Pathobiology of Anemia in MDS
Peripheral blood cytopenias in myelodysplastic disorders (MDS) arise as the consequence of abnormal regulation of survival and differentiation programs affecting proliferation, apoptosis, and differentiation of primitive hematopoietic progenitors. The homeostatic balance between proliferation and programmed cell death shifts during disease progression such that apoptosis predominates in early stages of this disease, whereas in patients with higher risk MDS, the proliferative fraction may escalate and exceed the apoptotic index. Uregulation of cellular survival signals such as NF-κB, phospho-Akt, Bim-1, Bcl-2, Bcl-XL, and heat-shock protein chaperones are linked to suppression of apoptosis and consequent propagation and evolution of the malignant clone.

Impaired clonogenic growth of primitive erythroid progenitors and a suboptimal response to growth factor stimulation contribute to the development of peripheral blood cytopenias in MDS. While the erythroid progenitor response to erythropoietin (EPO) may be only modestly depressed in vitro, excessive apoptosis associated with overexpression of fas ligand undermines physiologic terminal differentiation. Negative microenvironmental signals mediated through excess elaboration of inflammatory cytokines amplify inherent defects in erythroid maturation and further attenuate survival potential. Evidence now supports a complex interplay between aptogenic cytokine generation and autocrine production of angiogenic molecules, such as vascular endothelial growth factor (VEGF), which reinforce the malignant phenotype. Elucidation of these pathogenetic mechanisms have been critical to the development of novel therapeutic targets intended to ameliorate anemia and suppress the malignant clone.

Prognostic Impact of Transfusion-Dependent Anemia
The World Health Organization (WHO) MDS classification has emerged as an invaluable refinement of the former French-American-British (FAB) system by incorporating greater discrimination in blast percentage and the number of dysplastic lineages, coupled with the introduction of a cytogenetic disease marker. Prospective validation of the WHO by the Dusseldorf MDS registry confirmed its usefulness as a prognostic discriminator for disease outcome. The international prognostic scoring system (IPSS) further refines the risk of leukemia transformation and overall survival by the inclusion of discriminators such as the number of cytopenias, myeloblast percentage, and cytogenetic pattern. Nonetheless, neither system recognizes the independent impact of red blood cell (RBC) transfusion dependence. A Cox regression analysis of prognostic variables in the University of Pavia MDS database was the first and only analysis to identify RBC transfusion dependence as an independent variable adversely affecting survival in patients with lower risk disease (hazard ratio [HR] = 2.16; P < .001). The negative effect was restricted almost exclusively to patients without excess blasts, which included the WHO subtypes of refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), MDS with 5q deletion, and refractory cytopenia with multilineage dysplasia (RCMD) with or without ringed sideroblasts (RCMD-RS). Furthermore, the total number of RBC transfusion and
the transfusion frequency as measured by the number of transfusions administered per month were associated with a proportional decline in both overall and leukemia-free survival.11 Nonleukemic causes of death also occurred with greater frequency in transfusion-dependent patients, although the causes of death were not specified. In addition to the impact on mortality, chronic anemia contributes to cardiac morbidity per se through hypertrophic cardiac remodeling as a result of long-term hemodynamic compensation. The adverse effect of transfusion dependence may be viewed as a surrogate clinical measure of the magnitude of maturation impairment in the MDS clone and, in return, raises the possibility that therapeutic strategies that restore effective erythropoiesis might therefore favorably alter survival and leukemia potential.

The Pavia study has suggested that transfusion-related iron loading is associated with unfavorable disease outcome through the inherent risks for organ complications.11 An inverse relationship was demonstrated between graded elevations in serum ferritin concentration and median overall survival. Moreover, the presence of secondary iron overload as measured by serum ferritin threshold greater than 1000 µg/mL was associated with a significant decrease in overall survival in patients with RA or RARS (HR = 1.51; P < .001).10 The relatively prolonged clinical course for patients with RA or RARS permits a longer duration for cumulative iron loading that places these otherwise favorable disease categories at greatest risk for end-organ iron damage. These findings are provocative, but will need to be independently validated. Finally, an improvement in cytopenias that has been observed in a select group of patients with MDS who received chronic iron chelation therapy raises the tantalizing notion that chelation may similarly have favorable and direct effects on the MDS clone through, perhaps, reduction in medullary generation of reactive oxygen species from excess non–transferrin-bound iron.12

Anemia Management in Low- and Intermediate-1–Risk MDS

Erythropoiesis-stimulating agents
Recombinant human erythropoietin (rhu-EPO) has remained the mainstay of initial therapy for lower-risk, transfusion-dependent patients with MDS over the past decade. However more recently, coverage has been challenged by the Centers for Medicare & Medicaid Services (CMS). Among unselected patients with MDS, 15% to 30% will experience an erythroid response to rhu-EPO, with considerably higher rates, 40% to 70% expected for the minority of selected patients with a favorable response profile.13-19 Features predictive for response to erythropoiesis-stimulating agents (ESAs) include low endogenous erythropoietin concentration (<500 U/mL), low transfusion requirements (<2 U/month), and bone marrow blasts fewer than 10%.13,14 Retrospective analysis of Groupe Francophone des Myélodysplasies (GFM) trials demonstrated that the presence of deletion 5q, with or without an additional cytogenetic abnormality, did not affect response rate in patients treated with ESA, but did significantly shorten response duration (mean 12 months vs 24 months, P = .019).19 Furthermore, there are conflicting data regarding the contribution of multilineage dysplasias to response to ESA. Experience from the Nordic MDS group suggests that patients with RCDM-RS respond poorly to ESA compared with patients with RARS (75% vs 9%; P = .003).17 Conversely, data from the GFM ESA studies did not show a difference in response rate for those with RARS versus RCMD-RS.18 For those patients refractory to rhu-EPO monotherapy, the addition of granulocyte-colony stimulating factor (G-CSF) may augment erythroid response with a response frequency ranging from 20% to 40%.15,16 Darbepoetin, a hypersyalated ESA with a longer half-life, has yielded comparable response rates when administered at intervals of every 1 to 3 weeks as monotherapy or combined with G-CSF.16,17 A median response duration of 1 to 2 years has been reported with rhu-EPO, with longer response duration associated with lower medullary blast percentage, low to intermediate-1 IPSS score, and achievement of major erythroid response.17,20

Amelioration of anemia in patients with MDS may improve quality of life in responding patients and can obviate the need for transfusional support. Perhaps of greater importance, emerging evidence indicates that sustained amelioration of anemia may also affect the adverse effect of transfusion dependence on the natural history of disease. A retrospective matching study of patients with MDS in the Pavia database managed solely with supportive care was compared to patients treated with rhu-EPO with or without G-CSF in three Nordic studies (Table 1).21 Patients were matched for response and prognostic variables, including frequency and number of RBC transfusions, and WHO and IPSS categories. Those patients with a lower transfusion need, defined as less than 2 U RBC/month, had a survival advantage with rhu-EPO treatment (HR = 0.57, P = .015) with no adverse effect on leukemia evolution. Of particular interest, responding patients had a significantly lower risk of AML progression compared with nonresponders or those patients managed only with supportive care (HR = 0.39, P = .001). Similar findings were reported from an analysis of the GFM experience involving 419 patients treated with ESAs in clinical trials performed between 1998 and 2005, which were compared with case-matched MDS patients managed solely with supportive care in the IPSS/International MDS Risk Analysis Workshop (IMRAW) database22 (Table 1). A survival advantage was also observed in responding patients enrolled in a phase 3 prospective cooperative group study of patients with MDS treated with rhuHEPO with or without G-CSF versus supportive care (Table 1). The median survival of patients responding to treatment was 53 months compared with 23 months in nonresponding patients (P = .009).15 These studies further suggest that response to ESA treatment may override or
lessen the inherent risk for AML progression and improve survival in lower-risk patients. It is unclear if these effects relate to a direct effect of ESA treatment on the natural history of MDS, or if nonresponding patients possess an intrinsically more aggressive disease biology. With the exception of the Eastern Cooperative Oncology Group (ECOG) phase 3 trial reported in abstract form, survival data are limited to retrospective case control–matching studies, and therefore randomized control trials are needed to further elucidate the role of ESA on MDS outcomes.

**Immunosuppressive therapy**

Aberrant autoimmune hematopoietic inhibitory activity appears to play a central role in the pathogenesis of MDS in a subset of patients. Clonal amplification of T lymphocytes is demonstrable in up to 50% of patients with MDS, which has been implicated in the suppression of hematopoiesis through CD8+ cytotoxic T lymphocytes, While the mechanisms underlying the generation of T-cell clones remains elusive, clonal suppression by immunosuppressive therapy has shown clinical success in a select patient population. Phase 2 trials using antithymocyte globulin with or without cyclosporine have yielded hematologic improvement in approximately one-third of patients with MDS. Trilineage responses have been noted, with most responding patients having lower-risk disease. Among hematologic responders, clonal CD8+ T cells have been shown to contribute to MHC class I–mediated suppression of colony-forming unit–granulocyte macrophage (CFU-GM), in isolated cases, balanced by immunologic recovery with a polyclonal T-cell population confirmed by T-cell receptor variable beta chain (TCR-Vβ) profile. While clonal T cells can be identified in patients with either high- or low-risk MDS, discrimination of clinical features permits identification of immunoresponsive patients. Pretreatment variables linked to response to immunosuppressive therapy (IST) in univariate analyses include younger age (< 60 years), short duration of RBC transfusion requirement (< 6 months), hypocellular marrow, and presence of a paroxysmal nocturnal hemoglobinuria (PNH) clone and human leukocyte antigen (HLA)–DR15 phenotype, whereas, in a multivariate analysis of the National Institutes of Health experience, only age, transfusion duration, and presence of HLA-DR15 retain independent predictive power. Furthermore, a comparative cohort survival comparison suggested that response to IST may be associated with a decreased risk of leukemia transformation and improved overall survival, findings consistent with the notion that restoration of maturation potential favorably affects the natural history of disease. A comparison of more than 800 patients in the IMRAW with patients with MDS matched for prognostic variables that responded to IST at the NIH showed that IST treatment was associated with an improvement in overall survival (> 8.1 vs 5.2 years; P < .001) and a decreased risk of leukemic transformation (P = .001) in Intermediate-1–risk patients aged < 60 years. While the influence of IST on survival will need to be confirmed by randomized control trials, this treatment can offer durable hematologic remission in lower-risk, younger patients.

**Immunomodulatory agents**

Immunomodulatory drugs (IMiDs) were targeted as potential MDS therapeutics based upon their anti-angiogenic and cytokine-modulating features, and their inherent ability to alter the bone marrow microenvironment. In addition to their ability to suppress tumor necrosis factor-alpha (TNF-α) elaboration, IMiDs affect the generation of a cascade of pro-inflammatory cytokines that activate cytotoxic T cells even in the absence of costimulatory signals. Moreover, IMiDs suppress endothelial responsiveness to angiogenic stimuli as well as the elaboration of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), thereby antagonizing neoangiogenesis within the bone marrow stroma. Thalidomide is the first IMiD investigated in MDS in a trial involving 83 patients. At daily doses ranging between 100 and 400 mg, 13% of patients experienced a major erythroid response, whereas platelet or neutrophil improvement was rare. Nevertheless, erythroid responses were durable, with a median duration of response of 306 days. Thalidomide has since been investigated in multiple trials at doses of 200 to 1000 mg per day in the treatment of both lower- and higher-risk patients.

### Abbreviations

- NA: not available
- SC: supportive care
- mos: months
- HR: Hazard ratio

### Table 1. Phase 3 and case-matching studies evaluating effect of erythropoiesis-stimulating agent (ESA) treatment on disease outcome in lower-risk myelodysplastic syndrome (MDS).

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Cohorts</th>
<th>No. patients</th>
<th>Erythroid response</th>
<th>AML transformation</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al14</td>
<td>Phase 3, crossover</td>
<td>ESA, SC</td>
<td>105</td>
<td>35%, 9% P=.002</td>
<td>0%, 3.6%</td>
<td>Median 53 mos vs 26 mos; P=.009*</td>
</tr>
<tr>
<td>Jadersten et al21</td>
<td>Case matching</td>
<td>ESA, Control</td>
<td>129</td>
<td>41%</td>
<td>HR=0.39, P=.001</td>
<td>HR=0.44, P&lt;.001*</td>
</tr>
<tr>
<td>Park et al22</td>
<td>Case matching</td>
<td>ESA, IPSS/IMRAW</td>
<td>284</td>
<td>NA</td>
<td>8% at 5 y, HR=0.2</td>
<td>82% at 5 y, HR=0.3</td>
</tr>
</tbody>
</table>

*Comparison of overall survival in ESA responders versus non-responders and controls.

Abbreviations: NA, not available; SC, supportive care; mos, months; HR, Hazard ratio.
MDS, with either hematologic improvement or partial responses reported in approximately 20% to 60% of patients. Although a relationship between dose and response has not been demonstrated, thalidomide tolerance with prolonged administration is poor, with a high frequency of dose-limiting fatigue, constipation, neuropathy, and sedation. For this reason, enthusiasm for the development of thalidomide in the treatment of MDS has been tempered, leading to the creation of structural analogs with enhanced potency and favorable toxicity profiles.

The thalidomide derivative CC5013 (lenalidomide; Revlimid), is a 4-aminoglutarimide analog with more potent inhibition of TNF-α and other inflammatory cytokines, and greater capacity to promote T-cell activation and suppress angiogenesis. Lenalidomide lacks the neurotoxicity of thalidomide but displays intrinsic myelosuppressive properties. Lenalidomide’s actions are complex and incompletely understood. Lenalidomide has shown remarkable activity in the treatment of MDS, particularly in patients with an interstitial deletion of chromosome 5q. The MDS-001 study was the initial safety and efficacy study of lenalidomide in MDS, which included 43 patients with symptomatic anemia who had either failed treatment with rhu-HEPO or were predicted to be poor candidates for benefit from rhu-EPO therapy. At doses of either 25 mg daily, 10 mg daily, or 10 mg/day for 21 of every 28 days, 56% of patients experienced durable erythroid responses according to International Working Group (IWG) criteria, with 20 of 32 patients who previously required RBC support achieving transfusion independence. Moreover, erythroid response rates were karyotype dependent, with 10 of 12 patients with deletion 5q experiencing an erythroid response compared with 57% of patients with a normal karyotype and 12% of patients with other chromosomal abnormalities. Responses were durable, with the median duration of major response exceeding 2 years. In contrast to thalidomide, in which the predominant dose-limiting toxicities are neurosedative, myelosuppression is dose limiting with lenalidomide, with grade 3 or greater neutropenia occurring in 58% of patients with deletion 5q and thrombocytopenia in 50%.

Two multicenter, confirmatory trials validated the karyotype-dependent erythroid response rate in low/intermediate-1 risk, transfusion-dependent patients with MDS (MDS-002 and MDS-003). Study schemas were identical in the two trials in which patients received treatment with lenalidomide at a dose of 10 mg daily or for 21 days every 4 weeks. The MDS-002 trial was limited to patients without deletion 5q and included 215 patients. In an intention-to-treat analysis, the overall transfusion response rate was 43%, with 26% of patients achieving transfusion independence that was sustained for a median of 43 weeks. Although a minority of patients had clonal cytogenetic abnormalities, only 19% experienced a cytogenetic response. Myelosuppression remained the principal adverse effect responsible for dose adjustment; however, grade 3 or greater neutropenia or thrombocytopenia developed in fewer than 25% of patients.

More robust erythroid responses were observed in patients with deletion 5q treated on the MDS-003 trial. Using the same study design, 148 patients with deletion 5q with or without further cytogenetic complexity received study treatment. Erythroid responses were reported in 76% of patients, and 67% achieved transfusion independence with a 1 g/dL or greater rise in hemoglobin. Unlike the MDS-002 study, cytogenetic responses were common (73%; complete, 45%) and closely linked to achievement of transfusion independence and resolution of cytologic dysplasia, indicating that suppression of the deletion 5q clone is inextricably linked to erythroid response. Moreover, additional chromosomal abnormalities accompanying deletion 5q did not adversely affect the rate of erythroid or cytogenetic response despite the recognized association between cytogenetic complexity and more aggressive disease natural history. Of particular biological intrigue, disappearance of non–deletion 5q chromosome abnormalities consistently accompanied complete suppression of the deletion 5q clone, thereby supporting the leukemogenesis model proposed by Pedersen-Bjergaard et al, in which deletion 5q represents an initiating oncogenic event responsible for clonal propagation, whereas acquisition of additional aberrations is secondary.

Myelosuppression was more common in the MDS-003 study, consistent with lenalidomide’s inherent ability to suppress the deletion 5q clone. Treatment interruption for grade 3 or greater neutropenia or thrombocytopenia was reported in 55% and 44% of patients, respectively. Indeed, a recent multivariate analysis of co-variates showed that a greater than 50% reduction in platelet count or the need for treatment interruption for myelosuppression in the initial 8 weeks of treatment were the most powerful independent predictive variables for achievement of transfusion independence, confirming that cytopenias early in the treatment course are necessary to achieve adequate suppression of the deletion 5q clone. Myeloid growth factors were used infrequently in the MDS-003 trial; however, experience from the pilot study indicates that growth factor support is effective in ameliorating treatment-related neutropenia. In order to limit dosing delays or reductions, growth factors may be considered when the neutrophil count declines below a threshold of 1000/µL. This strategy must be tempered by the limited knowledge of potential adverse effects arising from the interaction between lenalidomide and growth factor therapy. Clonal evolution with emergence of chromosome 7 deletions, the most common acquired cytogenetic abnormality in MDS, was reported in 3 of 12 patients with deletion 5q treated in the MDS-001 trial in which myeloid growth factors were routinely applied, whereas this chromosome abnormality was rare in the MDS-003 and -002 trials in which growth factors where used sparingly. The known G-CSF dependence of deletion 7/7q clones mandates restricted rather than prolonged...
growth factor administration.

Correlative biomarker studies offer additional insight into the agent’s contrasting karyotype-dependent mechanism of action. A direct cytotoxic effect leading to suppression of the deletion 5q MDS clone is supported by a marked rise in apoptotic index in major erythroid responders with deletion 5q compared to non-deletion 5q responders (207% vs 48%, respectively). In contrast, restoration of effective erythropoiesis in patients without deletion 5q is associated with proliferation arrest. Major responders without deletion 5q had a marked reduction in the Ki67 index (−76%) compared with deletion 5q responders (−9%). Furthermore, lenalidomide significantly suppressed elaboration of an array of inflammatory cytokines in bone marrow plasma, including TNF-α, interleukin (IL)–1β, interferon (IFN)–α, IFN-γ, stromal cell–derived factor-1β, and IL-2, in erythroid responders by 16 weeks of treatment. Consistent with lenalidomide’s action to suppress the deletion 5q clone, reduction in medullary microvessel density is greatest in major erythroid responders with the 5q deletion. These findings provide added support for the duality in drug action in MDS in which lenalidomide promotes erythropoiesis within non-deletion 5q clones, whereas in deletion 5q MDS, it is cytotoxic, leading to suppression of the dominant clone.

Long-term outcome with lenalidomide treatment in patients with deletion 5q was recently analyzed among 168 patients participating in four clinical trials. These data show that transfusion independence response to lenalidomide is durable, with a median duration of 2.2 years and some patients now exceeding 5 years. Multivariate analysis of features associated with longer duration of transfusion independence included deletion 5q syndrome, RBC transfusions less than 4 U/8 wks, low-risk IPSS, age younger than 70 years, and lower ECOG score, indicating that more favorable disease features are linked to longer response duration. Among overall survival variables, cytogenetic response had the greater predictive power for extended survival (HR = 5.295; P < .001). In fact, Kaplan-Meier estimates of overall survival adjusted for interval from diagnosis to first date of lenalidomide treatment (i.e., left truncation) showed that partial and complete cytogenetic responders (n = 90) had a significant survival advantage compared to nonresponders (NR) or nonevaluable (NE) patients (N = 78) (median, not reached vs = 28 months; P < .0001), with a 10-year survival estimate for cytogenetic responders of 78% compared to 4% in the NR/NE cohort. Not surprisingly, cytogenetic response afforded protection from acute myeloid leukemia (AML) progression compared with cytogenetic NR/NE patients, with a 10-year estimate of risk for leukemia progression of 15% in responding patients compared to 67% in the NR/NE cohort (P = .010). These data, although retrospective, suggest that lenalidomide may alter the natural history of disease and perhaps extend survival in patients with higher risk features such as those patients with greater cytogenetic complexity. A phase 3 placebo-controlled trial (MDS-004) that is comparing the frequency of lenalidomide-induced transfusion independence in patients with deletion 5q recently completed enrollment. This trial evaluates two doses of lenalidomide, 5 mg and 10 mg, administered on a 21-day schedule, with crossover allowed after 24 weeks of treatment. Although this trial will provide important new data on an alternate dose and schedule of lenalidomide administration, it will likely not address the question of impact of lenalidomide treatment on natural history of disease. The ability of lenalidomide to enhance erythroid progenitor responsiveness to rhu-EPO is the subject of a phase 3 Intergroup trial E2905 comparing major erythroid response rate to treatment with lenalidomide monotherapy or combined with rhu-EPO in lower-risk patients that either failed prior treatment with an ESA or have a poor response profile. The Southwest Oncology Group is currently investigating augmented-dose lenalidomide treatment in elderly patients with AML with a deletion 5q cytogenetic abnormality.

### Alternate Strategies and Novel Therapeutics

High-dose chemotherapy followed by stem cell allografting is the only treatment modality with curative potential in MDS and remains the standard of care for younger, higher-risk patients. Nevertheless, only a minority of patients are candidates due to either lack of donor availability or comorbidities. Alternative treatment strategies have been explored in higher-risk disease with the primary therapeutic goal of ameliorating cytopenias and suppressing leukemic transformation in order to prolong survival. Chemotherapies used for leukemia treatment can induce remission in higher-risk patients with MDS but have been unsuccessful in yielding prolonged disease-free survival and are associated with excessive morbidity and mortality. Conversely, hypomethylating agents such as decitabine and azacitidine are effective in both higher- and lower-risk patients. These

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Serum EPO &lt; 500mU/mL</th>
<th>RBC, &lt; 2 U/mo*</th>
<th>Age, &lt; 60 y</th>
<th>Deletion 5q</th>
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<tr>
<td>ESA</td>
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<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ESA</td>
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<td>NR</td>
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<tr>
<td>IST</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* RBC transfusion dependence for less than 6 mos is predictive of response to therapy.

Abbreviations: ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agents; IST, immunosuppressive therapy; sEPO, serum erythropoietin concentration; RBC, red blood cells; mos, months; yes, predictive for response; no, not predictive for response; NR, not relevant for prediction of response to therapy.
agents have assumed the position as the standard of care for patients with higher-risk disease and are emerging as immediate treatment considerations for patients who are not candidates for primary treatment with ESA, lenalidomide, or immunosuppressive therapy. The hypomethylating agents are discussed in more detail elsewhere by Dr. Garcia-Manero.

Selection of primary therapy for the management of anemia can now be made by considering four key response determinants: age, RBC transfusion burden and duration, endogenous erythropoietin production, and karyotype (Table 2). Finally, many novel therapeutics are emerging with new targets of action, such as farnesyl transferase inhibitors, glutathione transferase inhibitors, VEGF antagonists, tyrosine kinase inhibitors, p38 MAP kinase inhibitors, and histone deacetylase inhibitors; or that may meet a currently unmet need, such is the case of thrombopoietic agonist antagonists for the management of thrombocytopenia. Several of these agents have shown promise in the treatment of both low- and high-risk MDS, with the expectation that one or more will be considered for registration for a treatment indication in MDS.

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References


