



Treatment of MDS: something old, something new, something borrowed...

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As opposed to the treatment landscape for myelodysplastic syndromes (MDS) two decades ago, potential therapies now abound for the treatment of lower-risk and higher-risk populations. In lower-risk patients, decision tools can be used to determine the likelihood of response to erythropoiesis stimulating agents (ESAs), which have demonstrated survival advantages in retrospective studies in patients with MDS, and whether these patients should be treated initially with ESAs or non-growth factor (“active”) therapies. Lenalidomide has shown good activity in transfusion-dependent patients with the del(5q) cytogenetic abnormality and modest activity in other lower-risk patients. In higher-risk patients, the DNA methyltransferase inhibitors produce complete and partial responses in 20% to 30% of patients, and for the first time, the MDS drug azacitidine has demonstrated a survival advantage when compared with conventional therapies. Newer therapies stimulate platelet production and target novel pathways, while a panoply of combination studies are underway or recently completed and that likely represent the next frontier in MDS therapy.

Fifteen years ago, there was a paucity of possible therapies for the treatment of the myelodysplastic syndromes (MDS), it was considered not only acceptable, but even standard to treat patients with what has loosely been called, “supportive care”: blood product transfusions and antibiotics to control infections. Now, at the time of publication, three drugs—azacitidine, lenalidomide, and decitabine¹⁻³—are approved by the U.S. Food and Drug Administration (FDA) specifically for MDS-related indications, along with at least five hematopoietic growth factors that can potentially be used for patients with MDS: epoetin, darbepoetin, filgrastim, sargramostim, and pegfilgrastim. While the thrombopoietin agonists romiplostim and eltrombopag have activity in MDS,^{4,5} their use is currently restricted to patients with immune thrombocytopenia. Other active therapies used off-label for treating MDS include cytotoxic agents (such as cytarabine and clofarabine) and those with immune-modulating mechanisms of action (such as thalidomide and anti-thymocyte globulin). In a survey of physicians across the United States conducted from 2005 through 2007 and yielding over 4500 responses, the overwhelming majority of patients were receiving some type of therapy. Among established MDS patients, therapy included erythropoiesis-stimulating agents (ESAs) in up to 63%; azacitidine in up to 15%; decitabine in up to 4%; and lenalidomide in up to 9% of patients.⁶ The therapeutic landscape has changed so dramatically, it is now considered unethical to randomize

certain MDS subtypes (such as those with higher-risk disease or transfusion-dependent patients with a deletion 5q abnormality) to studies containing supportive care only control arms in the United States, and it has become a challenge to design clinical trials or write drug labels for an untreated population. This paper reviews the available MDS therapies, placing them in context of appropriate MDS subtypes, and new drugs and combinations of drugs on the horizon.

Some Things Old

The treatment of MDS is often divided into those drugs that are more appropriate for lower-risk disease and those yielding more robust responses in higher-risk MDS. Patients included in the therapeutic category of lower-risk MDS have < 5% blasts using the French-American-British (FAB) and World Health Organization (WHO) systems, or an IPSS score of ≤ 1.0 .⁷⁻⁹ Those with higher-risk disease have $\geq 5\%$ blasts or an IPSS score of ≥ 1.5 (**Table 1**). Therapies directed at sustaining residual functioning bone marrow cells, at immunomodulation (eg, through abrogation of the effects of pro-inflammatory, pro-apoptotic cytokines), or that affect the bone marrow microenvironment (eg, via vascular endothelial growth factor) are generally applied to patients with lower-risk MDS, for whom treatment goals center on minimizing transfusions, restoring effective blood cell production, and maximizing quality of life.¹⁰ Cytotoxic therapies, or drugs that abrogate the gene-silencing effects

Table 1. Classification of lower- and higher-risk MDS patients.

Lower-risk MDS Survival of 3-10 years Low rate of AML transformation	Higher-risk MDS Survival <1.5 years High rate of AML transformation
RA, RARS	RAEB (-1, -2)
RCUD, RCMD	IPSS Int-2, High (Score \geq 1.5)
MDS-U, MDS del(5q)	
IPSS Low, Int-1 (Score 0-1.0)	

MDS indicates myelodysplastic syndromes; AML, acute myeloid leukemia; RA, refractory anemia; RARS, RA with ring sideroblasts; RCUD, refractory cytopenia with unilineage dysplasia; RCMD, refractory cytopenia with multilineage dysplasia; MDS-U, MDS unclassifiable; IPSS, International Prognostic Scoring System; RAEB, RA with excess blasts

of hypermethylation, on the other hand, are used in patients with higher-risk MDS, where treatment goals are similar to those applied to patients with AML: attaining a partial or complete remission, prolonging survival, and also maximizing quality of life.^{10,11} It is another question entirely whether we should be applying the same survival goals to patients with lower-risk disease.

Once a patient with MDS develops cytopenias and/or blood product transfusion dependency, treatment with growth factors may be initiated. These include ESAs (approved by the FDA for the treatment of chemotherapy-induced anemia in 1993, and which include epoetin and now darbepoetin) and colony-stimulating factors (filgrastim, sargramostim, and pegfilgrastim), either alone or in combination, though few data exist to support an advantage to combination therapy. A number of trials have been published on using

ESAs alone, at varying schedules and doses, or in combination with granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), in patients with MDS, with responses of approximately 40% in lower-risk patients using International Working Group (IWG) criteria for response.¹²⁻¹⁶ Attention has been drawn recently to the use of ESAs in patients with solid tumors, with an adverse outcome shown for treated patients in at least eight trials. For this reason, it is recommended that, in those patients responding to growth factors, hemoglobin levels be maintained no higher than 11 to 12 g/dL.

Given the deleterious effect of ESAs on progression-free and overall survival (OS) in the solid tumor literature, should they be avoided in MDS patients? To the contrary, three retrospective studies suggest a survival advantage for ESAs, possibly through their effect on minimizing transfusion needs in patients, along with their salutary effect on iron overload (**Table 2**). The first study compared 121 Nordic patients with MDS treated with ESAs to a disease- and time-matched cohort of 237 patients in Pavia, Italy, who received no therapy.¹⁷ Those receiving ESA-based therapy had a significant survival advantage (HR = .61, 95% CI: .44-.83, $P = .002$). The second study, from the Groupe Francophone des Myelodysplasies, compared 200 ESA-treated patients in a matched-pair analysis with 200 patients from the ESA-untreated subset of subjects used to define the IPSS, and again demonstrated improved OS in the ESA cohort (HR = .43, 95% CI: .25-.72),¹⁸ despite no difference in rates of acute myeloid leukemia (AML) transformation. The third study, from the Cleveland group, examined 162 trials published over a 20-year period that enrolled lower-risk MDS patients and compared 1587 patients treated with ESA-based therapy with 1005 patients

Table 2. Retrospective studies supporting the use of erythropoiesis stimulating agents (ESAs) in MDS patients.

Study group	Study design	N	Results	Comments
Nordic ¹⁷	Matched cohort of ESA-treated Nordic patients to untreated Pavia patients	121 Nordic 237 Pavia, Italy	Survival advantage for ESA-treated group (HR = .61, $P = .002$)	Nordic patients were treated with combination ESAs and CSFs. Survival improvement mainly in patients with low transfusion needs.
GFM ¹⁸	Matched cohort of ESA-treated GFM patients with untreated IMRAW patients	403 GFM	Survival advantage for ESA-treated group (HR = .43, 95% CI: .25-.72)	GFM patients were treated with epogen or darbepoietin
Cleveland ¹²	Systematic review of 162 trials published from 1985-2005 comparing ESA-treated patients with non-GF-treated patients	1587 ESA 1005 Non-GF	Survival advantage for ESA-treated group at 2 years follow-up (79% vs. 68%, $P = .005$)	Included only lower-risk MDS patients and used IWG response criteria. Differences remained significant in multivariate analyses controlling for baseline characteristic differences.

MDS indicates myelodysplastic syndromes; ESA, erythropoiesis stimulating agent; HR, hazard ratio; CSF, colony stimulating factor; GFM, Groupe Francophone Myelodysplasies; GF, growth factor; IWG, International Working Group.

treated with non-growth factor approaches.¹⁹ Patients who received ESA-based therapy had significantly better survival at up to 2 years of follow-up, compared with the non-growth factor group. All three studies attempted to control for selection biases by using inclusion criteria or multivariate analyses that adjusted for differences between patient groups in baseline characteristics.

Which patients are most likely to benefit from ESAs? Two decision tools assist in defining appropriate MDS populations. The first, developed by Hellström-Lindberg and colleagues,^{20,21} included 94 patients across three ESA studies to determine predictors of response to a combination of ESAs and G-CSF. Patients with low transfusion needs (< 2 units packed red blood cell transfusions [pRBC] monthly) and a low baseline serum erythropoietin level (less than 500 IU—the “good” ESA predictive group) had a 74% chance of responding to ESAs, while those with high transfusion needs (≥ 2 units pRBC per month) and a high serum erythropoietin level (> 500 IU—the “poor” ESA predictive group) had only a 7% chance of responding. Patients who had a mixed picture (low transfusion needs and high erythropoietin level, or high transfusion needs and low erythropoietin level—the “intermediate” ESA predictive group) had a 23% chance of responding to ESAs.

A second decision tool incorporated individual patient data, including response rates, OS, and quality of life, on 799 patients treated with either ESAs (394 patients) or non-growth factor (405 patients) approaches from 90 articles published over a 20-year period and applied these data to the Hellström-Lindberg model to determine the most appropriate up-front therapy for patients with low-risk MDS.²² This treatment algorithm suggests that lower-risk patients with MDS falling into a good ESA predictive group should initially be treated with ESAs, while other low-risk patients with MDS (those falling into intermediate or poor ESA predictive groups) should probably be treated initially with other, non-growth factor therapies.

Some Things New

What to do with the lower-risk MDS patient with thrombocytopenia necessitating platelet transfusions or resulting in bleeding episodes, or with the patient who has failed ESAs or who falls into the Hellström-Lindberg intermediate or poor ESA predictive groups?

A phase I/II study of romiplostim in lower-risk patients with MDS, a peptibody that increases platelet production through the thrombopoietin (TPO) receptor (c-Mpl), has been completed recently.⁴ Of 44 patients enrolled into one of 4 dose cohorts to receive weekly injections of 300, 700, 1000, or 1500 µg romiplostim, 41 continued into the

extension phase of the study with continued weekly injections. Although no dose-limiting toxicity level was reached, treatment-related serious adverse events were reported in 5 patients (11%), all of whom were in the 1500 µg dose cohort. Two patients progressed to AML during the study, and 4 others had transient increases in blast percentage. Contrary to findings with previous TPO agonists, no neutralizing antibodies to either romiplostim or endogenous thrombopoietin were seen. Median platelet counts improved throughout the study, and a durable platelet response was achieved by 19 patients (46%). The go-forward dose was established as 700 µg weekly, and a phase II study has been initiated, along with combination studies with azacitidine and lenalidomide. Eltrombopag, another thrombopoietic growth factor, is being studied in higher-risk patients with MDS.

For the patient who has failed ESAs or is unlikely to respond to ESAs, or for the pRBC transfusion-dependent patient with MDS with the del(5q) cytogenetic abnormality, FDA-approved options are limited. Probably the best approach is lenalidomide (**Table 3**).

Lenalidomide is a 4-amino-glutarimide analog of the older immunomodulatory drug thalidomide. Its purported mechanism of action involves modulation of cellular response to receptor/ligand activation signals, via suppression of pro-inflammatory, pro-apoptotic cytokine generation; preventing angiogenesis; altering cell adhesion to bone marrow stroma; and direct cytotoxicity of dysplastic clones.²³⁻²⁶ By using RNA interference screening, preliminary work has identified haploinsufficiency of the ribosomal protein encoding the RSP14 gene as being necessary for the characteristic 5q- syndrome phenotype.²⁷ Another group has shown that cell cycle regulatory phosphatases Cdc25C and PP2A determine the sensitivity of del(5q) MDS cells to lenalidomide.²⁸

The phase II registration study focused on patients with lower-risk, transfusion-dependent MDS with the del(5q) abnormality.³ Lenalidomide was administered at a dose of 10 mg/day for a 28-day cycle or 10 mg/day for 21 days of a 28-day cycle. Among 148 patients enrolled, and using IWG criteria for response,¹¹ 99 (67%) achieved transfusion independence, including every patient who experienced a cytogenetic response. The complete cytogenetic responses rate was 45%, indicating at least temporary eradication of the malignant clone. The median duration of RBC transfusion-independence, when these patients were combined with del(5q) patients treated in other MDS studies (N = 168), was 2.2 years (range, 0.1-4.4 years), and approximately one third of transfusion-independent responders remained transfusion independent after 3 years of therapy.

Table 3. Seminal trials in drugs approved for use in MDS by the United States Food and Drug Administration (FDA).

MDS drug	Study design	N	Results	Comments
Lenalidomide ³	MDS-003: Phase II	148 transfusion-dependent, lower-risk, del(5q)	Transfusion independence in 67%; cytogenetic CR in 45%; median response duration >2 years	US Registration study. Treatment-related cytopenias shown to correlate with response; cytogenetic CRs in some patients with complex karyo types.
Lenalidomide ³¹	MDS-002: Phase II	215 transfusion-dependent, lower-risk, non-del(5q)	Transfusion independence in 26%; median response duration 41 weeks Non-FDA approved indication; treatment-related cytopenias have no correlation with response.	
Azacitidine (AZA) ¹	CALGB 9221: Phase III	99 randomized to AZA 92 randomized to BSC All MDS subtypes	CR+PR rate 16% for AZA using IWG criteria; Time to AML progression or death longer for AZA (21 vs 12 months, $P = .007$)	US Registration Study. No significant OS advantage for AZA likely due to crossover allowed for BSC group and mixed MDS population.
Azacitidine (AZA) ³³	AZA-001: Phase III	179 randomized to AZA 179 randomized to conventional care (CC: 105 to BSC; 49 to LDARaC; 25 to IC) Higher-risk MDS	CR+PR rate 29% for AZA vs 21% for CC; median OS 24 months for AZA vs 15 months for CC (HR = .58, $P = .0001$)	EU Registration Study. 34% of patients had AML; results driven by comparison to BSC arm; responses seen particularly in patients with chromosome 7 abnormalities.
Decitabine (DAC) ²	Phase III	89 randomized to DAC 81 randomized to BSC All MDS subtypes	CR+PR rate 17% for DAC; Time to AML progression or death longer for DAC only in higher-risk group (11 vs 6 months, $P = .028$)	US Registration Study. Did not meet primary endpoint due to low median # cycles given and mixed MDS population.
Decitabine (DAC) ³⁶	EORTC 06011: Phase III	119 randomized to DAC 114 randomized to BSC Higher-risk MDS	CR+PR rate 23% for DAC; median OS 10.1 months for DAC vs 8.5 months for BSC (HR = .88, $P = .38$)	No significant OS advantage for DAC likely due to fewer median cycles given (4).

MDS indicates myelodysplastic syndromes; US, United States; EU, European Union; HR, hazard ratio; CR, complete response; BSC, best supportive care; PR, partial response; OS, overall survival; IWG, International Working Group; AML, acute myeloid leukemia; LDARaC, low-dose cytarabine; IC, intensive chemotherapy.

The remainder of patients ultimately relapsed, with recurrent anemia and/or transfusion dependence, coinciding with re-emergence of the del(5q) clone.²⁹

The bugaboo of successful lenalidomide therapy in the del(5q) population is grade 3-4 myelosuppression, which occurred in approximately half the patients, necessitating dose-reduction in 84%. Subsequent analyses of these data have identified features predictive for transfusion-independence response to lenalidomide, including younger age, shorter duration of MDS, lower transfusion needs, and treatment-related thrombocytopenia. Patients whose platelets declined by 50% or more within the initial 8 weeks of treatment, and for those with no baseline neutropenia, whose neutrophils declined by 75% or more, were significantly more likely to achieve pRBC transfusion independence, compared with patients experiencing less severe myelosuppression, both in univariate and (for platelet decline) in multivariate analyses.³⁰ Treatment-related thrombocytopenia also correlated with cytogenetic

responses, emphasizing the importance of successful suppression of the del(5q) clone with lenalidomide to achieve meaningful responses.

Lenalidomide is often used off-label for the treatment of lower-risk, transfusion-dependent MDS patients who do not harbor the del(5q) lesion, based on a similarly designed phase II study.³¹ A total of 215 patients were enrolled. Among study participants, 56 patients (26%) achieved transfusion independence, similar to the 29% response rate among non-growth factor therapies administered to lower-risk patients with MDS over a 20-year period. Duration of response was less than for del(5q) patients, at a median of 41 weeks (range, 8-136 weeks). Significant myelosuppression (grade 3 or 4 neutropenia or thrombocytopenia) occurred in only 20% to 25% of patients, and development of cytopenias was not associated with subsequent attainment of a transfusion-independence response to therapy. This, coupled with the findings from the del(5q) study and the importance of cytopenias, bolsters

the argument that for del(5q) patients, lenalidomide appears to have a direct, cytotoxic effect on the dysplastic clone; whereas for lower-risk patients with MDS without the del(5q) abnormality, lenalidomide's clinical benefits appear to be mediated through its effects on the bone marrow microenvironment.

Some Things Borrowed

For patients with higher-risk MDS, the pathobiology and clinical spectrum for which resembles AML, investigators have turned to therapies that have had at least a modicum of success in the AML population.

The most successful of these have been the DNA methyltransferase inhibitors and nucleoside analogues, 5-azacytidine (azacitidine) and 5-aza-2'-deoxycytidine (decitabine) (**Table 3**). Azacitidine was synthesized in 1963 and demonstrated activity in four AML trials in the 1970s, resulting in CRs in 17% to 36% of patients. The registration study that resulted in FDA approval for azacitidine for all MDS subtypes was a phase III trial in which all subtypes of MDS patients were randomized to receive the azacitidine or to supportive care,¹ with patients in the supportive care arm being allowed to cross over to the treatment arm with disease progression. Ninety-nine patients were randomized to the treatment arm, in which azacitidine was administered at 75 mg/m² daily for 7 days of a 28-day cycle; and 92 to the supportive care arm, of whom 49 crossed over to receive active therapy. When these and other CALGB data were analyzed using IWG criteria, Silverman et al reported response rates of 14% CR + PR and 30% hematologic improvement.³² There was a significant delay in transformation to AML or death, but not a significant prolongation of survival in the treatment arm. Major toxicities, as with any active agent for the treatment of MDS, included cytopenias. Patients also reported nausea and injection site–related complications.

Azacitidine was next explored in a phase III trial in which higher-risk patients with MDS were randomized to receive azacitidine at the dose used in the registration study or to conventional care, including best supportive care; low-dose cytarabine; or intensive, AML-type induction chemotherapy, as selected by investigators prior to randomization.³³ Of 358 patients, 179 were randomized to azacitidine and 179 to conventional care, with the majority (n = 105) receiving best supportive care. CR + PR rates for azacitidine were significantly greater than for conventional care, at 29% versus 21%. With a median follow-up of 21.1 months, median overall survival was 24.5 months for the azacitidine arm, and 15 months for the conventional care arm (hazard ratio .58, *P* = .0001). The superior activity of azacitidine, compared with both conventional care and previous

azacitidine studies, has been credited to an appropriately selected population of higher-risk patients with MDS and to a median duration of therapy of over 9 months.

Decitabine was developed in 1964 and also explored in AML populations prior to entering the MDS arena. The phase III registration trial for all MDS subtypes randomized 89 patients to receive the drug, compared with 81 managed with supportive care.² Patients received decitabine at a dose of 15 mg/m² every 8 hours over 3 days, with a cycle repeated every 6 weeks. Using IWG criteria, complete responses occurred in 9%, partial responses in 8%, and hematologic improvement in 13%, for an overall response rate of 30%. As with 5-azacytidine, major toxicities were hematologic.

Unlike with azacitidine, there was not a significant delay in transformation to AML or death in this study. As the two drugs are considered by most to be clinically equivalent and biologically similar, this difference has been attributed to different patients enrolled to each study (with more patients with early MDS in the decitabine study) and to an inadequate number of cycles of decitabine given (with a median of 2). Alternate dosing schedules, including once-daily dosing of decitabine over 5 days every 28-day cycle, have been explored in higher-risk patients given a median of > 5 cycles of therapy, and have yielded equivalent or higher CR rates.^{34,35} A phase III survival study in higher-risk patients with MDS was thus conducted in Europe, comparing 119 patients treated with decitabine at the registration study dosing schedule to 114 patients randomized to best supportive care, with preliminary results being presented 1 year ago at the American Society of Hematology (ASH) annual meeting.³⁶ While the CR + PR rate was 23% (similar to that with azacitidine), the study was not able to demonstrate a survival advantage, with patients randomized to the drug living a median of 10.1 months, and those randomized to best supportive care living a median of 5.8 months (hazard ratio 0.88, *P* = .38). Notably, patients received a median of only 4 cycles of decitabine. It is unknown whether shorter duration of therapy, subsequent therapies off-study, differences in patient populations, or true differences in drug activity account for the survival advantage for one DNA methyltransferase inhibitor over the other.

Some Other Things New

Another newer single-agent treatment approach for higher-risk patients with MDS that borrows from the acute leukemia model is clofarabine. This purine analog, FDA approved for the treatment of relapsed pediatric patients with acute lymphoblastic leukemia, has been explored in both oral and intravenous formulations in 61 patients with higher-risk MDS or AML by the MD Anderson group, 52% of whom had been exposed previously to DNA

methyltransferase inhibitors and 45% of whom had frank AML.³⁷ Most patients received either 30 mg orally or 15 mg/m² intravenously. CR rates were 30% for all patients, and 13% for patients failing DNA methyltransferase inhibitors, the likely target population given profound rates of myelosuppression.

For patients with lower-risk MDS, the drug ezatiostat (TLK 199), a glutathione-S transferase P1-1 inhibitor, has been tested recently in a phase I study of 45 patients.³⁸ In oral doses that ranged from 200 mg to 6000 mg daily in divided doses for 7 days of a 21-day cycle, no dose-limiting toxicity was reached, and common side effects were gastrointestinal, with 3 patients experiencing esophagitis as a serious adverse event related to study medication. Seventeen patients (38%) achieved a hematologic improvement response using IWG criteria. Extended dosing schedules are being evaluated in a phase II study.

Most agree that the next frontier in the treatment of MDS lies in combination therapies. Current and future iterations of lenalidomide-based studies are exploring combination therapy with ESAs, TPO agonists, and DNA methyltransferase inhibitors and use of the drug in higher-risk populations of MDS and AML patients.^{5,39} DNA methyltransferase inhibitors themselves are being combined with a panoply of agents, ranging from growth factors and histone deacetylase inhibitors, which maximize chromatin remodeling (particularly in an Eastern Cooperative Oncology Group trial),⁴⁰ to gemtuzumab ozogamicin, in a Southwest Oncology Group trial. Most importantly, future survival studies will become de rigueur, as azacitidine has set the bar for measurement of “hard” outcomes in MDS.

And a Silver Sixpence In Your Shoe

Finally, this chapter would not be complete without a mention of the need for pharmacoeconomic evaluations of our treatment approach to MDS. The median age at diagnosis of MDS in the US is 71 years, implying that the majority of patients receive Social Security and Medicare, and may be dependent on these alone for healthcare costs, including drugs and co-pays. At the time of this writing, cost-of-living adjustments will be eliminated for Social Security in 2010, leaving seniors more vulnerable to depleting life savings to pay for healthcare. It is our responsibility then, as healthcare providers, to be judicious in recommending expensive therapies because of their “newness,” and as researchers to develop medically and economically sound algorithms for how to rationally treat the patient with MDS.

Disclosures

Conflict-of-interest disclosure: The author is on an advisory committee for Genzyme; is on the steering committee for

Seattle Genetics; and receives honoraria and research funding from Celgene Corp.

Off-label drug use: Lenalidomide in non-del(5q) MDS; TLK 199 in MDS.

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