignant clone by inducing G1 arrest via a p21-dependent pathway. Another primary mechanism of lenalidomide in MDS is its pro-erythropoietic effects involving an increase in red blood cells and hemoglobin levels. Secondary mechanisms include anti-angiogenesis and immunomodulatory effects.<sup>8</sup> The drug also enhances erythropoietin receptor signaling.<sup>9</sup> Preliminary work using RNA interference screening has identified haploinsufficiency of the ribosomal protein encoding the *RSP14* gene as being necessary for the characteristic 5q- syndrome phenotype.<sup>10</sup> Another group has shown that cell cycle regulatory phosphatases Cdc25C and PP2A determine the sensitivity of del(5q) MDS cells to lenalidomide.<sup>11</sup>

In lower risk MDS, treatment approaches range from a watch-and-wait approach in patients with limited numbers or depth of cytopenias, to recombinant erythropoietin stimulating agent (ESA) treatment, for which typical responses range 7–74% depending on baseline transfusion needs and serum erythropoietin levels, to nongrowth factor approaches including lenalidomide.<sup>12,13</sup> In reviewing the published literature of non-growth factor therapies for patients with early MDS, typical response rates are low with

**Table 1.** Lenalidomide in del(5q) MDS: Transfusion Response

Feature	MDS 002/003 (%)	MDS 001/PK (%)	Total (%)
No. Patients	149	19	168
<b>Erythroid response, n (%)</b>			
• TI	99 (66)	15 (79)	114 (68)
• Minor (>50% ↓)	13 (9)	1 (5)	14 (8)
• TI + minor	112 (75)	16 (84)	128 (76)
<b>Time to response, weeks</b>			
• Median	4.6	7.7	4.7
• Range	1–49	2–40	1–49

Adapted from List et al. *Blood*. 2006;108:251a.

TI=transfusion independence.

a median response rate (major and minor) of approximately 31% using IWG response criteria.<sup>14</sup> However, clinical trials investigating lenalidomide in the treatment of patients with lower risk MDS showed substantially higher response rates in the del(5q) population.

MDS-001 was an open-label, single-center phase I/II clinical trial which investigated the safety and efficacy of lenalidomide in MDS.<sup>15</sup> Specifically, 43 patients with MDS were enrolled, all of whom either had no response to conventional therapy with recombinant erythropoietin or were not likely to benefit from this therapy. A total of 74% of the study participants were transfusion-dependent at study initiation. Importantly, 46% of patients had an abnormal karyotype, and 12 patients (28%) displayed the del(5q) abnormality. Patients were divided into 3 treatment groups and administered lenalidomide (10 mg daily, 25 mg daily, or 10 mg daily for 21 days of a 28-day cycle); the response to therapy was assessed after 16 weeks. Overall, 49% of patients were classified as having a major erythroid response, defined as either the conversion from transfusion-dependent to -independent disease or maintaining a sustained increase in hemoglobin of  $\geq 2$  g/dL for at least 8 weeks (Table 1).

The response was durable, and approximately one-third of patients achieving a major response remained



transfusion-independent for over 4 years.<sup>2</sup> The median time to therapeutic response ranged 9–11.5 weeks. Importantly, the response to lenalidomide was significantly influenced by patient karyotype. The overall erythroid response rate was significantly higher in patients with an isolated del(5q) abnormality (83%) compared with those with normal cytogenetics (57%) or patients with other cytogenetic abnormalities (12%;  $P=.007$ ). Response to lenalidomide was also influenced by patient risk, with low-risk (68%) and intermediate-1 risk (50%) patients having a higher rate of response than patients with intermediate-2 risk disease (20%). A safety analysis of lenalidomide in this study found that neutropenia (65%) and thrombocytopenia (74%) were the most commonly reported adverse effects, leading to a dose reduction or interruption of therapy in 58% of patients.

A phase II trial, MDS-003, was a pivotal single-arm study of 148 patients with the del(5q) abnormality where the majority (81%) had lower risk, transfusion-dependent MDS,<sup>16</sup> and 73% had failed prior recombinant erythropoietin therapy. Most patients (74%) had no additional cytogenetic abnormalities; 17% had 1 additional abnormality, and 8% had 2 or more additional abnormalities. Initially, patients received 10 mg lenalidomide daily for 21 days of a 28-day cycle. However, when analysis of the MDS-001 trial showed a shorter time to response with 10 mg daily dosing, the treatment schedule was amended to this regimen. An intent-to-treat analysis was performed after 24 weeks of treatment, with a primary study endpoint of transfusion independence. This analysis showed that 67% (95% confidence interval [CI]: 59–74%) of patients became completely transfusion-independent in a median of 4.6 weeks (range, 1–49 weeks); Table 1 shows the response data of del(5q) patients across studies. The median duration of transfusion independence response across studies for del(5q) patients was reported as 2.2 years.<sup>17</sup> Unlike in the MDS-001 study, the karyotype phenotype in the MDS-003 trial when it included the del(5q) lesion had no significant effect on the rate of transfusion-independence (72%, 48%, and 67% for patients with 0, 1, or  $\geq 2$  additional abnormalities, respectively). Lenalidomide also induced a cytogenetic response, defined as achieving a  $\geq 50\%$  reduction in the number of cells exhibiting an abnormal metaphase, in 73% of 85 evaluable patients. A complete cytogenetic response was achieved by 45% of the evaluable patients (Table 2).

This correlated with clinical response, and all patients who exhibited a cytogenetic response also achieved transfusion independence. Cytogenetic response was also unaffected by karyotype complexity (77%, 67%, and 50% for patients with 0, 1, or  $\geq 2$  abnormalities in addition to the del[5q] lesion, respectively). Again, a safety analysis showed that grade 3 or 4 neutropenia (55%) and thrombocytopenia

**Table 2.** Cytogenetic Response in Evaluable Patients With 20 or More Metaphases

Variable	MDS 002/003 n (%)	MDS 001/PK n (%)	Total n (%)
No. Evaluable	86	18	104
Cytogenetic Response*	63 (73)	15 (83)	78 (75)
CCR	38 (44)	12 (67)	50 (48)
Minor (>50% ↓)	25 (29)	3 (17)	28 (27)
CCR in 5q + 1			9 (50)
CCR in complex (>3)			3 (50)

\*All cytogenetic responders achieved an erythroid response.

CCR=complete cytogenetic response.

Adapted from List et al. *Blood*. 2006;108:251a.

(44%) were the most frequent reasons for dose reduction or interruption of therapy.

Because it was hypothesized that these drug-induced cytopenias were a result of direct cytotoxic mechanisms and may be a necessary prerequisite to lenalidomide response, the predictive values of these adverse effects were analyzed.<sup>18</sup> For this analysis, treatment-related thrombocytopenia was defined as a 50% or higher decline in platelet count, and treatment-related neutropenia was defined as a 75% or greater decline in absolute neutrophil count (ANC), both occurring during the first 8 weeks of treatment. These investigators found that patients with treatment-related thrombocytopenia were significantly more likely to become transfusion-independent compared with those not experiencing severe thrombocytopenia (75% vs 47% for patients with no baseline thrombocytopenia; 58% vs 33% for patients having thrombocytopenia at baseline;  $P<.01$  for both comparisons). A similar relationship was observed for treatment-related neutropenia only among those without baseline neutropenia (82% vs 51%,  $P=.02$ ). Multivariate analyses confirmed the predictive value of these lenalidomide-induced cytopenias, which were also shown to significantly correlate with cytogenetic response. Because of these results, it is important to note that the development of these cytopenias should not necessarily be a reason to discontinue lenalidomide therapy.

Finally, the MDS-002 study was a phase II trial designed similarly to MDS-003 and included lower-risk and transfusion-dependent MDS patients.<sup>19</sup> However,

the major difference in the MDS-002 trial was that it restricted enrollment to patients without the del(5q) phenotype. This study found that lenalidomide exhibited clinical activity in this patient population, although the results were somewhat mixed. In an intent-to-treat analysis, 26% of these patients became transfusion-independent—a much lower proportion than observed in the del(5q) population in the MDS-003 study. Notably, this proportion of patients achieving transfusion independence is similar to the 31% response to nongrowth factor treatment approaches previously observed.<sup>10</sup> The median time to response (4.8 weeks) was similar to that observed in the MDS-003 trial. However, the response was less durable in this patient population, with a median duration of transfusion independence of 41 weeks. Interestingly, neither thrombocytopenia nor neutropenia were found to be significantly predictive of therapeutic response.<sup>18</sup> Due to this finding, it is theorized that instead of the direct cytotoxic effects thought to be responsible for the therapeutic response in the del(5q) population, lenalidomide acts on the tumor microenvironment in patients without the del(5q) phenotype.

Due to its easier oral administration and more favorable safety profile, lenalidomide may be a good choice for initial nongrowth factor therapy of lower risk MDS in patients without the del(5q). Upon failure of lenalidomide, these patients may be good candidates for clinical trials or one of the hypomethylating agents. However, the most recent NCCN guidelines recommend that until a more extensive evaluation in clinical trials is completed, lenalidomide therapy should be reserved for the treatment of non-del(5q) MDS patients with symptomatic anemia who did not respond to initial therapy.<sup>11</sup>

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## All MDS Patients Are Not the Same

Guillermo Garcia-Manero, MD

Although patients with low- and intermediate-1-risk MDS are often grouped into one “lower risk” category, it is important to recognize that these patients are actually clinically distinct from each other. These disease subtypes were originally defined in the IPSS classification as an improved method for evaluating MDS prognosis.<sup>1</sup>

The IPSS classification system uses multivariate analysis of 3 characteristic scores, percentage of bone marrow blasts, number of cytopenias present, and the presence of the del(5q) and other cytogenetic abnormalities, to generate a prognostic model. This model classifies patients into 4 distinctive subgroups: low, intermediate-1, intermediate-2, and high risk, with each showing significantly different clinical outcomes. Specifically, the low-risk group is defined as having <5% of bone marrow blasts, either a normal karyotype or a del(5q) or del(20q) deletion, and either 0 or 1 cytopenias present. The intermediate-1-risk group is characterized by 5–10% bone marrow blasts, various other cytogenetic abnormalities not including del(5q) or del(20q), and either 2 or 3 cytopenias. Using a large patient data set, it was shown that the low and intermediate-1 subgroups exhibited distinct clinical outcomes in both median survival (5.7 vs 3.5 years, respectively) and median time to AML evolution (9.4 vs 3.3 years, respectively), with patients in the low risk group displaying superior time to event in both cases.<sup>1</sup> Therefore, even though patients with intermediate-1 risk disease are often grouped together with low risk patients, the clinical course of their disease is not as benign. Additionally, patients with low-risk disease may not benefit from early therapeutic interventions, while those with intermediate-1 disease could. Approximately 70% of patients with MDS are classified as having lower risk disease, and therefore a significant portion of patients present with this category of MDS, leading to a need to identify which patients should be treated.<sup>1,2</sup>

Despite the advantages over other systems such as the French-American-British (FAB) and WHO classifications, the IPSS classification has limitations in predicting survival in patients with lower risk disease (ie, only 1 cytopenia such as thrombocytopenia) and it does not identify patients with poor prognosis lower risk disease (intermediate-1 risk) who may benefit from early therapeutic intervention.<sup>3-5</sup> One recent study from the M.D. Anderson Cancer Center performed an analysis of 856 patients with lower risk (IPSS low and intermediate-1-risk groups) MDS, in order to further define this patient category.<sup>5</sup> This study used multivariate analyses

to identify several characteristics significantly associated with a poorer survival, including low platelet count, anemia, 60 years of age or older, high percentage of bone marrow blasts ( $\geq 4\%$ ), and poor-risk cytogenetics ( $P < .01$  for each characteristic). This allowed the generation of a new scoring system—separate from the IPSS system—in which IPSS lower risk patients could be further divided into 3 categories.

In this study, category 1 had the best prognosis (median 4-year survival, 80.3 months), category 2 had an intermediate prognosis (median 4-year survival, 26.6 months), and category 3 had the worst prognosis (median 4-year survival, 14.2 months). Importantly, fewer patients in this study were category 1 (21%), compared with category 2 (48%) or category 3 (31%), and therefore the majority of patients had poorer prognosis disease. This point is critical to remember when considering the initiation of therapy. Although many oncologists may opt for a watch-and-wait approach for the IPSS lower risk patient, this data indicate that a number of these patients may actually have a poorer prognosis and would benefit from an earlier therapeutic intervention (Tables 3 and 4).

Other classification systems which address the need to identify those patients having both lower risk disease and a poorer prognosis have also been developed. One of these, the WHO classification-based prognostic scoring system (WPSS), developed a 5-subgroup model based on several variables including WHO subgroup, karyotype, and transfusion requirements.<sup>6</sup> These subgroups were very low, low, intermediate, high, and very high risk; each of these had a different rate of survival and probability of AML evolution. However, a major limitation of the WPSS is that WHO classification of MDS is not routinely performed in community hospitals throughout the United States. Therefore, it could be difficult for many oncologists and hematologists to apply this scoring system to their MDS patients.

Together, these studies indicate that the stratification of patients solely according to the IPSS criteria may not be sufficient to identify the IPSS lower risk patients who would most benefit from a therapeutic intervention. Each of these newly developed classifications—the M.D. Anderson system and the WPSS—need to be verified in a prospective study or other alternative data set.

Once an IPSS lower risk patient is identified as someone who would benefit from therapy, what therapy should then be used? According to the most recent NCCN guidelines, the primary intervention for the standard of care of patients



**Table 3.** Multivariate Analysis Parameters and Assigned Score

Adverse factor	Coefficient	P-value	Assigned score
Unfavorable cytogenetics*	0.203	<0.0001	1
Age ≥60 years	0.348	<0.0001	2
Hemoglobin <10 (g dL <sup>-1</sup> )	0.216	<0.0001	1
Platelets <50 × 10 <sup>9</sup> per L	0.498	<0.0001	2
50–200 × 10 <sup>9</sup> per L	0.277	0.0001	1
Bone marrow blasts ≥4%	0.195	0.0001	1

\*In this analysis, diploid and 5q only were favorable cytogenetic; all others were considered as unfavorable cytogenetics.

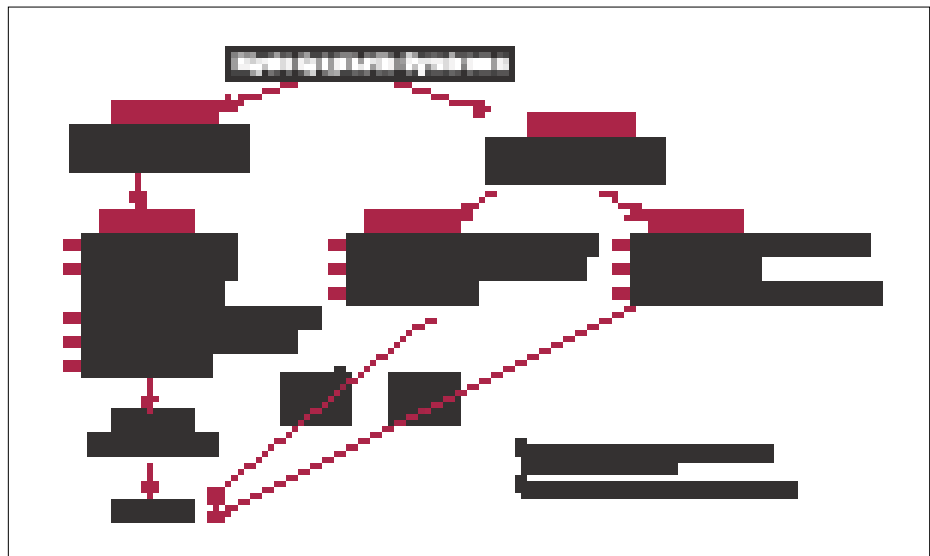
**Table 4.** Estimated Survival Outcomes Within Each Score Range and Proposed Risk Categories

Score	No. of patients	Median (month)	Four-year survival (%)	Category
0	11	NR	78	1
1	58	83	82	-
2	113	51	51	-
3	185	36	40	2
4	223	22	27	-
5	166	14	9	3
6	86	16	7	-
7	13	9	NA	-

NA=not assessable; NR=not reached.

**Figure 4.** Proposed treatment algorithm for patients with myelodysplastic syndrome.

alloSCT=allogeneic stem cell transplantation; BM=bone marrow; Epo=erythropoietin; G-CSF=granulocyte-colony stimulating factor; IPSS=International Prognostic Scoring System; MTI=methyltransferase inhibitor.



with IPSS low or intermediate-1 MDS with symptomatic anemia is lenalidomide (Figure 4).<sup>7</sup>

The use of lenalidomide is restricted to patients with a del(5q) phenotype, either in the presence or absence of other cytogenetic abnormalities. A prototypical patient who would derive the best benefit from lenalidomide therapy would have anemia with no or mild thrombocytopenia (platelet count ≥100,000) and have early-stage disease, having not received more than 4 transfusions. In fact, this patient may experience an increase in OS due to lenalidomide therapy.<sup>8</sup> Patients with thrombocytopenia, heavy transfusion dependence, or who are more advanced in the course of the disease

may not benefit as much from lenalidomide, and therefore the NCCN guidelines instead recommend treatment with either azacitidine or recombinant erythropoietin.<sup>7</sup> However, compared with higher risk MDS, there is significantly less data with azacitidine in lower risk MDS. Therefore, the optimal dose and regimen have yet to be established.

One alternative treatment strategy for patients with IPSS lower risk MDS would be to use lenalidomide in the setting of a non-5q(del) phenotype. It is imperative for the oncologist or hematologist to remember that this strategy is not currently an FDA approved indication for lenalidomide. This use of lenalidomide in this setting should be only considered for

patients with symptomatic anemia who are not responding to initial therapy,<sup>7</sup> and is not routinely used in clinical practice.

Another alternative treatment strategy for IPSS lower risk disease is the combination of growth factors.<sup>9</sup> This approach was investigated in a recent study in which patients were treated with either recombinant granulocyte-colony stimulating factor (G-CSF) plus erythropoietin (n=121) or were untreated (n=237).<sup>10</sup> This was not a randomized or a prospective study, but instead a cohort analysis. A multivariate analysis found that the combined growth factor therapy was associated with improved OS (hazard ratio [HR], 0.61; 95% CI, 0.44–0.83,  $P=.002$ ). This increase in survival was most apparent in patients who required more than 2 units of RBC transfusions per month. The combined growth factor therapy had no effect on the risk or rate of transformation to AML. After further investigation, this alternative therapy may become an important strategy in the treatment of lower risk MDS, due to its simple intervention with few associated toxicities.

A third alternative treatment strategy to treat patients with IPSS lower risk disease is the use of an iron chelating agent.<sup>11</sup> These iron chelating agents are thought to decrease the rate of cardiac and hepatic complications caused by the iron overload that results from the multiple RBC transfusions MDS patients often require. Because heart or liver failure can lead to death, prevention with iron chelation therapy may improve patient survival.<sup>12</sup> This may be particularly apparent in patients with IPSS lower risk disease, as they have the potential to live long enough to experience iron overload-associated complications. However, there is currently little data which illustrate this increase in survival. One retrospective review found that iron chelation therapy was significantly predictive of survival ( $P<.02$ ) in a group of 178 MDS patients.<sup>13</sup> Separately, a prospective study of 170 MDS patients showed that the median OS was significantly superior in patients receiving iron chelation therapy compared to those who were not (115 vs 51 months;  $P<.0001$ ).<sup>14</sup>

Evidently, there is a need for better therapies in lower risk MDS, including new schedules for hypomethylating agents. For this, more clinical trials for interventions such as PR1 vaccines, oral azacitidines, new immunomodulatory drugs and HDAC inhibitors, etc. are warranted.

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# The Community Hematologist/Oncologist's Perspective

Roger M. Lyons, MD, FACP

**A**s community hematologists/oncologists we provide care for many patients with MDS. The perspective of the community physician often differs from that of the physician in an academic medical center. We usually see a different distribution of MDS patients than those referred and able to travel to tertiary academic medical centers. In the community, our approach focuses on the rapid application of new data to benefit our patients in a practical “real world” setting.

Symptomatic anemia is a major MDS-related morbidity and is a prevalent problem in the elderly population. A recent analysis of data from the third National Health and Nutrition Examination Survey, which included data from 1988 to 1994, showed that 10–20% of “elderly” patients were anemic.<sup>1</sup> Specifically, 11.0% of males and 10.2% of females who were 65 years of age or older were found to be anemic, and the rate of anemia rose to over 20% in patients 85 years of age or older. The majority of these cases of anemia were mild in severity. In this patient set, the anemia was attributed to nutritional deficiency in approximately one-third of patients and to chronic inflammation or chronic renal disease in another third of the population; the final third of patients had idiopathic anemia. We in clinical practice believe that a substantial proportion of these patients either had MDS or will eventually be diagnosed as having MDS. The incidence of MDS is likely much higher than the 15,000 new diagnoses per year that surveys of U.S. academic centers suggest.

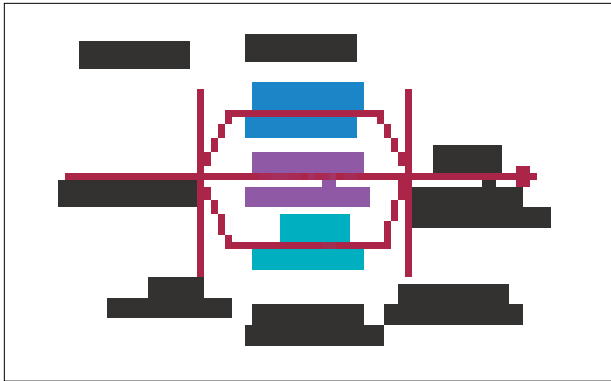
An example of a typical case presenting to the community physician would be a male patient with a slightly decreased hemoglobin level (approximately 12 g/dL) and mild fatigue. These types of patients are generally referred to the community hematologist/oncologist by their primary care physician, and it is often up to the consultant to determine the underlying cause of the anemia. Aside from MDS, other frequently considered causes of anemia include gastrointestinal bleeding, chronic inflammation, renal disease, and nutritional deficiency.<sup>2</sup> Although there may be some clues in the peripheral blood such as dimorphism or Pelger-Huet cells, these changes are often very subtle and difficult to identify. At this very early stage, bone marrow changes are so nonspecific that a MDS diagnosis often cannot be made in the absence of diagnostic chromosome abnormalities. In the community, a bone marrow examination is often deferred until the disease becomes more prominent and in need of treatment, when more definitive morphologic changes would be expected. The patient's blood count history and the history of comorbid diseases often aids in decision making, as they may determine the urgency to make a diagnosis.

When MDS is suspected but not confirmed in an asymptomatic patient, the initial treatment strategy would usually be a watch-and-wait approach. When it appears that disease progression occurs, evidenced either by decreased hemoglobin, platelet count or white blood count, or symptoms attributed to these cytopenias, the diagnosis of MDS must be confirmed by a bone marrow analysis reviewed by an experienced hematopathologist. We expect that the disease will be classified using both the FAB and WHO systems.<sup>3,4</sup> Hematologists/oncologists in clinical practice have not routinely applied the IPSS criteria. However, new Medicare regulations will require an IPSS score in order to initiate treatment ensuring universal application of this prognostic scoring system.<sup>5</sup>

Once a confirmation of MDS is made, further treatment strategies are dependent on the classification and subtype of the disease. These treatment strategies in the community are generally in line with those recommended by the most recent 2009 NCCN guidelines.<sup>2</sup> Lower risk patients are identified either as those who fall into the IPSS subgroups low or intermediate-1 risk, or those who have RA or RARS subtypes of MDS with fewer than 5% blasts.

RBC transfusion may be required for symptomatic anemia,<sup>2</sup> but avoidance of transfusion is a major objective of care in MDS patients. Erythroid stimulating agents (ESAs) are the mainstay for achieving this objective. However, ESA use in these lower risk patients is most effective in patients with less than or equal to 500 mU/mL of serum erythropoietin. Epoetin-alfa or darbepoetin-alfa (given less often and thus more conveniently) can produce a very good response rate—as high as 60–80%.<sup>2,6–8</sup> Granulocyte growth factors added to ESAs can increase the response rate. Community physicians will often administer intravenous iron to nonresponding patients if their ferritin level is less than 500, although this strategy is not mentioned in the NCCN guidelines.<sup>9</sup> Other options are to add the immune modulating drug cyclosporine, which is supported in the NCCN guidelines.<sup>2,6,10–14</sup> Anti-thymocyte globulin is rarely used because of the difficulty in its administration (eg, hospitalization, central line, intensive monitoring) and the risk of serum sickness.

Several agents are available to the community hematologist/oncologist to treat lower risk patients with thrombocytopenia. There appears to be an immune component to MDS-related thrombocytopenia that mimicks immune thrombocytopenic purpura (ITP).<sup>16,17</sup> Because of this, the community hematologist may initiate a trial of danocrine, corticosteroids, intravenous immunoglobulin,



**Figure 5.** Study design: phase II, prospective, multicenter, randomized, open-label, 3-arm trial.

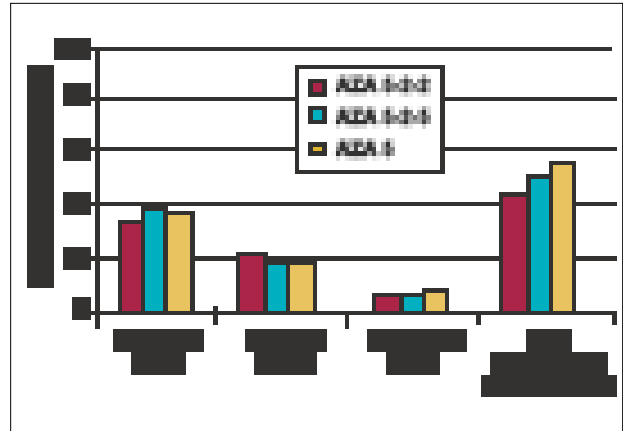
or even rituximab.<sup>18,19</sup> One promising agent in a phase II trial is AMG 531 (romiplostim).<sup>20,21</sup> This thrombopoietic “peptibody” is now FDA-approved only for the treatment of patients with ITP.<sup>22</sup> Treatment of leucopenia is more difficult, with only transient responses expected from the standard growth stimulating treatments.

Lower risk patients with anemia and del(5q) in their chromosome analysis are given lenalinomide with an expected excellent response rate. However, very close monitoring with dose interruption or modification is demanded for those who develop severe cytopenias during induction treatment.<sup>23</sup>

Failure of growth factors, immunomodulation or lenalinomide is most often followed by, or combined with, epigenetic modulation with a demethylating agent. The FDA-approved regimens for the 2 available agents (azacitidine and decitabine) are either inconvenient or impractical in the community setting. Studies from M.D. Anderson Cancer Center suggest that a daily dose of 20 mg/m<sup>2</sup> (intravenous) for 5 days may be equally effective as the approved regimen of 20 mg/m<sup>2</sup> given over 3 hours, every 8 hours, for 3 days, every 28 days.<sup>24</sup> The approved regimen for azacitidine is inconvenient for both patients and the practicing community oncologist because the recommended dosing schedule of azacitidine (75 mg/m<sup>2</sup> daily for 7 consecutive days subcutaneous or intravenous, every 28 days) demands weekend dosing, and responders continue treatment with the same regimen until relapse. This requires that both a skilled pharmacist and nurse be available through the weekend to mix and administer the drug.

Consequently, we decided to undertake a community-based study to look at more practical regimens: a phase II study of 151 patients designed to test 3 alternative azacitidine dosing schedules: 5-, 7-, or 10-day regimens with no weekend injections.<sup>25</sup> (Figure 5)

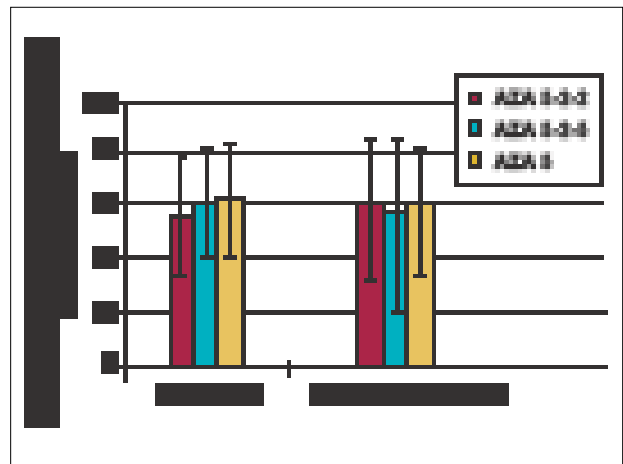
Preliminary results of this trial were presented at the 2007 ASH meeting,<sup>25</sup> and the manuscript from the initial



**Figure 6.** Hematologic improvement.

\*Patients counted only once for best response in an improvement category.

†Minor improvement at top of hematologic improvement columns.



**Figure 7.** Red blood cell transfusion independence in baseline-dependent patients.

FAB=French-American-British classification.

portion of the study has been accepted for publication in the *Journal of Clinical Oncology*<sup>26</sup>; results from the maintenance study, q4week versus q6week 5-day regimen, are pending. These data showed excellent response rates similar to the previously published 7-day-in-a-row regimen, with no major differences in the response rate between each of these treatment arms (Figure 6).

A total of 67%, 55%, and 60% of patients in the 5-, 7-, and 10-day respective treatment arms who were transfusion-dependent achieved transfusion independence after azacitidine treatment (Figure 7).

**Table 5.** Grade 3/4 Hematologic Adverse Events

Event	AZA 5-2-2 (N=50) n (%)	AZA 5-2-5 (N=48) n (%)	AZA 5 (N=50) n (%)
Neutropenia	21 (42)	15 (31)	11 (22)
Thrombocytopenia	13 (26)	7 (15)	6 (12)
Anemia	12 (24)	7 (15)	5 (10)
Leukopenia	7 (14)	4 (8)	4 (8)
Febrile neutropenia	4 (8)	4 (8)	1 (2)

Most patients with transfusion-dependent thrombocytopenia also exhibited substantial response to therapy, but patients with neutropenia did not respond as well. Although all of these groups had similar response rates, the group with the lowest dose (5-day arm) exhibited a lower rate of complications and adverse effects (Table 5).

Only 30% of patients in this study had higher risk MDS, reflecting the usual distribution of patients in the community. Application of this data to the higher risk group should be done with caution, especially in view of the data showing a near doubling of survival when using the 7-day-in-a-row regimen as compared to “standard of care” in higher risk MDS patients.<sup>27</sup>

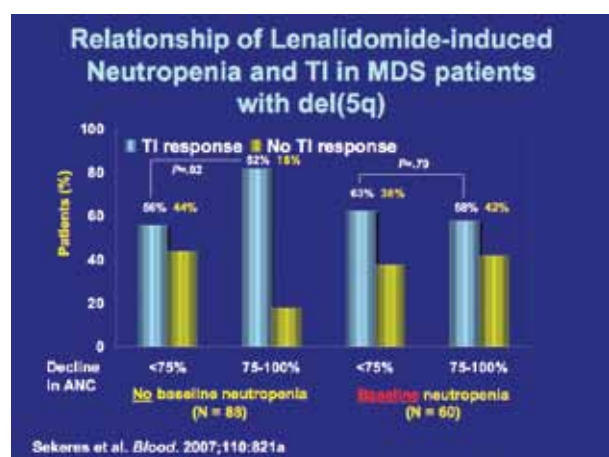
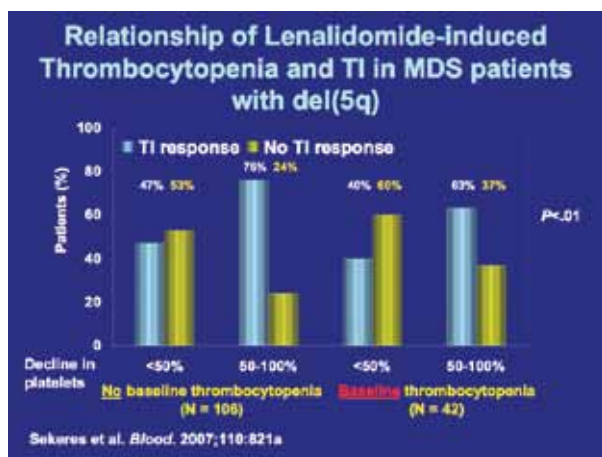
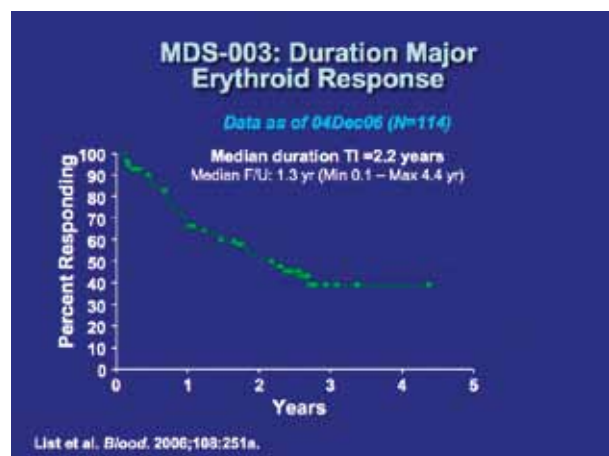
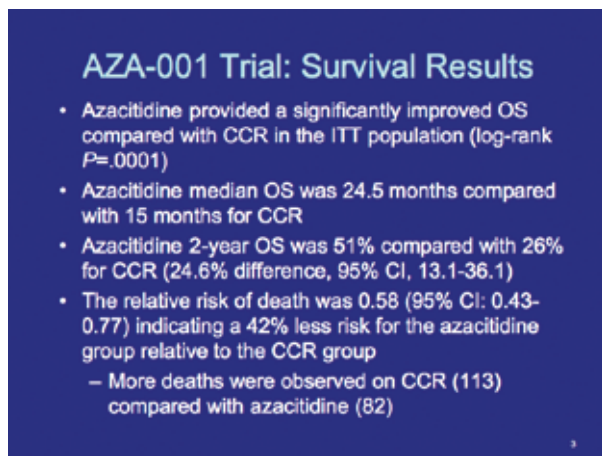
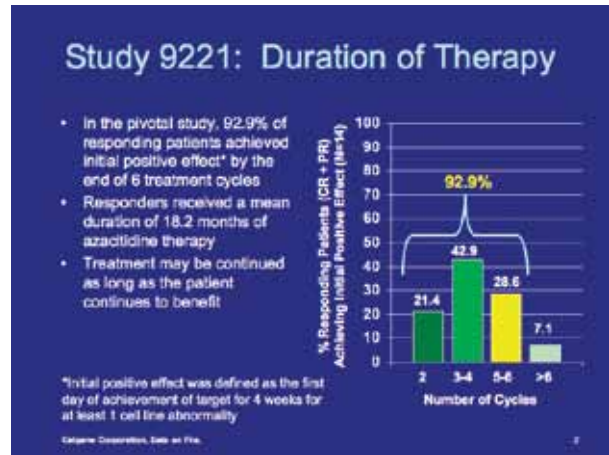
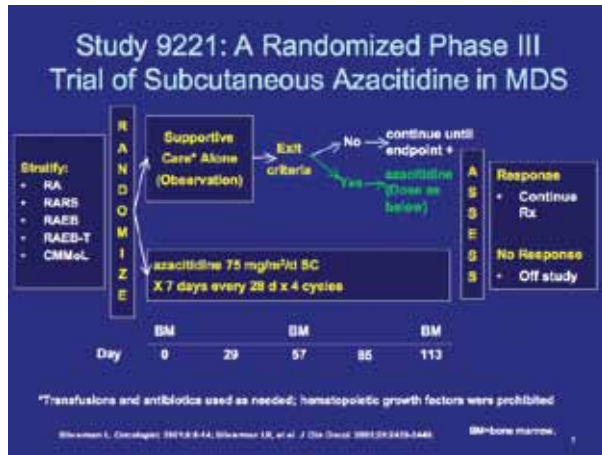
Despite the promising results described above, other therapies are desperately needed for nonresponders and for patients who respond and then fail demethylation therapy. Trials in the academic and the community setting are in progress to address the needs of these patients.

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- Fenaux P, Muftic GJ, Santini V, et al. Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): results of the AZA-001 phase III study. *Blood*. (ASH Annual Meeting Abstracts) 2007;110:817.



# Slide Library



**EPO + GCSF May Improve Survival in MDS with Low RBC Tx Needs**

- Comparison of Nordic studies (EPO; n=123) to Pavia (no EPO; n=240)
- Erythroid response 41%
- Median response duration 23 mos
- MVA: survival better with EPO if Tx needs < 2 URBCs/mo (HR 0.57; P=.015); no effect if higher Tx needs (P=.36)
- No impact of EPO ± GCSF on AML in low (P=.75) or high (P=.21) Tx needs

Jadersten. *Blood*. 108: abst 521, 2006

**Improved Survival in MDS with Iron Chelation Therapy**

- 178 patients; median age 69 years; IPSS low-Int-1 99/133
- Ferritin >2,000 µg/L in 28 patients; clinical evidence of iron overload in 22 patients; CHF 5; liver disease 18, endocrine dysfunction 4
- 18 patients received ICT: DFO 0.5–3 g s.c. infusion over 12 hours for 5 days a week
- Cox-regression analysis: factors significant for survival: IPSS score (P<.008); ICT (P<.02)
- For low-Int 1 IPSS: median survival >160 months with ICT vs 40 months if no ICT (P<.03)
- Improved LFS in chelated patients

Leitch HA, et al. *Blood*. 2006;108:[abstract 249], and ASH 2007 poster 1469

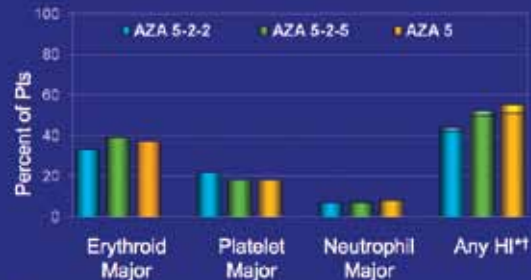
**NCCN Guidelines for Management of Iron Overload in MDS**

**NCCN guidelines**

- Consider iron chelation therapy for patients with MDS, particularly for Low/Int-1 patients
- Monitor iron burden and initiate therapy
  - After 20–30 units of RBCs
  - Serum ferritin levels >2500 mcg/L

NCCN, National Comprehensive Cancer Network.  
NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. v1.2007.

**Phase II Study: 5-, 7-, 10-day azacitidine dosing regimens Hematologic Improvement**



\*Pts counted only once for best response in an improvement category  
† Minor improvement at top of HI columns

**Phase II Study: 5-, 7-, 10-day azacitidine dosing regimens RBC Transfusion Independence in Baseline-Dependent Pts**



**Phase II Study: 5-, 7-, 10-day azacitidine dosing regimens Grade 3/4 Hematologic Adverse Events**

Event	AZA 5-2-2 (N=50) n (%)	AZA 5-2-5 (N=48) n (%)	AZA 5 (N=50) n (%)
Neutropenia	21 (42)	15 (31)	11 (22)
Thrombocytopenia	13 (26)	7 (15)	6 (12)
Anemia	12 (24)	7 (15)	5 (10)
Leukopenia	7 (14)	4 (8)	4 (8)
Febrile neutropenia	4 (8)	4 (8)	1 (2)

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