Recent Advances in the Treatment of Myelodysplastic Syndromes

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Target Audience

This activity has been designed to meet the educational needs of hematologist and oncologists involved in the management of patients with myelodysplastic syndromes (MDS).

Statement of Need/Program Overview

Data are emerging on novel agents as well as new combination regimens for the treatment of MDS. This monograph reviews some of the salient new data recently presented at international meetings of hematologists/oncologists.

Educational Objectives

After completing this activity, the participant should be better able to:

- Cite newly presented study findings related to treatment of MDS.
- Specify new study findings evaluating new treatment options in MDS according to applicability to practice.
- Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with MDS.
- Identify future research directions for agents in the treatment of MDS.

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Introduction

Several clonal disorders occurring in hematopoietic progenitor cells have been grouped together under the rubric of myelodysplastic syndromes (MDS). The disease is understood to arise through numerous pathways, which is reflected by the heterogeneity of clinical courses associated with the various disease subtypes.[1] Typical clinical manifestations of MDS, arising from ineffective hematopoiesis, include anemia, neutropenia, and thrombocytopenia.[2] Disease-related complications include transfusion-dependent anemia, increased risk of hemorrhage, and infectious complications. Furthermore, approximately 30% of patients with MDS progress to acute myeloid leukemia (AML), a potentially life-threatening malignancy.[3]

There is a paucity of data on the etiology of MDS, but a hospital-based case-control study of 354 adult patients with de novo MDS (with 452 control patients), published in 2005, investigated associations between lifestyle characteristics and subjects' risk of developing MDS.[4] It was found that risk profiles differ by disease subtype and gender, but for all subtypes combined, family history of hematopoietic cancer (odds ratio [OR]=1.92), smoking (OR=1.65), and exposure to agricultural chemicals (OR=4.55) or solvents (OR=2.05) were associated with MDS risk. Other than age, risk factors include prior chemotherapy, immunosuppression, and exposure to radiation. Moreover, increasing awareness of the disease, as well as higher life expectancy and survivorship of prior cancers treated with chemotherapy, has led to more diagnoses.[5] It is estimated that between 10,000 and 15,000 new cases of MDS occur each year, with most patients older than 60 years of age.

Three classification systems for MDS disease subtypes have been developed: French-American-British (FAB), World Health Organization (WHO), and International Prognostic Scoring System (IPSS). The FAB classification system includes 5 MDS subgroups based on bone-marrow morphology: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). A greater understanding of the molecular basis of MDS enabled the refinement of the FAB system by WHO in 1997. The most important difference between WHO and FAB classifications was the lowering of the blast threshold for AML diagnosis from 30% to 20% (thereby eliminating the FAB category RAEB-T). Other changes included the addition of a new category, refractory cytopenia with multilineage dysplasia (RCMD), subdividing RAEB according to percent marrow blasts, defining 5q- syndrome as a unique MDS subtype, and removing the CMML subgroup.[6] The IPSS was developed to evaluate prognosis in patients with MDS.[7] Using risk classifications of low, intermediate-1, intermediate-2,

or high, this system incorporates the number of peripheral cytopenias, percentage of bone marrow blasts, and cytogenetic abnormalities; it also assigns a score to predict survival and risk of disease progression to AML.

The most common cytogenetic abnormality in MDS is the deletion of chromosome 5q.[8] Patients with a chromosome 5q deletion as the sole karyotypic abnormality have a relatively good prognosis; del(5q) plus additional cytogenetic abnormalities ("5q-syndrome") is associated with macrocytic anemia, normal or elevated platelet count, unilobular megakaryocytes, and low risk of disease transformation to AML. Other chromosomal abnormalities include translocation at 11q23, trisomy 8, inversion or deletion of chromosomal region 3q, and deletions of the chromosomal regions 7, 20q, or 17p.[9] These abnormalities, however, are not unique to MDS. Moreover, half the patients with MDS have normal chromosomal patterns. The function of these abnormalities in the pathology of the disease remains poorly understood.

Historically, treatment of MDS consisted of "best supportive care," which typically entailed red blood cell (RBC) or platelet transfusions and antibiotics. Transfusional iron overload remained a difficult complication for many patients. Patients received active therapy only in the presence of severe cytopenias or upon transformation to AML. Since 2004, however, the availability of the disease-modifying treatments azacitidine, decitabine, and lenalidomide has changed the treatment paradigm of MDS. In addition, for patients who are transfusion-dependent, iron-chelator therapy with an oral agent, deferasirox, is available. The understanding of how best to deploy erythropoiesis-stimulating agents (ESAs) has also grown in recent years. Finally, the only potentially curative therapy, hematopoietic stem cell transplantation, has become a viable option for a growing number of elderly patients due to improvements in nonmyeloablative conditioning regimens.

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Recent Advances in the Treatment of Myelodysplastic Syndromes

221 Final Results from a Phase I Combination Study of Lenalidomide and Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes[1]

MA Sekeres, AF List, D Cuthbertson, R Paquette, D Latham, M Afable, K Paulic, TP Loughran Jr, JP Maciejewski

The thalidomide analog lenalidomide and the hypomethylating agent decitabine have previously demonstrated single-agent efficacy in patients with MDS.[2,3] It was hypothesized that a combination of lenalidomide and azacitidine would take advantage of the former's immunomodulatory, antiangiogenic, and cytotoxic properties and the latter's cytotoxic and hypomethylating properties. A phase I trial was undertaken to evaluate the safety of such a combination as well as the maximum tolerated dose and dose-limiting toxicities, which were grade 3/4 nonhematologic toxicities as defined by National Cancer Institute (NCI) common toxicity criteria (CTC) 3.0, 50% or higher prolonged decrease in absolute neutrophil count (ANC), or platelets without recovery by day 56. Modified International Working Group criteria were used to assess response as a secondary objective. Patients with higher-risk MDS (IPSS score ≥1.5 or FAB/WHO with ≥5% myeloblasts) who had not previously received either agent were enrolled in a 3+3 design. A maximum of seven 28-day cycles was allowed.

This trial enrolled 19 patients (median age, 68 years; range, 52–78), 1 of whom was excluded upon diagnosis of AML. Of these patients, 7 were women. Only 1 patient had del(5q) cytogenetics. Three patients had IPSS intermediate-1–, 9 had intermediate-2–, and 6 had high-risk disease. After a median follow-up of 5 months (range, 1–13), the maximum tolerated dose was not reached and no dose-limiting toxicities were observed. Grade 3/4 nonhematologic toxicities included 1 case each of atrial fibrillation, monocular blindness, basal-cell skin carcinoma, central nervous system hemorrhage, shortness of breath, and perforated appendix, as well as 2 cases of febrile neutropenia. Median ANC decrease was 21%, with a median platelet decrease of 1%. The overall response rate among 17 evaluable patients was 71%, with 7 complete responses (CRs), 1 partial response (PR), 3 hematologic improvements (HIs), and 1 marrow CR.

The researchers concluded that the combination of these 2 well-established treatments for MDS results in improved activity compared to either alone in patients with higher-risk disease. The combination was well tolerated; based on this study, the optimal combination dose appears to be azacitidine 75 mg/m² subcutaneously administered on days 1–5 and lenalidomide 10 mg orally administered on days 1–21. A further investigation of this combination administered in sequence is planned for the future.

222 Oral and Intravenous Clofarabine for Patients With Myelodysplastic Syndrome[4]

S Faderl, G Garcia-Manero, F Ravandi, G Borthakur, Z Estrov, DA Thomas, V Gandhi, W Plunkett, A Byrd, M Kwari, HM Kantarjian

Clofarabine is a second-generation nucleoside analog that has demonstrated activity in patients with AML.[5] Its role in MDS has not yet been defined; to that end, 2 phase II trials evaluated intravenous and oral formulations of clofarabine, respectively, in patients with MDS. Thirty-six patients received intravenous clofarabine (median age, 67 years; range, 25–89) and 25 received the oral formulation (median age, 70 years; range, 54–86). Eligible patients had at least 5% blasts, IPSS intermediate-2– or high-risk disease, or CMML or RAEB-T by FAB classification.

Patients receiving the intravenous formulation of clofarabine were adaptively randomized based on response to 15 or 30 mg/m² over 1 hour daily for 5 days every 4–6 weeks. The beginning oral dose was 40 mg/m² daily for 5 days every 4–6 weeks, then decreased to 30 mg/m² after 6 patients were treated on the higher dose. Seventeen (47%) of the patients in the intravenous study and 10 (40%) patients in the oral study had unfavorable cytogenetics by IPSS definition. A total of 39 (64%) patients had failed prior hypomethylating therapy with

either decitabine or azacitidine. The researchers observed that CR was achieved by 7 (29%), 7 (35%), and 4 (25%) patients in the oral and intravenous 15 mg/m^2 and 30 mg/m^2 studies, respectively. In addition, 2 (8%), 3 (15%), and 2 (13%) achieved CR with incomplete platelet recovery, respectively; 3 patients (13%) in the oral study experienced HI.

Six patients receiving the intravenous formulation died, mostly due to infectious complications. Common adverse events were nausea, vomiting, rash, hyperbilirubinemia, and transaminase elevations, with few grade 3 or higher adverse events observed. Acute renal failure was observed in 7 patients (2 each receiving oral and 15 mg/m^2 intravenous; 3 receiving 30 mg/m^2 intravenous). Myelosuppression and febrile neutropenia were common, but prolonged myelosuppression (>42 days) was uncommon. The overall results of the studies indicate that clofarabine has activity in patients with MDS, but the optimal dose and schedule remain to be elucidated. It was noted that lower doses of the agent are also associated with responses.

224 Effect of Romiplostim in Patients with Low or Intermediate Risk Myelodysplastic Syndrome Receiving Azacytidine[6]

H Kantarjian, F Giles, P Greenberg, R Paquette, E Wang, J Gabrilove, G Garcia-Manero, J Gray, K Hu, J Franklin

Clinically significant thrombocytopenia is a common complication in patients with MDS receiving hypomethylating agents.[7] An ongoing, multicenter, randomized, double-blind, placebo-controlled phase II trial is evaluating the effect of the recombinant Fc-peptide fusion protein romiplostim on the incidence of clinically significant thrombocytopenia in patients with low- or intermediate-risk MDS who are receiving azacitidine. Romiplostim stimulates production of platelets via a peptide fragment that shares no sequence homology with endogenous thrombopoietin, thereby preventing the production of neutralizing antibodies.[8] Forty patients received 4 cycles of azacitidine 75 mg/m^2/day for 7 days of a 28-day cycle plus placebo or subcutaneous romiplostim 500 mg or 700 mg per week on a randomized basis. The primary endpoint was clinically significant thrombocytopenic events (ie, platelet count <50/mL) after week 3 or receipt of platelet transfusions at any time during therapy. Secondary endpoints were platelet nadir and the need for platelet transfusions during azacitidine treatment.

Based on a planned interim analysis after all patients had completed treatment or withdrawn, the overall incidence of clinically significant thrombocytopenic events was 85%, 62%, and 71% for the placebo, romiplostim 500 mg, and 750 mg groups, respectively. The incidence of thrombocytopenic events per cycle was higher in the placebo group (50–85%) than in the romiplostim 500 mg (44–69%) and 750 mg (18–64%) groups. It was further observed that 69% of patients receiving placebo required platelet transfusions, in comparison to 46% and 36% for those receiving romiplostim 500 and 750 mg, respectively. Moreover, platelet counts on the first day of each azacitidine cycle and at the nadir of each 28-day cycle were lower in the placebo than in the romiplostim groups. The efficacy results indicate that among patients receiving azacitidine, romiplostim significantly reduces clinically significant thrombocytopenic events and platelet transfusions; it also improves platelet nadir levels.

In the safety analysis, all patients experienced at least 1 adverse event, with serious adverse events most common in the placebo group, at 77% versus 46% and 71% in the groups receiving romiplostim 500 and 750 mg, respectively. Two patients receiving romiplostim experienced more than 1 treatment-related serious adverse event (1 arthralgia, romiplostim 500 mg; 1 rash and hypersensitivity, romiplostim 750 mg). Two patients in the placebo group had grade 3 or higher bleeding events (1 pulmonary hemorrhage and 1 hemorrhage) versus a single case of epistaxis in the romiplostim 500 mg group and none in the higher-dose romiplostim group. Additionally, 2 deaths occurred among those receiving placebo due to fungal pneumonia and pulmonary hemorrhage, respectively. There were no deaths among patients receiving romiplostim; however, 1 patient receiving romiplostim 500 mg experienced leukemic transformation. The combination of romiplostim and azacitidine thus appears safe and effective.

226 Low Dose Decitabine Versus Best Supportive Care in Elderly Patients with Intermediate or High Risk MDS Not Eligible for Intensive Chemotherapy: Final Results of the Randomized Phase III Study (06011) of the EORTC Leukemia and German MDS Study Groups[9]

P Wijermans, S Suciu, L Baila, U Platzbecker, A Giagounidis, D Selleslag, B Labar, H Salih, F Beeldens, P Muus, T de Witte, M Lübbert

Final results were reported from a randomized phase III study initiated in 2002 to evaluate low-dose decitabine

versus best supportive care in patients over 60 years of age with intermediate- or high-risk MDS. A previously reported dose-optimization study showed that a dose-intense 20 mg/m^2 5-day schedule of intravenous low-dose decitabine was associated with a CR rate of 39% in patients with advanced MDS or CMML.[10] Nonetheless, not all patients are eligible for dose-intense therapy, and the standard of care for such patients remains to be defined. The present research administered decitabine intravenously at 15 mg/m^2 over 4 hours every 8 hours for 3 consecutive days of a 6-week cycle, for a maximum of 8 cycles. Results were evaluated every second cycle, and if CR was achieved, 2 more cycles ensued. Overall survival (OS) was the primary endpoint, with AML-free survival, progression-free survival (PFS), response rate, toxicity, and quality of life as secondary endpoints.

Overall, 233 patients (median age, 70 years) were recruited for the research (149 men). Most patients had IPSS intermediate-2– or high-risk disease (55% and 38%, respectively). Poor-risk cytogenetic features were found in 46% of patients, and 20% had received prior therapy (not intensive chemotherapy). After a median follow-up of 2.5 years, the median number of cycles administered was 4, with 40% receiving 2 or less. Response results are displayed in Table 1. The median time to response consisting of CR, PR, or HI was 0.32 years, with a duration of response of 0.72 years. Median OS was 0.84 versus 0.71 years for patients receiving decitabine versus supportive care, respectively (*P*=.38; 95% confidence interval [CI], 0.66–1.17). The median PFS was significantly better among patients receiving decitabine at 0.55 versus 0.25 years (*P*=.004; 95% CI, 0.52–0.88). Importantly, however, time to AML transformation or death was not significantly improved, with a median of 0.73 versus 0.51 years for decitabine versus supportive care (*P*=.24; 95% CI, 0.64–1.12).

Table 1. Efficacy Findings: Low-dose Decitabine Versus Best Supportive Care

	Decitabine, %	Best Supportive Care, %
Complete Response	13	0
Partial Response	6	0
Hematologic Improvement	15	2
Stable Disease	14	22
Progressive Disease	29	68
Hypoplasia	14	0
Inevaluable	8	8

Toxicity in the study consisted mainly of cytopenia-related events. Patients receiving decitabine experienced more grade 3/4 febrile neutropenia than those receiving supportive care (26% vs 7%); grade 3/4 infection was also greater among those receiving decitabine (59% vs 47%). Nonhematologic toxicities were mainly gastrointestinal and of low grade. During the study, 29 patients receiving decitabine died, compared to 25 receiving supportive care. The deaths were due to disease progression (7 vs 20), toxicity (9 vs 0), progression and/or toxicity (10 vs 1), or other causes (3 vs 4). Additionally, among survivors, 10% and 11% of patients received subsequent therapy consisting of stem cell transplantation or induction chemotherapy, respectively.

Wijermans and colleagues determined that the overall response to decitabine in this study was similar to that found in previous research, which resulted in a significant increase in PFS in comparison to supportive care alone. But the difference in death rates between the 2 arms of the study was considered nonsignificant. In addition, the researchers speculated that the difference in OS was low (hazard ratio [HR]=0.88) and not statistically significant due to treatment not lasting longer than 8 cycles and possibly due to subsequent treatments offered upon progression.

227 The Effects of Continued Azacitidine Treatment Cycles on Response in Higher-Risk Patients With Myelodysplastic Syndromes[11]

LR Silverman, P Fenaux, GJ Mufti, V Santini, E Hellström-Lindberg, N Gattermann, G Sanz, AF List, SD Gore, JF Seymour, J Backstrom, D McKenzie, CL Beach

Silverman and colleagues for the Cancer and Leukemia Group B (CALGB) initially demonstrated that the hypomethylating agent azacitidine is associated with significantly higher response rates, improved quality of life, reduced risk of leukemic transformation, and improved survival, compared with supportive care.[12] Fenaux and coworkers amplified these findings by demonstrating that azacitidine significantly extends OS for patients with higher-risk MDS.[13] Recently, however, the importance of CR to survival in MDS has been questioned by Cheson and coworkers for the International Working Group (IWG).[14] The results of the international, phase III multicenter trial of azacitidine[12] were reanalyzed in order to validate the recommendations of the IWG, and it was determined that azacitidine improves 1-year OS in comparison to conventional-care regimens.[15] Moreover, CR was found

not to be obligatory for the extension of OS in patients with higher-risk MDS; PR and HI were found to be predictors of prolonged survival as well. Therefore, Silverman and colleagues undertook an analysis of the results of the initial study[12] to determine the median number of treatment cycles with azacitidine that were associated with the achievement of first response (CR, PR, or major + minor HI); the researchers also measured the number of cycles from first response to best response.

In this analysis, patients with higher-risk disease were included (FAB criteria: RAEB, RAEB-T, or CMML; IPSS: intermediate-2– or high-risk). Of 179 patients treated with subcutaneous azacitidine 75 mg/m² for 7 days of a 28-day cycle, 91 (51%) achieved CR, PR, or HI; the median number of cycles to first response for these patients was 3 (range, 1–22). First response by 6 cycles was achieved by 81% of patients and 90% achieved first response by 9 cycles (the median number of cycles administered in the study; range, 1–39). First response was also best response for 52 responders (57%), whereas the remainder experienced an improvement in response at a median of 4 treatment cycles after first response (range, 1–11). These observations led the researchers to conclude that although many responders to azacitidine achieve a response early in their treatment, continued dosing can further improve response unless disease progression or unacceptable toxicity occurs.

228 Randomized Phase II Study of Combined Epigenetic Therapy: Decitabine vs. Decitabine and Valproic Acid in MDS and AML[16]

J-P Issa, R Castoro, F Ravandi-Kashani, S Faderl, X Huang, E Estey, G Borthakur, G Morris, G Garcia-Manero, HM Kantarjian

Early-stage research has suggested that histone deacetylase (HDAC) inhibition is a safe approach in the treatment of MDS and advanced leukemia.[17,18] HDAC inhibition has been shown in vitro to interact synergistically with DNA methylation inhibition in MDS, resulting robustly in anticancer effects such as apoptosis correlated with inhibition of nuclear factor κb.[19,20] In order to elucidate the best schedule of administration of inhibitors of DNA methylation and HDAC, as the latter can interfere with the former, a phase II study administered decitabine alone or decitabine plus the HDAC inhibitor valproic acid on an adaptive randomized basis to 74 patients with MDS or AML over 60 years of age. Decitabine was administered intravenously at a dose of 20 mg/m² for 1 hour, 5 days of a 4-week cycle, and valproic acid was

administered orally at 50 mg/kg for 7 days beginning at the first administration of decitabine. DNA methylation was measured by bisulfite pyrosequencing on peripheral blood prior to and during therapy. Of the total enrollment, 43 patients with MDS had a median age of 66 years (range, 38–89). Ten patients had intermediate-1–, 19 had intermediate-2–, and 14 had high-risk disease as measured by the IPSS; 40 (54%) patients overall had abnormal cytogenetics, mostly of poor-risk.

In this ongoing study, 42 patients received decitabine alone; the median number of cycles administered at time of presentation was 4 (range, 1–17), with 26% remaining on therapy at a median follow-up of 14 months. Of 67 patients who were evaluable for response, 46% with MDS experienced response. Among patients receiving decitabine alone, the overall response rate was 43%, as compared to 52% among those receiving the combination (P=NS). The median time to first response was 64 days (range, 18–194) among those receiving decitabine alone, as compared to 57 days (range, 23–123) among those receiving the combination (P=NS). It was observed that the addition of valproic acid significantly increased neurotoxicity, leading to discontinuations due to somnolence or confusion. The median survival among patients with MDS was 14.9 months (P=.04), but Kaplan-Meier analysis showed no difference in survival between the 2 arms in the first year of the study. Analysis showed similar degrees of demethylation in both study arms. The authors concluded that their preliminary results indicate that the addition of valproic acid to decitabine marginally improves time to first response and response rate but has no effect on survival in patients with MDS or AML. They suggested that more potent HDAC inhibitors may have greater clinical efficacy due to synergy with hypomethylating agents in future randomized studies.

633 Efficacy and Safety of Deferasirox during 1 Year of Treatment in Transfusion-dependent Patients with Myelodysplastic Syndromes: Results from EPIC Trial[21]

N Gattermann, M Schmid, M Della Porta, K Taylor, JF Seymour, D Habr, G Domokos, A Hmissi, A Guerci-Bresler, C Rose

Patients with MDS, particularly low-risk disease, who undergo repeated RBC transfusions are at risk of developing iron overload, a pernicious cumulative effect that can lead to tissue damage. Deferasirox is an iron-chelating agent that has previously been found safe and efficacious in patients receiving blood transfusions for nonmalignant

conditions.[22] Gattermann and colleagues undertook the 1-year, open-label, single-arm EPIC trial to investigate the safety and efficacy of deferasirox in patients with various anemic conditions, including MDS. The primary efficacy endpoint was change in serum ferritin level from baseline to 12 months, with safety monitoring for adverse events and laboratory parameters. Patients received an initial dose of deferasirox of 10–30 mg/kg/day. Transfusion-dependent patients were included if their serum ferritin was at least 1,000 ng/mL or if the level was lower than 1,000 ng/mL, but they had required more than 20 transfusions or 100 mL/kg of blood and had a liver iron concentration over 2 mg Fe/g dry weight as measured by magnetic resonance imaging. Serum ferritin levels were assessed monthly and protocol-specified dose adjustments in steps of 5–10 mg/kg/day (range, 0–40) occurred every 3 months based on serum ferritin trends and safety markers.

A total of 341 patients with MDS were enrolled (mean age, 67.9 years; range, 11–89) with a median baseline serum ferritin of 2,730 ng/mL (range 951–9,465). Their mean duration of transfusion was 3.6 years. Approximately half of the patients had not received any prior chelation therapy; 40% had previously received deferoxamine, 4.1% deferiprone, 7.0% combination deferoxamine/deferiprone, and 0.3% other therapy. Overall, the mean dose of deferasirox over 1 year of treatment was 19.2 mg/kg/day (±5.4). At the end of the study, a significant reduction in median serum ferritin from baseline was observed (last observation carried forward, -253.0 ng/mL; P=.0019). The patients' median serum ferritin values at baseline, 3, 6, 9, and 12 months were respectively 2,729.5 ng/mL (range, 951–9,465; n=336), 2,358.0 ng/mL(534–46,569; n=263), 2,209.5 ng/mL (357–10,066; n=230), 2,076.0 ng/mL (358–25,839; n=197) and 1,903.5 ng/mL (141–10,155; n=174). Overall, 48.7% of patients (n=166) discontinued therapy, 23% due to adverse events (n=78), 13% for drug-related adverse events (n=44), 10% for consent withdrawal (n=33), and 2% for unsatisfactory therapeutic effect (n=6), with 2 patients lost to follow-up. There were 26 deaths (8%; none treatment-related as per investigators' assessments) and 21 discontinuations for other reasons (6%). Drug-related adverse events consisted of diarrhea (32%), vomiting (8%), abdominal pain (8%), upper abdominal pain (7%), rash (7%), and constipation (6%); 25 patient discontinuations were the result of gastrointestinal-related adverse events. The researchers observed that most adverse events were mild to moderate in severity. A total of 19 patients' doses were decreased, and 10 were interrupted due to abnormal levels of creatinine. In conclusion, deferasirox significantly reduced levels of serum ferritin over 1 year in patients with transfusion-dependent MDS. The safety profile in this study was similar to that seen in other research with deferasirox. Discontinuations, it was noted,

were more prevalent in the MDS cohort of the EPIC study, and researchers are currently attempting to discern the causes of this observation.

Another iron-chelation study of deferasirox in patients with MDS was reported at the 2008 ASH annual meeting.[23] The ongoing US03 trial is intended to evaluate the long-term efficacy and safety of once-daily, orally administered deferasirox in patients with lower-risk transfusion-dependent MDS. A total of 93 of 176 enrolled patients (mean age, 70 years; range, 21–90) completed 12 months of the 3-year study at time of presentation. This study used a starting dose of 20 mg/kg/day, which could be increased to 40 mg/kg/day based on response and tolerability. Over the 12 months, patients received a mean dose of 21 mg/kg/day, and the mean transfusion rate was 3.4 units/month. From baseline to month 12, mean serum ferritin levels decreased from 3,397 to 2,501 ng/mL. Among patients whose baseline labile plasma iron level was elevated, sustained suppression of the level to the normal range was achieved after 3 months of therapy. Eight patients (5%) achieved HI by IWG criteria. A total of 18 patients (10%) discontinued because of suspected adverse events, and another 5 (3%) due to serious adverse events. Common adverse events were diarrhea, rash, and nausea; serious adverse events were rash and nausea. No new-onset cases of neutropenia or thrombocytopenia was suspected to be related to deferasirox. A total of 17 deaths occurred in the study, all of which were considered to be unrelated to deferasirox. These preliminary results indicate that deferasirox is well tolerated, but as this portion of the study generally replicates the 1-year EPIC study, further follow-up that evaluates long-term safety and efficacy is awaited.

635 Development and Validation of a New Prognostic Model for Myelodysplastic Syndrome That Accounts for Events Not Considered by the International Prognostic Scoring System[24]

HM Kantarjian, S O'Brien, F Ravandi, J Cortes, J Shan, JM Bennett, AF List, P Fenaux, G Garcia-Manero

The IPSS risk model, which has been widely adopted in clinical trials of novel and investigational therapies for MDS, provides survival projections for patients with de novo MDS that is managed with supportive measures alone; it was developed prior to the introduction of novel therapies such as hypomethylating and immunomodulatory agents. Kantarjian and colleagues noted that for patients receiving investigational treatment, a more robust

Table 2. New Prognostic Model for MDS: Survival Data

		Findings					
		Study Group	Test Group				
Risk	Score	N	Median survival, months	3-year survival, %	N	Median survival, months	3-year survival, %
Low	0–4	157	54	63	159	45	58
Intermediate-1	5–6	229	25	34	228	23	35
Intermediate-2	7–8	233	14	16	244	13	15
High	³9	341	6	4	326	6	3

prognostic stratification model, one which accounts for subsets not included in the IPSS, refines prognostic subsets, and applies at any time during course of MDS, is needed. Specifically, this model would be suited for application at intervals after diagnosis, adjusting for the effect of prior therapy, secondary forms of disease, proliferative CMML, and adverse cytogenetic subsets.

The researchers analyzed 1,915 patients with MDS including CMML, secondary MDS, and MDS with prior therapy. Of these, 507 patients (26%) had primary MDS without prior therapy, meaning that they could be categorized under the IPSS. The patients were assigned on a randomized basis to either a study group (n=958) or a test group (n=957). Multivariate analysis of prognostic factors in the study group identified adverse independent factors as continuous and categorical values (*P*<.001), which were assigned weighted points based on coefficient (score point=coefficient, 0.15): performance status, age, platelet count, hemoglobin level, marrow blast (%), white blood cell count, karyotype, and prior transfusion status. Cutoffs for anemia, thrombocytopenia and blasts, and cytogenetic subsets were different from the cutoffs defined in the IPSS. The new MDS prognostic model divided patients into 4 prognostic groups with significantly different outcomes (Table 2). The new model was found to be highly prognostic within the 4 IPSS risk groups, overall, and in primary MDS without prior therapy. The new model accounts for duration of MDS and prior therapy, and it is applicable to any patient with MDS at any time during the course of disease.

The new risk model was also tested in a 3-arm trial of decitabine (n=124) in which patients were divided by this model into low- (4%), intermediate-1– (17%), intermediate-2– (30%), and high-risk disease (43%). The respective median survivals were not reached (100% at 3 years), 42, 19, and 13 months, respectively, indicating the applicability of the model in another group

of patients. Survival rates better than expected were observed among the newly categorized patients, possibly due to a therapy effect. To verify the findings, a cumulative score for the 124 patients was calculated and an average score deducted; the associated predicted historical median survival was 13 months overall, 30 months for low- or intermediate-1–risk, and 10 months for intermediate-2– or high-risk, versus median survival of 20 months overall, 44 months for low- or intermediate-1–risk, and 15 months for intermediate-2– or high-risk among the newly defined categories. In the independent test, the new prognostic model was shown to be superior to the IPSS, and it was further shown to demonstrate improved survival with decitabine compared with historical survival. Further validation, however, is required for this model in independent MDS populations.

876 Patterns of Treatment Among Patients With Recently Diagnosed Myelodysplastic Syndromes in a National Registry, 2006–2008[25]

CM Van Bennekom, G Abel, T Anderson, RM Stone, DW Kaufman

Researchers at Boston University have compiled a national disease-based registry for which any patient with MDS (diagnosed in the previous 4 months) is eligible. Patients can enroll themselves based on recommendations from their physicians or online self-education. The registry collects information on treatment, clinical events, and quality of life via a questionnaire and review of medical records at baseline and at 6-month intervals. Van Bennekom and colleagues reported on 290 patients from 44 states enrolled from June 2006 to June 2008 with the goal of characterizing the importance of disease-modify-

ing treatments that have been recently introduced for the therapy of recently diagnosed MDS. Of these patients, 71 (24%) had received disease-modifying treatment since diagnosis: azacitidine (9%), decitabine (7%), lenalidomide (6%), and multiple agents (2%). In comparison, 167 (58%) reported receiving supportive care, sometimes of multiple types, including erythropoiesis-stimulating agents (43%), myeloid growth factors (12%), iron-chelating therapy (1%), and antibiotics (16%). Patients who received disease-modifying treatment were likely to receive supportive care as well. The prevalence of disease-modifying treatment administration increased as patients' risk increased, with 9% and 60% of low- and high-risk patients, respectively, receiving this type of therapy (by IPSS). Two of 12 patients receiving azacitidine and 5 of 10 receiving decitabine were classified as having intermediate-1–risk disease. A total of 16 patients had del(5q) disease; of these, 5 received lenalidomide. Seven patients without this chromosomal feature also received lenalidomide; 7 of the 12 lenalidomide-receiving patients had intermediate-2–risk disease.

A significant factor affecting the type of therapy given was prescription-drug coverage, with 11% of the uninsured versus 25% of those with coverage receiving disease-modifying treatment. It was noted that patients in New England had the lowest prevalence of disease-modifying treatment (6%). These registry data suggested that despite the availability of disease-modifying treatment for patients with MDS, the majority of newly diagnosed patients receive only supportive care. Additionally, supportive care is likely to be administered in conjunction with disease-modifying treatment and likely to ameliorate the hematologic side effects associated with this therapy. Moreover, it was observed that approximately one-third of patients who received a DNA hypomethylating agent were classified as having intermediate-1–risk disease, and many who received lenalidomide did not have del(5q) disease or had intermediate-2–risk disease, thus falling outside the drug's US Food and Drug Administration (FDA) approved indications.

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Commentary

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Although there are now 3 drugs specifically approved by the FDA for patients with MDS—azacitidine, decitabine, and lenalidomide—we are still learning the best ways to use these medications, and new therapies are urgently needed. MDS-related clinical trial data presented at the 2008 Annual Meeting of the American Society of Hematology (ASH) focused primarily on the 3 approved therapies, either as single agents or in combination, and there were relatively few studies of novel drugs. The paucity of new agents in development for MDS compared to other neoplasms highlights the need for a better understanding of the pathobiology of MDS so that targeted treatments can be developed, just as the discovery of JAK2 mutations in myeloproliferative neoplasms spawned a new class of experimental therapeutics.[1] Even with respect to the existing therapies for MDS, review of practice records indicates that many patients do not receive them—even higher-risk patients who would potentially be eligible.[2] Whether this is because of concerns about adverse events, skepticism about published trial results or clinical inertia, or barriers to access to care, is unclear. However, the practice patterns are alarming.

In my opinion, the most clinically significant MDS-related news at the 2007 ASH Annual Meeting was the result of the AZA-001 survival study, which demonstrated that in higher-risk patients with MDS, azacitidine conferred a median 9-month survival advantage compared to conventional care (most patients in the control group were treated solely with "supportive care"—hematopoietic growth factors and transfusions).[3] Because azacitidine and decitabine represent chemically similar aza-substituted nucleoside analogs that may work by identical epigenetic mechanisms,[4] a key question prompted by the AZA-001 results was whether similar survival benefit would accrue to patients treated with decitabine. At the 2008 ASH Annual Meeting, Dr. Pierre Wijermans presented data on behalf of the European Organization for the Research and Treatment of Cancer (EORTC) from a 233-patient study that enrolled patients with higher-risk MDS.[5] In contrast to the AZA-001 results, progression-free survival improved by only up to 3 months with decitabine, and there was no overall survival advantage compared to supportive care in the EORTC study. Overall survival for all patients was quite short (just 9 months), suggesting that the enrolled patients were a particularly high-risk group. It is unclear whether the EORTC results indicate that decitabine is inferior to azacitidine, or whether instead the study's methodology was suboptimal given what we now know about this class of drugs.

In the EORTC survival study, which began in 2002, patients received a median of 4 cycles of decitabine therapy. Responding patients had to stop treatment after 8 cycles; 40% of patients assigned to decitabine received 2 cycles of therapy or less. Decitabine was administered over 3 days as an inpatient therapy, whereas currently the most common way to administer decitabine in the United States is over 5 days as an outpatient therapy. Although the 3-day and 5-day regimens have not been directly compared, some investigators believe the 5-day regimen is superior because of higher reported response rates.[6-8] (It is certainly more convenient.) If decitabine and azacitidine truly work via epigenetic mechanisms as hypothesized, prolonged treatment with lower doses should be more effective than several quick pulses and no further therapy as done in the EORTC study. An analysis of the AZA-001 study presented by Dr. Lewis Silverman at the 2008 ASH meeting emphasized again the need for continued treatment with azacitidine for patients to achieve maximum benefit with the hypomethylating agents.[9] In the AZA-001 study, in which patients received a median of 9 cycles of azacitidine treatment, 48% of patients who initially responded to drug therapy achieved a better response if the drug was continued, and the maximal response was not achieved until a median of 4 cycles after the initial response.

It is clear that we do not yet know the best schedule, or even the optimal dosing, for azacitidine or decitabine. Regardless, the EORTC survival data are important to discuss with patients with MDS when deciding which hypomethylating agent to use. In my opinion, the 7-day subcutaneous azacitidine regimen used in the AZA-001 study must be considered the standard of care for higher-risk patients with MDS.

With existing treatments, no matter how they are given, there is still a large proportion of patients who do not respond to treatment or achieve only a mediocre response of uncertain clinical relevance. In addition, all 3 of the approved therapies are difficult for many patients with MDS to tolerate, primarily due to cytopenias. Several studies presented at the 2008 ASH meeting focused on combination therapy using hypomethylating agents as a backbone in an attempt to improve response rates and the quality of responses, and to ameliorate treatment-related adverse effects.

The 5-site Bone Marrow Failure Disease Consortium (BMFDC), led by Drs. Mikkael Sekeres and Jaroslaw Maciejewski at Cleveland Clinic, reported final results from a phase I trial of a lenalidomide-azacitidine combination.[10] Although these agents appear to lack in vitro synergy and share at least 1 common adverse event (cytopenias), they are believed to have distinct and nonoverlapping mechanisms of action. An encouraging 41% overall complete response rate was observed in the BMFDC, with few serious adverse events. A phase II study will follow, and we will see if further experience confirms these promising preliminary findings.

Dr. Jean-Pierre Issa and his colleagues at the M.D. Anderson Cancer Center (MDACC) added valproic acid, a weak histone deacetylase (HDAC) inhibitor, to decitabine, but did not see any additional benefit over treatment with decitabine alone, and neurotoxicity was problematic.[11] In vitro, HDAC inhibitors are synergistic with hypomethylating agents with respect to effects on transcriptional activity, so this approach is still of great interest in MDS, despite the failure of the valproic acid-decitabine combination.[12] It remains to be seen whether valproic acid was simply too weak of a HDAC inhibitor to be useful, or whether HDAC inhibitors as a class do not offer clinical benefit above and beyond that seen with hypomethylating agents alone, despite the in vitro data. Ongoing trials such as the Eastern Co-operative Oncology Group (ECOG) E1905 study, where patients are being randomized to treatment with a 10-day azacitidine regimen either with or without SNDX-275 (entinostat, formerly MS275, a potent HDAC inhibitor), should go a long way towards answering these questions.

Thrombocytopenia, including that developing in association with treatment with hypomethylating agents or lenalidomide, has been a serious problem for MDS patients in the past, particularly because, until recently, there has been no practical platelet growth factor.[13] This may be changing, however, as there are now data suggesting that the use of romiplostim, a novel thrombopoietic "peptibody" that is a thrombopoietin receptor agonist, improves the platelet nadir and diminishes the need for platelet transfusion that is associated with azacitidine therapy. In a single-agent study of weekly subcutaneous romiplostim in patients with MDS presented by Hagop Kantarjian and colleagues at the 2007 ASH Annual meeting, romiplostim raised the platelet count, but was associated with an increase in marrow, blood blasts, and possible marrow fibrosis in some patients.[14] In contrast, an azacitidine and romiplostim combination discussed by Kantarjian at ASH 2008 was still efficacious in terms of ameliorating thrombocytopenia, but was not associated with serious safety concerns.[15] Unfortunately, the use of romiplostim in routine clinical practice is limited by the restrictive prescribing protocol that was mandated by the FDA when the drug was approved in August 2008 for patients with immune thrombocytopenia (ITP) who had failed other therapies. Patients with MDS and severe thrombocytopenia have few other options, but despite data suggesting romiplostim is effective in this setting, the limited approval and cumbersome distribution system make it difficult for patients to obtain it.

One newer agent that has entered clinical trials in MDS is clofarabine, a purine nucleoside analog that is currently FDA-approved for relapsed pediatric acute lymphoblastic leukemia. In small pilot studies, clofarabine has demonstrated cytoreductive activity in both AML and high-risk MDS.[16,17] Data from 61 high-risk MDS patients enrolled in an ongoing clofarabine study at MDACC were presented at the 2008 ASH meeting, with some complete responses observed.[18] However, whether clofarabine is given intravenously or orally, current schedules are too myelosuppressive and associated with a relatively high infection rate. In the MDACC trial, 6 patients died from infection, and the dose of oral clofarabine had to be reduced from the initial 40 mg/m^2 x 5 days to 30 mg/m^2 x 5 days because of extensive myelosuppression. Alternative doses and schedules are currently being explored with clofarabine, and hopefully a more tolerable regimen can be developed.

Deciding on the most appropriate treatment for individual patients with MDS requires accurate assessment of prognosis. Although the 1997 International Prognostic Scoring System (IPSS) is useful for determining clinical trial eligibility and as a general guide to prognosis, a number of investigators have criticized various aspects of the IPSS.[19] Kantarjian and colleagues at MDACC developed a new prognostic scoring system that, although slightly more complicated than the IPSS, overcomes some of the limitations of the older scoring system.[20] These IPSS limitations include the lack of sensitivity to severity of cytopenias,[21,22] overemphasis on blast proportion compared to high risk cytogenetics,[23] and the lack of validation in patients with secondary MDS or previously treated patients. Hopefully the MDACC prognostic system and other similar systems (eg, the World Health Organization-based Prognostic Scoring System [WPSS])[24] will spur a reassessment of the IPSS and a much-needed update.

Although patients with MDS now have several options for therapy, these treatments remain inadequate, and much work has yet to be done. Hopefully at future ASH meetings, we will see not only modifications of ways to administer the existing drugs (although such studies are important, because there are still many clinically relevant questions about existing drugs for which there are no data to guide practice), but also further development of novel mechanistically-based therapies.

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Recent Advances in the Treatment of Myelodysplastic Syndromes

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following MDS subgroups did the WHO classification system eliminate from the FAB classification system in 1997?

   a. RA
   b. RARS
   c. RAEB
   d. RAEB-T
   e. CMML

2. In the phase I study of the combination of lenalidomide and azacitidine reported by Sekeres et al, how many CRs were observed and what was the overall response rate?

   a. 7 and 71%
   b. 1 and 71%
   c. 7 and 21%
   d. 1 and 21%
   e. none of the above

3. Clofarabine is what type of agent?

   a. immunomodulatory
   b. first-generation nucleoside analog
   c. second-generation nucleoside analog
   d. histone deacetylase inhibitor
   e. hypomethylating

4. In the study of the effect of romiplostim on thrombocytopenic events in patients receiving the hypomethylating agent azacitidine, reported by Kantarjian et al, what was the lowest overall incidence of thrombocytopenic events and with what dose was it associated?

   a. 85% and 500 mg
   b. 71% and 700 mg
   c. 46% and 500 mg
   d. 69% and 700 mg
   e. 62% and 500 mg

5. Wijermans et al reported how many deaths due to disease progression among patients receiving decitabine versus best supportive care in their phase III study?

   a. 7 vs 20
   b. 9 vs 0
   c. 10 vs 1
   d. 3 vs 4
   e. 10 vs 11

6. Silverman et al determined that among responders to azacitidine with MDS, continued dosing can have what effect?

   a. delay progression
   b. increase toxicity
   c. improve response
   d. decrease response
   e. none of the above

7. What is a potential synergistic effect of the combination of decitabine and valproic acid?

   a. apoptosis correlated with inhibition of C-reactive protein
   b. apoptosis correlated with inhibition of nuclear factor κb
   c. apoptosis correlated with inhibition of DNA methyltransferase
   d. apoptosis correlated with inhibition of tumor necrosis factor
   e. all of the above

8. After 1 year, deferasirox was associated with what effect in patients with transfusion-dependent MDS in the trial reported by Gattermann et al?

   a. serum ferritin levels increased
   b. serum ferritin levels remained unchanged
   c. serum ferritin levels decreased
   d. disease progression

9. The new prognostic model for MDS developed by Kantarjian et al adjusts for what?

   a. the effect of prior therapy
   b. secondary forms of disease
   c. proliferative CMML
   d. adverse cytogenetic subsets
   e. all of the above

10. What was a major finding of the national registry for patients with recently diagnosed MDS reported by Van Bennekom et al?

    a. the majority of newly diagnosed patients receive only supportive care
    b. the majority of newly diagnosed patients receive only hypomethylating agents
    c. the majority of newly diagnosed patients receive only immunomodulatory agents
    d. the majority of newly diagnosed patients receive only histone deacetylase inhibitors
    e. none of the above

Evaluation Form Recent Advances in the Treatment of Myelodysplastic Syndromes

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)

1. Extent to Which Program Activities Met the Identified Objectives
After completing this activity, I am now better able to:

- Cite newly presented study findings related to treatment of MDS.   1 2 3 4 5
- Specify new study findings evaluating new treatment options in MDS according to applicability to practice.   1 2 3 4 5
- Explain how to integrate into clinical practice the latest knowledge and methods for treating patients with MDS.   1 2 3 4 5
- Identify future research directions for agents in the treatment of MDS.   1 2 3 4 5

2. 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

3. 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: _____

4. 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.

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Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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☐ I participated in the entire activity and claim 1.0 credits.   ☐ I participated in only part of the activity and claim _____ credits.