Evolving Strategies in the Treatment of MDS and AML

Abstract

Myelodysplastic syndrome (MDS) is a clonal hematopoietic disorder characterized by a hyperproliferative bone marrow, cellular dysplasia, and ineffective hematopoiesis. This heterogeneous malignancy is composed of several subtypes, the classification of which has evolved over several years. The treatment of MDS involves improving patient survival and quality of life while decreasing the likelihood of progression to acute myelogenous leukemia (AML). In addition to supportive care with transfusions and hematopoietic growth factors as well as stem cell transplantation, three chemotherapeutic agents have been approved to treat MDS—lenalidomide, azacitidine, and decitabine. In addition, multiple agents and novel combinations are currently in development to treat both MDS and AML. Several clinical studies which have investigated these therapeutic approaches, as well as the incorporation of new tools used in the diagnosis of MDS, have been published since the 2008 American Society of Hematology (ASH) Annual Meeting and Exposition, and are discussed here. By becoming familiar with these studies, the physician will be better able to provide the optimal treatment for their patients, as well as become aware of novel therapeutic strategies to offer their patients in ongoing clinical trials.
Release date: August 2009
Expiration date: August 31, 2010
Estimated time to complete activity: 1.25 hour

Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hemato-oncology nurses involved in the management of patients with myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML).

Statement of Need/Program Overview: Several new prognostic factors have been identified in MDS/AML, leading to greater specificity of subgroups, prognosis, and treatment options. In addition, many new drugs are being evaluated for the treatment of MDS/AML. These emerging data may not be fully understood by practicing hematologists/oncologists in the community setting. A Clinical Roundtable Monograph is the ideal vehicle through which community-based physicians can learn about these recent advances.

Educational Objectives
After completing this activity, the participant should be better able to:
• Identify important cytogenetic factors in the planning of treatments for patients with conditions such as MDS/AML.
• Select appropriate frontline treatments for patients with MDS/AML.
• Cite findings of trials related to treatment of patients with MDS/AML.

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Therapy Management with Currently Available Therapies—Schedule and Dosing

Richard Stone, MD

**Lenalidomide**

Lenalidomide is currently approved for the treatment of patients with transfusion-dependent anemia that is due to low- or intermediate-1-risk myelodysplastic syndrome (MDS) associated with a deleted chromosome 5q \([\text{del}(5q)]\) cytogenetic abnormality.\(^1\) Patients may or may not have additional cytogenetic abnormalities. Lenalidomide is an immunomodulatory drug (IMiD) that is a derivative of the parent compound thalidomide, but with more potent and less toxic properties.\(^2,3\) In addition to its immunomodulatory effects such as inhibition of tumor necrosis factor alpha (TNFa) production and stimulation of CD4-positive and CD8-positive cells, other actions attributed to lenalidomide include inhibition of angiogenesis, inhibition of cellular adhesion, and induction of growth arrest and apoptosis.\(^4-9\) However, its exact mechanism in MDS remains unclear. Recent data have suggested that lenalidomide can significantly affect the expression of multiple genes in erythroblasts, including the upregulation of the tumor suppressor gene SPARC and the apoptosis-promoting gene activin A.\(^10\) It is unclear if the promotion of erythroid differentiation represents the mechanism of action of lenalidomide in MDS.\(^10-12\)

The approval of lenalidomide was based on its efficacy in MDS patients with \([\text{del}(5q)]\) and/or low- or intermediate-1 risk disease in several clinical trials. The first, an open-label single-center study to determine the safety and efficacy of lenalidomide, enrolled 43 patients with transfusion-dependent or symptomatic anemia regardless of their cytogenetic profile.\(^13\) Del(5q) alone or with other cytogenetic abnormalities was identified in 46% of patients (n=11 and n=9, respectively). Patients received lenalidomide (10 mg or 25 mg daily) for 21 days of a 28-day cycle, with sequential dose reductions allowed as necessary due to adverse events; response was assessed after 16 weeks of therapy. Approximately half (56%) of the patients experienced a response to treatment, including sustained transfusion-independence (n=20), a reduction of more than 50% in the need for transfusion (n= 3), or an increase in hemoglobin levels higher than 2 g/dL (n=1). Significantly, the response rate was found to be higher among patients with a del(5q) phenotype compared with patients with either a normal karyotype or other cytogenetic abnormalities (83% vs 57% and 12%, respectively, \(P=0.007\)). Additionally, the median time to response was shorter in patients with del(5q) compared with other patients (8.0 ± 4.4 vs 11.2 ± 6.7 weeks, \(P=0.029\)). The most frequently reported adverse events of any grade in this study were thrombocytopenia (74%) and neutropenia (65%); severe myelosuppression (≥ grade 3) was found to be dose-dependent and required dose interruption or reduction in 58% of patients.

That clinical study, which established lenalidomide as effective in MDS, restricted enrollment to patients with a del(5q) cytogenetic abnormality (either alone or in conjunction with other cytogenetic abnormalities). In this study, a multicenter, international trial, 148 patients with low- or intermediate-1-risk MDS with del(5q) received lenalidomide (10 mg daily) initially for 21 days of a 28-day cycle, and then subsequently every day.\(^1\) Response to therapy was assessed following 24 weeks of treatment; 76% of patients had a reduced transfusion requirement, and 67% of patients achieved transfusion-independence. This benefit was experienced whether del(5q) was the sole abnormality or was associated with others. The median time to response was 4.6 weeks (range, 1–49 weeks). The response to lenalidomide was also durable among these patients (median duration of transfusion independence not reached after a median follow-up of 104 weeks). Among 85 patients who were evaluable for cytogenetic response, the majority (n=62) exhibited improvement; most (n=38) achieved complete cytogenetic remission. Similar to the previous study, moderate-to-severe neutropenia (55%) and thrombocytopenia (44%) were the most frequently reported adverse events requiring treatment interruption or dose reduction.

Another clinical study, a multicenter phase II trial, evaluated lenalidomide specifically in low- or intermediate-1-risk patients with transfusion-dependent MDS that did not have the del(5q) cytogenetic abnormality.\(^14\) Lenalidomide (10 mg daily) was initially administered for 21 days of a 28-day cycle, but was later modified to be given on a daily basis due to additional data suggesting no associated increase in toxicity.\(^13\) A total of 214 patients were enrolled in the study. Transfusion-independence was achieved by approximately one-quarter of the patients (26%). The median time to response was 4.8 weeks. The median duration of this transfusion-independence was 41.0 weeks.
Several additional patients experienced a reduction of more than 50% in transfusion requirement, producing an overall hematologic improvement rate of 43%. Grade 3/4 neutropenia (30%) and thrombocytopenia (25%) were the most common reasons for dose adjustment.

Interestingly, an analysis of the latter 2 trials demonstrated that lenalidomide-associated cytopenias could be related to treatment response. For example, 70% of patients who experienced severe thrombocytopenia (platelet count decreased by ≥50%) achieved a response to treatment, compared with only 42% of patients with stable or less severe thrombocytopenia (platelet count decreased by <50%; *P*=.01). Similarly, more patients with severe neutropenia (absolute neutrophil count [ANC] decreased by ≥75%) achieved a response compared with patients with stable or less severe neutropenia (ANC decreased by <75) (82% vs 51%, *P*=.02). However, this relationship was only apparent among patients with the del(5q) cytogenetic abnormality.

Lenalidomide is currently under investigation for the treatment of acute myelogenous leukemia (AML). For example, one recent case study reported the induction of sustained complete morphological and cytogenetic remission in 2 older AML patients with the administration of high-dose, single-agent lenalidomide. Notably, both patients both had a poor-risk cytogenetic form of AML (trisomy 13). However, the development of lenalidomide in this setting is still experimental, and should not be used to treat AML patients outside of a clinical trial.

### Azacitidine

Azacitidine is indicated for the treatment of patients with all subtypes of MDS. The main mechanism attributed to the action of azacitidine in MDS is DNA hypomethylation, whereby methyl groups are removed from DNA bases in promoter regions of genes. This effect is antineoplastic when the expression of genes required to control growth, such as tumor suppressors and pro-differentiation genes, are re-expressed. In addition to its action as a DNA hypomethylating agent, azacitidine may also interfere with nucleic acid metabolism. Azacitidine is administered chronically, for 4–6 cycles but preferably until disease progression or toxicity develops.

The Cancer and Leukemia Group B (CALGB) 9221 study was a phase III randomized controlled trial that compared azacitidine to supportive care. A total of 191 MDS patients were randomized to receive either subcutaneous azacitidine (75 mg/m²/day) for 7 days of a 28-day cycle or supportive care, and both arms received transfusions and antibiotics as needed. Patients whose disease progressed while on the supportive care arm were allowed to cross over to azacitidine. Compared with supportive care, patients receiving azacitidine experienced a significantly higher treatment response rate (60% vs 5%, *P*<.001). Although all responses in the supportive care arm were classified only as an improvement, patients in the azacitidine arm experienced a complete response (7%), partial response (16%), or improvement (37%; Table 1). The median time to AML transformation or death was also significantly prolonged in the azacitidine group (21 vs 13 months, *P*=.007). AML transformation was the first event in over twice as many patients in the supportive care arm compared with the azacitidine arm (38% vs 15%, *P*=.001). When crossover to the azacitidine arm was eliminated, a landmark analysis showed that median overall survival (OS) was significantly prolonged among patients receiving azacitidine (18 vs 11 months, *P*=.03). The most commonly reported adverse event associated with azacitidine treatment was grade 3/4 myelosuppression, including granulocytopenia (81%), thrombocytopenia (70%), and leukopenia (59%). However, the investigators noted that these toxicities were transient, and patients were generally able to recover between treatment cycles. Other adverse events included infection (20%) and nausea or vomiting (4%). Overall, patients in the azacitidine arm also experienced significant improvements in quality of life, including less fatigue (*P*=.001), less dyspnea (*P*=.0014), improved physical functioning (*P*=.0002), positive affect (*P*=.0077), and diminished psychologic distress (*P*=.015). The positive results from this study were pivotal in the approval of azacitidine for the treatment of all MDS subtypes.

Three alternative dosing schedules of azacitidine were recently evaluated in MDS patients. A total of 151 patients were randomized to receive subcutaneous azacitidine every 4 weeks for 6 cycles, administered as either a 5-2-2 regimen (75 mg/m² for 5 days, followed by 2 days of no treatment,

| Table 1. Cancer and Leukemia Group B 9221 Study: Azacitidine Versus Supportive Care |
|----------------------------------------|---|---|---|
| Evaluated number of patients | Supportive Care | Azacitidine | Cross over |
| Complete response | 0 (0%) | 7 (7%)<sup>†</sup> | 5 (10%) |
| Partial response | 0 (0%) | 16 (16%)<sup>‡</sup> | 2 (4%) |
| Improved | 5 (5%) | 37 (37%)<sup>‡</sup> | 16 (33%) |
| Total response rate | 5 (5%) | 60 (60%)<sup>‡</sup> | 23 (47%) |

*Using CALGB criteria.

Using International Working Group criteria, complete response + partial response=11%<sup>†</sup>

*P*<.01; ‡*P*<.0001

followed by 75 mg/m² for 2 days), a 5-2-5 regimen (subcutaneous 50 mg/m² for 5 days, followed by 2 days of no treatment, followed by 50 mg/m² for 5 days), or a single regimen (75 mg/m² for 5 days). Similar rates of hematologic improvement (44%, 45%, and 56%, respectively) and transfusion independence (50%, 55%, and 64%, respectively) were observed among each treatment group. The frequency of adverse events was also similar among each treatment group. The investigators concluded that each alternative dosing regimen produced similar rates of hematologic improvement, transfusion independence, and toxicity compared with the conventional azacitidine dosing regimen. However, the conventional 7-day regimen was not included in the trial as a comparator arm. An intravenous formulation of azacitidine is also available.24

Standard dose of azacitidine was recently shown to be superior to conventional care in a randomized, open-label, multicenter, phase III study (MDS-001).25 A total of 358 patients with higher-risk (intermediate-2- or high-risk) MDS were randomized to receive subcutaneous azacitidine (75 mg/m²/day) for 7 days in a 28-day cycle or conventional care (investigator chosen from best supportive care, low-dose cytarabine, or intensive chemotherapy). An improvement in median OS was apparent in the azacitidine group compared with conventional care (24.5 vs 15.0 months; hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.43–0.77; P=.001). The 2-year OS was also significantly superior among patients receiving azacitidine (50.8% vs 26.2%; P<.001). Cytopenias were the most frequently reported adverse event, regardless of treatment arm.

Azacitidine has been evaluated in the treatment of AML, although its use remains restricted to the clinical trial setting.17 For example, one study reported an overall response of 60% in AML patients treated with azacitidine, while a case study showed that single-agent azacitidine induced a complete response in a patient with refractory AML.26,27 Several clinical trials are currently underway to evaluate azacitidine as treatment for AML.28-30

Decitabine

Decitabine, like azacitidine, is a hypomethylating agent approved for the treatment of intermediate-1, intermediate-2, and high-risk MDS subtypes.31 Decitabine was first approved for use in MDS based on the results of a phase III trial which randomized 170 patients to receive either intravenous decitabine (15 mg/m² administered over 3 hours every 8 hours for 3 days) or best supportive care.32 A significantly superior response rate was achieved by patients in the decitabine group compared with the best supportive care group (17% vs 0%; P<.001); 9% of the responses attributed to decitabine were a complete response. These responses were durable (median duration of response, 10.3 months) and were associated with transfusion-independence. Although not statistically significant, patients receiving decitabine experienced a prolonged median time to AML transformation or death (12.1 vs 7.8 months; Figure 1). However, this difference reached statistical significance when restricted to only patients with intermediate-2- or high-risk disease (12.0 versus 6.8 months; P=.03), de novo disease (12.6 vs 9.4 months; P=.04), or to those with no prior treatment exposure (12.3 vs 7.3 months; P=.08).

After these initial results, a subsequent phase II trial was conducted to determine the optimal dosing schedule for decitabine.33 A total of 95 patients (higher-risk MDS, AML=acute myelogenous leukemia; MDS=myelodysplastic syndrome; IPSS=International Prognostic Scoring System

![Graph](image-url)
MDS to receive either decitabine (15 mg/m² over 4 hours randomized 223 patients with intermediate-2 or high-risk Research and Treatment of Cancer (EORTC) 06011 trial good candidates for chemotherapy. These successful results have led to the testing of this decitabine schedule in older patients with AML who are not all, an objective response was observed by 73% of patients, and 34% achieved a complete response. The intravenous, high-dose, 5-day schedule was determined to produce both an optimal complete response rate (39% vs 21% and 24%, respectively; \( P<.05 \)) as well as the best epigenetic modulation. The reason for the lack of benefit in OS in the EORTC 06011 trial failed to show a survival advantage compared to conventional care. Unfortunately, the clinical experience with each of these approved therapies to treat MDS is rather limited, therefore causing physicians to rely on available clinical trial data. Future efforts remain focused on combining lenalidomide with either azacitidine or decitabine, and evaluating each of the agents as monotherapy to treat patients with AML.

The multicenter phase III European Organization for Research and Treatment of Cancer (EORTC) 06011 trial randomized 223 patients with intermediate-2 or high-risk MDS to receive either decitabine (15 mg/m² over 4 hours every 8 hours on days 1–3) or supportive care. The design of this study was similar to the MDS-001 trial, which randomized higher-risk MDS patients to azacitidine or conventional care. However, unlike the MDS-001 study, the EORTC 06011 trial failed to show a survival benefit with decitabine treatment. No significant difference was observed in median OS between the decitabine and supportive care groups (10.1 vs 8.5 months; Figure 2), and the time to AML transformation or death was also not significantly improved (8.8 vs 6.1 months; Figure 3).

However, the median progression-free survival (PFS) was significantly prolonged in the decitabine arm (6.6 vs 3.0 months; HR, 0.68; 95% CI, 0.52–0.88; \( P=.004 \)). The reason for the lack of benefit in OS in the EORTC 06011 trial could be due to the treatment schedule used in this study. Patients received a median of only 4 cycles of decitabine; 40% of patients received 2 cycles or less and only 21% received 8 cycles.

**Summary**

Overall, the best drug for the treatment of MDS has not been established. Azacitidine is associated with a survival advantage compared to conventional care. Unfortunately, the clinical experience with each of these approved therapies to treat MDS is rather limited, therefore causing physicians to rely on available clinical trial data. Future efforts remain focused on combining lenalidomide with either azacitidine or decitabine, and evaluating each of the agents as monotherapy to treat patients with AML.

**References**

Disease Pathology—Impact of Novel and Targeted Therapies

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Pathology of MDS

MDS, a heterogeneous collection of clonal hematopoietic disorders, is derived from an abnormal and multipotent progenitor cell. These malignancies are characterized by hyperproliferative bone marrow, cellular dysplasia, and ineffective hematopoiesis. Recently, the World Health Organization (WHO) updated the 2001 MDS classification scheme to reflect the delineation of several new subtypes.\(^1,2\) One of the newly identified subtypes, refractory cytopenias with unilineage dysplasia (RCUD), describes patients with either a refractory anemia or cytopenia of at least 6 months in duration, with a unilineage dysplasia in more than 10% of cells in a single cell line. RCUD is further subcategorized into refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT). The median survival times associated with RCUD are 6–7 years, and approximately 10% of patients experience AML transformation. RA occurs more frequently than RN and RT, which account for less than 10% of all MDS cases. The WHO retained the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol. 2002;20:2441-2452.

category refractory cytopenia with multilineage dysplasia (RCMD) to describe patients with 1 or more cytopenias in the blood and dysplasia in more than 10% of cells in 2 or more myeloid lineages (including erythroid, granulocytic, and/or megakaryocytic).

Another change in the updated WHO classification is a slight modification of nomenclature: RARS is now referred to as refractory anemia with ring sideroblasts. A previous change made to the WHO classification scheme in 2001 was retained, which subdivided the category refractory anemia with excess of blasts (RAEB) into 2 subcategories—RAEB-1 and RAEB-2—dependent upon the marrow blast percentage (<5% vs 5–19%, respectively). Two other distinctions, which were retained, included patients having mild MDS with an isolated del(5q) cytogenetic abnormality, and patients with unclassifiable MDS.

The largest study evaluating the impact of karyotype on patient prognosis involves a large database of 2,124 MDS patients from 8 institutions throughout Austria and Germany, for which morphologic, clinical, cytogenetic, and follow-up data exist. Cytogenetic analyses of patients in this database showed that approximately half of patients (52.3%) had cytogenetic abnormalities; a total of 684 unique cytogenetic categories were identified. Using a subset of patients (n=1,286) who were treated with supportive care only, the impact of the karyotype on the natural history of MDS was determined. Median OS was prolonged among patients with normal karyotype compared with those with complex cytogenetics (53.4 vs 8.7 months). Further, 13 unique cytogenetic abnormalities were classified as being associated with good, intermediate, and poor prognosis.

In a presentation at the 2008 American Society of Hematology (ASH) Annual Meeting and Exposition, a single-nucleotide polymorphism (SNP)-array based karyotype was found to complement routine cytogenetic analysis to determine MDS diagnosis and risk stratification schemes. SNP karyotyping is beneficial over conventional metaphase cytogenetics, the standard for detection of chromosomal abnormalities, because it does not require a dividing cell (it can use interphase cells) and also allows for detection of smaller lesions. Although SNP karyotyping is advantageous in that it is more sensitive, its clinical relevance in determining MDS classification and prognosis in the past has been unclear. In this study, a total of 352 patients with various subtypes of MDS (MDS, n=218; MDS/myeloproliferative disorder [MPD], n=59; MDS-derived AML, n=75) were included in the analysis. Compared with metaphase cytogenetics alone, the detection of cytogenetic abnormalities was improved with the combined use of metaphase cytogenetics plus SNP analysis (44% vs 57%, P=.0096). A number of abnormalities detected only by SNP analysis included somatic uniparental disomy. Further, median OS was found to be significantly worsened among patients who were found to have cytogenetic abnormalities (including those detected by SNP analyses) compared with a normal karyotype (also including SNP analyses: 39 vs 73 months, P=.03); this effect was also true for other outcomes. Thus, SNP-detected lesions were found to complement conventional metaphase cytogenetics and to have a significant impact on patient prognosis. The clinical development of SNP arrays will be based on their ability to detect differences in patient survival.

**Clofarabine**

Clofarabine is a second-generation nucleoside analog which is currently approved to treat certain types of pediatric acute lymphoblastic leukemia. The mechanism of action of clofarabine is thought to include inhibition of DNA polymerases, inhibition of ribonucleotide reductase, and induction of apoptosis. Several clinical trials have evaluated the safety and efficacy of clofarabine to treat MDS.

One report at ASH 2008 of 2 phase II trials evaluated 2 formulations of clofarabine in MDS. Patients with MDS and 5% or more blasts or those who were intermediate-2 or high-risk according to the IPSS were eligible for enrollment. A total of 61 patients were administered clofarabine as either an intravenous (15 or 30 mg/m² over 1 hour daily for 5 days every 4–6 weeks; n=36) or oral (30 or 40 mg/m² daily for 5 days every 4–6 weeks; n=25) formulation. The median patient age was 67 years (range, 25–89 years) and 70 years (range, 54–86) for the intravenous and oral groups, respectively. Among both studies, more than 80% of patients were over 60 years of age. Unfavorable cytogenetics were detected in 47% and 40% of the intravenous and oral groups, respectively. Approximately two-thirds of patients (64%) had failed prior treatment with a hypomethylating agent (azacitidine or decitabine). After treatment with 15 or 30 mg/m² intravenous clofarabine, a complete response was achieved by 35% and 25% of patients, respectively. A 29% rate of complete response was achieved by all patients receiving oral clofarabine. Commonly reported adverse events included myelosuppression, febrile neutropenia, nausea, vomiting, skin rash, hyperbilirubinemia, and elevated transaminase levels. A total of 6 patients died while on study; all mortalities were among patients receiving intravenous clofarabine and were most frequently related to infection. Importantly, this study provides evidence that clofarabine is active in patients with MDS who have previously failed treatment with a hypomethylating agent. This subset of patients will likely be targeted in the future development of this drug.

Clofarabine also displayed activity in older adults with untreated AML in the CLO24300606/CLASSIC II study, a phase II, nonrandomized, multicenter, prospective, single-arm, open-label trial. This study included 112 patients with de novo or secondary AML who were 60 years of age...
or older and had an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2. Further, patients had at least 1 adverse prognostic factor, including being 70 years of age or older, having an ECOG performance score of 2, an antecedent hematologic disorder, or an intermediate or unfavorable risk karyotype. Patients received induction therapy with clofarabine (30 mg/m² daily on days 1–5), followed by a second induction cycle of clofarabine (20 mg/m² daily on days 1–5) if the disease was found to be persistent but not progressive on day 21. Patients who achieved a complete response received further consolidation therapy with clofarabine (20 mg/m² daily on days 1–5 for 5 cycles if the response occurred with the first induction, or 4 cycles if the response occurred with the second induction; Figure 1). Patients were followed for a median of 17 weeks (range, 1–62 weeks). The rate of overall response was 46%; of these, 38% had a complete response, and 4% a partial response (Table 1). The median time to response was 5.1 weeks (range, 3.3–19.6 weeks), and at the time of follow-up, the median duration of remission had not yet been reached. The rate of median overall response was found to be similar among patients with and without adverse prognostic factors. For example, the confidence intervals for the rates of overall response overlapped among patients 70 years or older (39%; 95% CI, 27.6–51.6%) versus those who are younger than 70 years old (56%; 95% CI, 39.9–70.9%); for patients with an ECOG performance score of 0–1 (49%; 95% CI, 38.5–60.4%) versus those with ECOG performance score of 2 (32%; 95% CI, 15.0–53.5%), and for patients with unfavorable cytogenetics (42%; 95% CI, 29.5–55.2%) versus those with intermediate cytogenetics (54%; 95% CI, 39.0–69.1%). While the median OS was not yet able to be determined at the time of the report, the 30-day rate of all-cause mortality was 9.8%. It is unknown in the study precisely how much time the treated patients spent being hospitalized, and whether this drug should be compared to mid-range therapy, such as low-dose cytarabine, or intensive remission induction therapy. These results suggest that clofarabine is active in older patients with untreated AML.

**Novel Combinations**

Based on their successful results as single-agents, a phase I clinical trial was initiated to evaluate the combination of azacitidine plus lenalidomide in patients with higher-risk MDS. Using a classic 3+3 enrollment design, subcutaneous azacitidine was administered (75 mg/m² on days 1–5) with a dose escalation of oral lenalidomide (5 mg on days 1–14, 5 mg on days 1–21, and 10 mg on days 1–21; Table 2). Subcutaneous azacitidine was then escalated (50 mg/m² on days 1–5 and 8–12) with the same dose-escalation of oral lenalidomide (5 mg on days 1–14, 5 mg on days 1–21, and 10 mg on days 1–21). A total of 18 patients (median age, 68 years) were enrolled in the study. Patients had either intermediate-1 (n=3), intermediate-2 (n=9), or high-risk (n=6) disease. The median time from diagnosis was 5 weeks (range, 2–106 weeks). No dose-limiting toxicities were observed in any of the dosing cohorts, but cycle 2 of therapy was delayed (≥9 days) in 5 patients. No treatment-related nonhematologic grade 3/4 adverse events were reported. A median ANC decrease of 26% and a mean platelet decrease of 24% was observed within the first 8 weeks of the study. The overall response rate among all patients was 72%, 39% of which was a complete response, 6% a partial response, and 17% was a hematologic improvement. Two patients achieved a bone marrow complete response. From these data, the combination regimen chosen for future phase II testing was azacitidine (75 mg/m² on days 1–5) plus lenalidomide (10 mg on days 1–21).
Another combination that has been recently tested is romiplostim combined with azacitidine. Romiplostim is an Fc-peptide fusion protein (peptibody) which has shown activity as a single agent in patients with low-risk MDS experiencing severe thrombocytopenia. In this multicenter, double-blind, placebo-controlled, phase II trial, 40 patients with low-, intermediate-1, or intermediate-2-risk MDS who were undergoing treatment with azacitidine (75 mg/m² on days 1–7 of a 28-day cycle) were randomized to 3 arms in which they received 4 cycles of either romiplostim (500 mg/week or 750 mg/week) or placebo. Although patients receiving low- and high-dose romiplostim experienced improvements in clinically significant thrombocytopenia compared with placebo (62%, 71%, and 85%, respectively), this difference did not reach statistical significance (Figure 2).

Remissions (CR + CRp) after cycles 1 and 2 of therapy (N=51):
- 38/51 (75%) remissions after cycle 1 (induction)
- 13/51 (25%) remissions after cycle 2 (re-induction)

Time to OR (N=51): Median 5.1 weeks, range 3.3–9.6 weeks
Median time to peripheral blood blast clearance: 5 days

Similarly, the number of patients requiring a platelet transfusion was also decreased among patients receiving romiplostim (46%, 36%, and 69%, respectively). By the fourth cycle, only 33% and 0% of patients receiving low and high dose romiplostim required a platelet transfusion, compared with 40% of patients receiving placebo. Adverse events were generally mild to moderate in severity; severe adverse events including grade 3/4 bleeding were similar between patients receiving romiplostim and placebo (1 and 2 patients, respectively). This study suggested that the addition of romiplostim to azacitidine increased platelet counts and decreased platelet transfusion dependence. Because of previous data suggesting romiplostim may induce an increase in blast percentage, its use is recommended to be limited to patients without evidence of excess blasts.

Table 1. CLO243: IRRP Response (N=112)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Number of Patients</th>
<th>Response Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>51</td>
<td>46% (36, 55)</td>
</tr>
<tr>
<td>CR</td>
<td>42</td>
<td>38% (29, 47)</td>
</tr>
<tr>
<td>CRp</td>
<td>9</td>
<td>8% (ND)</td>
</tr>
<tr>
<td>PR</td>
<td>4</td>
<td>% (ND)</td>
</tr>
</tbody>
</table>

Remissions (CR + CRp) after cycles 1 and 2 of therapy (N=51):
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Time to OR (N=51): Median 5.1 weeks, range 3.3–9.6 weeks
Median time to peripheral blood blast clearance: 5 days

Table 2. Azacitidine Plus Lenalidomide: Dosing Table

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Azacitidine (Subcutaneous) Schedule</th>
<th>Lenalidomide (Oral) Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75 mg/m² days 1–5</td>
<td>5 mg days 1–14</td>
</tr>
<tr>
<td>2</td>
<td>75 mg/m² days 1–5</td>
<td>5 mg days 1–21</td>
</tr>
<tr>
<td>3</td>
<td>75 mg/m² days 1–5</td>
<td>10 mg days 1–21</td>
</tr>
<tr>
<td>4</td>
<td>50 mg/m² days 1–5, 8–12</td>
<td>5 mg days 1–14</td>
</tr>
<tr>
<td>5</td>
<td>50 mg/m² days 1–5, 8–12</td>
<td>5 mg days 1–21</td>
</tr>
<tr>
<td>6</td>
<td>50 mg/m² days 1–5, 8–12</td>
<td>10 mg days 1–21</td>
</tr>
</tbody>
</table>

Figure 2. Romiplostim in MDS: efficacy.
Our understanding of MDS has dramatically evolved in recent years to include a very complex and heterogeneous group of hematopoietic disorders. Several classification systems have been developed, including the French-American-British (FAB) and the WHO classification systems. These classifications are largely morphologically based and require a great deal of hematopathologic expertise in order to properly diagnose each patient. Increasingly, it has become evident that although morphology allows for a diagnosis, a morphological assessment of the disease is not enough to properly prognosticate patients with MDS. Furthermore, the molecular heterogeneity of MDS is becoming evident. Analysis of a database of 2,124 MDS patients revealed 684 unique cytogenetic categories, suggesting a very high level of heterogeneity. Importantly, this analysis also showed that abnormal karyotypes were associated with distinct patient outcomes. Patients could be grouped into specific cytogenetic subsets dividing patients into those with either good, intermediate, or poor prognosis. These data indicate that understanding cytogenetic alterations of MDS is critical to properly calculate patient prognosis and determine the appropriate therapy.

**Impact of Classification Systems**

The most commonly used classification system to determine patient prognosis is the International Prognostic Scoring System (IPSS). The IPSS was developed using data from 7 large previously reported studies of nearly 900 MDS patients. It should be noted that a significant fraction of these patients had AML (blasts more than 20%) when judged with more recent criteria. The IPSS categorizes patients into 4 distinctive subgroups: low-risk, intermediate-1-risk, intermediate-2-risk, and high-risk. This classification is based on 3 main factors, including the number of cytopenias present, the type of cytogenetic alterations, and the blast percentage. The IPSS also allows clinicians to calculate the risk of transformation to AML. A careful analysis of this criteria shows that the IPSS is highly weighted toward the patients’ blast percentage. In particular, the IPSS classification is not an ideal tool for classifying patients with low- or intermediate-1 risk disease. Traditionally, patients with lower-risk disease were considered to have an excellent prognosis, with many of these patients not requiring therapy. It is now becoming clear that a significant fraction of so-called “lower-risk” patients have a poor prognosis, a fact not identifiable by the IPSS score. For this reason, there have been recent efforts to develop new prognostic systems for MDS.

One alternative system, the WHO classification-based prognostic scoring system (WPSS), was developed to classify patients into 5 risk groups associated with different survivals and probabilities to AML transformation. The WPSS is essentially a combination of the WHO and IPSS systems, with an important emphasis on transfusion dependence.

**References**


**Incorporating Classification Systems, Cytogenetics, and Algorithms When Choosing Therapy**

Guillermo Garcia-Manero, MD
The 5 risk groups defined by the WPSS include very low, low, intermediate, high, or very high. Each risk group is associated with significantly different median OS (very low: 103-141 months; low: 66–72 months; intermediate: 40–48 months; high: 21-26 months; and very high: 9–12 months) as well as risk of AML progression (very low: 0-0.03; low: 0.06–0.11; intermediate: 0.21–0.28; high: 0.38–0.52; and very high: 0.80). Importantly, the WPSS was found to be capable of significantly predicting patient survival and progression to AML at any point during follow-up. The WPSS was recently validated and compared with IPSS in 149 patients with de novo MDS, which showed it to have more powerful prognostic impact.5 However, a major limitation of the WPSS is its reliance on the WHO classification, which is not available at every center and incorporates a great deal of variability. Additionally, recent modifications to the WHO may affect the prognostic ability of the WPSS.6

A novel classification of MDS scheme has recently been published and was developed specifically for patients with lower-risk (low- and intermediate-1-risk) disease.7 In this model, 856 patients with lower-risk MDS who were referred to a single center since 1975 were evaluated. Patients had not received any therapy either prior to or after referral. The IPSS score was calculated at the time of the initial referral, survival was calculated from the time of referral until death from any cause, and AML progression was censored at the time of last contact for patients with no report of progression. This new system is based on the calculation of a score that then allows the calculation of the patients’ specific survival. For simplicity, patients were divided in 3 categories (Table 1). This type of analysis therefore allows better discrimination of patient outcomes and may prove to be particularly important for the decision of the timing to initiate therapy, for instance when to undergo early allogeneic stem cell transplantation in this group of patients.

Recently, a new risk model was proposed for all patients with MDS to account for events not considered by the IPSS. This model used 1,915 MDS patients referred to a single center from 1993 to 2005.8 Patients included those with CMML, secondary MDS, and previously treated MDS. Significant adverse and independent factors which were identified as continuous and categoric values included poor performance, older age, thrombocytopenia, anemia, increased bone marrow blasts, leukocytosis, complex cytogenetic abnormalities, and prior transfusions (P<.001 for all). This new model, referred to as the Global MDS M.D. Anderson Cancer Center (MDACC) Model, grouped patients into 4 prognostic categories (low-, intermediate-1-, intermediate-2-, high-risk) with significantly different survival outcomes (Table 2 and Figure 1). Importantly, this model can be used in either treated or untreated patients, at any point during follow-up.

Future efforts are focused on the development of a novel IPSS classification, derived from nearly 10,000 patients worldwide. The goal of this new IPSS classification would be to have a unified prognostic tool that could be applied throughout multiple centers, in order to allow improved inter-trial comparison. The development of such a unified IPSS classification will have significant implications in both clinical trial design and the standardization of care for MDS patients worldwide.

**Impact of Cytogenetics**

From a therapeutic perspective, one of the most important cytogenetic alterations which impact treatment decisions is the presence of a del(5q) in patients with low-risk disease, particularly in those with anemia. Currently, the standard of therapy for these patients is lenalidomide; however this therapy, while it has a significant impact on anemia, does not affect thrombocytopenia or neutropenia.

A second important cytogenetic alteration affecting therapy is the presence of an alteration of chromosome 7.
Traditionally, patients with chromosome 7 abnormalities have very poor prognosis. Recent data from the AZA-001 study have demonstrated that patients with an alteration of chromosome 7 who were treated with 5-azacitidine derived significant benefit. Therefore, the identification of this cytogenetic alteration may help select proper therapy and improve survival among these patients.

Future Directions

In the coming years, a number of new molecular markers will become available with increasing understanding of the MDS disease. Although these markers are not yet ready to be incorporated into routine clinical use, they will eventually revolutionize how MDS treatment is approached. Until then, the first step for clinicians is to classify their MDS patient according to whichever prognostic system they are most familiar—be it IPSS, WPSS, or the newly developed alternative systems. For example, for patients with lower risk disease, patients have a wide variety of therapeutic strategies available to them including growth factor support, immune modulation, and the use of lenalidomide or hypomethylating agents. Conversely, for patients with higher risk disease, age may be a critical factor as this will help determine if they are candidates for high-dose chemotherapy with subsequent transplantation (perhaps for younger patients) or candidates for hypomethylating-based therapy that should be considered standard of care, particularly in older patients with this disease.

Further research into why patients fail hypomethylating therapy is needed, especially because until this is better understood, effective therapeutic alternatives for these patients remain limited. What is beginning to be recognized about patients who fail hypomethylating-based therapy is that they generally have a poor prognosis with a median OS of 4–5 months. Although those patients could potentially be rescued with stem cell transplantation, this is a rare option because of the higher incidence of the disease in older patients. The molecular basis of hypomethylating-based therapy is not known. One possibility is that it is mediated by the acquisition of distinct epigenetic alterations, although no solid data have confirmed this. Other possibilities include a pharmacologic mechanism that is unique to these patients or the generation of a new genetic lesion. Regardless, these represent an important group of patients who are currently candidates for clinical trials.

References

1. Which of the following statements is TRUE regarding a clinical study evaluating lenalidomide which restricted enrollment to patients with low- or intermediate-1 risk MDS and a del(5q) cytogenetic abnormality, discussed by Dr. Stone?
   A. Fewer than half of patients achieved transfusion-independence.
   B. A majority of patients had a reduced transfusion requirement.
   C. The benefit in reduced transfusion was experienced regardless of the cytogenetic abnormality complexity.
   D. Although the lenalidomide response was rapid, it was not durable.

2. In CALGB 9221, a phase III randomized controlled trial which compared azacitidine to supportive care in MDS patients, what rate of tumor response was achieved in the azacitidine group?
   A. 20%  B. 40%  C. 60%  D. 80%

3. MDS-001, which evaluated an intravenous formulation of azacitidine in patients with intermediate-2- or high-risk MDS, showed all of the following to be true, EXCEPT:
   A. A significant improvement in median OS was apparent in the azacitidine group compared with conventional care.
   B. The 2-year OS was significantly superior among patients receiving azacitidine.
   C. Cytophenias were only reported among patients receiving intravenous azacitidine.
   D. Cytophenias were the most frequently reported adverse event, regardless of treatment arm.

4. Which of the following statements regarding the EORTC 06011 trial, which randomized patients with intermediate-2- or high-risk MDS to receive decitabine or supportive care, is TRUE?
   A. Median PFS was not significantly prolonged in the decitabine arm.
   B. Decitabine significantly prolonged the median time to AML transformation or death.
   C. The EORTC 06011 trial showed a significant survival benefit with decitabine.
   D. The EORTC 06011 trial failed to show a survival benefit with decitabine treatment.

5. In a large study which evaluated the impact of karyotype on MDS patient prognosis, discussed by Dr. Sekeres, the combined use of SNP karyotyping and conventional metaphase cytogenetics improved the detection of cytogenetic abnormalities from 44% to __________.
   A. 57%  B. 73%  C. 86%  D. 95%

6. The phase II CLO24300606/CLASSIC II study, which evaluated the safety and efficacy of clofarabine in older adults with untreated AML, showed all of the following to be true, EXCEPT:
   A. The overall response rate was 46%.
   B. The rate of median overall response was found to be similar among patients with and without adverse prognostic factors.
   C. The rate of median overall response was significantly improved among patients without adverse prognostic factors.
   D. The median time to response was 5.1 weeks.

7. All of the following outcomes are true regarding a placebo-controlled phase II trial, which evaluated the combination of romiplostim with azacitidine compared with azacitidine alone, EXCEPT:
   A. The addition of romiplostim to azacitidine increased platelet counts compared with placebo.
   B. The addition of romiplostim to azacitidine decreased platelet transfusion dependence compared with placebo.
   C. The incidence of severe adverse events was similar between romiplostim and placebo.
   D. Overall survival was significantly improved among patients receiving romiplostim compared with placebo.

8. Which of the following systems categories patients into five risk groups associated with different survivals and probabilities to AML transformation?
   A. WHO  B. IPSS  C. WPSS  D. Global MDACC

9. The IPSS classification scheme is not an ideal tool for classifying patients with which disease risk?
   A. Low- or intermediate-1-risk
   B. Intermediate-1- or intermediate-2-risk
   C. Intermediate-2- or high-risk
   D. High-risk

10. Which of the following characteristics does NOT pertain to the new Global MDACC risk model?
    A. Validated using several types of MDS patients, including those with CML, secondary MDS, and previously treated MDS.
    B. Can be used in either treated or untreated patients.
    C. Can be used at any point during follow-up.
    D. Divides patients into two groups, dependent upon if they would have an optimal survival response with intervention compared with a survival of 9 months.
Evaluation Form: Evolving Strategies in the Treatment of MDS and AML

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

**Extent to Which Program Activities Met the Identified Objectives**

After completing this activity, I am now better able to:

1. Identify important cytogenetic factors in the planning of treatments for patients with conditions such as MDS/AML.  
   1 2 3 4 5

2. Select appropriate frontline treatments for patients with MDS/AML.  
   1 2 3 4 5

3. Cite findings of trials related to treatment of patients with MDS/AML.  
   1 2 3 4 5

**Overall Effectiveness of the Activity**

The content presented:
- Was timely and will influence how I practice  
  1 2 3 4 5
- Enhanced my current knowledge base  
  1 2 3 4 5
- Addressed my most pressing questions  
  1 2 3 4 5
- Provided new ideas or information I expect to use  
  1 2 3 4 5
- Addressed competencies identified by my specialty  
  1 2 3 4 5
- Avoided commercial bias or influence  
  1 2 3 4 5

**Impact of the Activity**

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

**Follow-up**

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey.  ☐ No, I’m not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

**Post-test Answer Key**

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<tr>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
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</table>

**Request for Credit**

Name ___________________________ Degree ________________________
Organization ___________________ Specialty ______________________
Address __________________________ ____________________________
City, State, Zip ______________________ __________________________
Telephone __________________ Fax __________________ E-mail __________________
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**For Physicians Only:**

I certify my actual time spent to complete this educational activity to be: __________________________

☐ I participated in the entire activity and claim 1.25 credits.

☐ I participated in only part of the activity and claim _____ credits.