



Linda Holmes. *The Bayfront*. Oil on canvas, 22" × 28". 2004 Emmett Fritz award.

*Indications for the use of lenalidomide in myelodysplastic syndromes are expanding.*

# Evolving Applications of Lenalidomide in the Management of Anemia in Myelodysplastic Syndromes

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*Lenalidomide has emerged as an effective therapeutic alternative for the management of anemia in lower-risk myelodysplastic syndromes (MDS). Compelling results from phase I and phase II clinical studies prompted the US Food and Drug Administration to approve lenalidomide for the treatment of transfusion-dependent MDS patients with interstitial deletion of chromosome 5q [del(5q)]. Subsequently, the National Comprehensive Cancer Network (NCCN) has incorporated lenalidomide into their current treatment algorithm for the treatment of lower-risk del(5q) patients. This discussion examines the current NCCN guidelines for the treatment of these patients, including the management of anemia in lower-risk MDS, and discusses the potential future therapeutic applications of lenalidomide in this disease.*

## Introduction

Chronic anemia negatively affects morbidity and mortality in patients with myelodysplastic syndromes (MDS) through the cumulative risk for cardiac failure, complications of iron loading, and a greater frequency of transformation to acute myeloid leukemia (AML) that increases in direct proportion to the severity of anemia.<sup>1,2</sup> Despite progress in cytokine development, treatment of anemia continues to remain the principal therapeutic challenge in patients with lower-risk disease.<sup>1-3</sup> The primary treatment goal in these patients should be to sustain improvement in hematologic deficits with consequent improvement in quality of life

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*Dr List receives grant/research support from Scios Inc and honoraria from Celgene Corp and Pharmion Corp, and he is a consultant for Kanisa Pharmaceuticals Inc, Schering-Plough Corp, Celgene Corp, Scios Inc, and Pharmion Corp.*

*Abbreviations used in this paper:* MDS = myelodysplastic syndromes, FDA = US Food and Drug Administration, NCCN = National Comprehensive Cancer Network, AML = acute myeloid leukemia, EPO = erythropoietin, RBC = red blood cell.

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Cancer Control Journal,  
Vol. 13, December Supplement.

Fig 1. — Adaptation of current NCCN treatment algorithm for the management of anemia in low- and intermediate-1-risk MDS. EPO = erythropoietin, RS = ringed sideroblasts, rhuEPO = human recombinant EPO, G-CSF = granulocyte-colony stimulating factor, IST = immunosuppressive therapy, AZA = 5-azacitidine. Reproduced and adapted with permission from the NCCN.<sup>6</sup>

of the affected individual, as well as to possibly obviate the long-term complications of anemia and extend overall survival.<sup>4,5</sup>

After years of reliance on best supportive measures for the management of anemia (eg, administration of red blood cell [RBC] transfusions, iron chelation, and myeloid growth factors), new therapeutic options are now available that offer active treatment interventions to restore erythropoiesis.<sup>6</sup> With the recent approval of lenalidomide for the treatment of lower-risk MDS patients with an interstitial deletion of the long arm of chromosome 5 [del(5q)] by the US Food and Drug Administration (FDA), we discuss how this agent can be incorporated into the National Comprehensive Cancer Network (NCCN) treatment algorithm. Evolving alternate applications for this agent are also examined.

## NCCN Treatment Algorithm

The most recent revision of the NCCN Practice Guidelines (version 4.2006) features important changes in the treatment of low- and intermediate-1-risk MDS with del(5q) and the management of anemia in these patients.<sup>6</sup> The most notable change is the recommendation for lenalidomide administration in patients with del(5q). Fig 1 illustrates a modified version of the current NCCN treatment algorithm. Anemia management decisions in this model are guided by the response probability profile that discriminates using two variables: serum erythropoietin (EPO) level, and the presence of a del(5q) chromosome abnormality. This approach then directs the practitioner to one of three treatment alternatives: recombinant EPO, lenalidomide, or alternate strategies.

## Lenalidomide in the NCCN Algorithm

Cytogenetic evaluation of patients with MDS plays an important role in confirming the diagnosis and predicting clinical outcome.<sup>5,7</sup> Cytogenetic abnormalities are detected in approximately 40% to 50% of patients with de novo MDS and in up to 95% of patients with treatment-dependent MDS.<sup>7,8</sup> A variety of nonrandom cytogenetic abnormalities have been identified in MDS, in which partial or complete chromosome losses predominate.<sup>7</sup> Interstitial deletions commonly involve the long arm of chromosomes 5, 7, and 20, either as the sole karyotypic abnormality or in conjunction with other cytogenetic aberrations [ie, del(5q), del(7q), and del(20q)].<sup>5,7</sup> Other common abnormalities include del(11q), del(12p), -Y, and +8.<sup>9</sup> Cytogenetic pattern offers powerful predictive power for disease natural history and is therefore segregated by the International Prognostic Scoring System (IPSS) into three distinct prognostic categories based on the specific chromosome abnormality and karyotype complexity.<sup>10</sup> Favorable features include a normal karyotype and isolated del(5q), del(20q), or -Y, whereas isolated del(7) or (7q) and complex karyotypes ( $\geq 3$  clonal abnormalities) are unfavorable, and trisomy 8 (+8) and all other abnormalities are regarded as intermediate.

The most commonly observed cytogenetic abnormality, however, involves the del(5q) with specific involvement of a common deleted 1.5 Mb region located at 5q31-5q32.<sup>11</sup> As illustrated in Fig 2, del(5q) accounts for approximately 15% to 18% of all cases of primary MDS<sup>7,12</sup> and up to 50% of secondary or treatment-dependent MDS.<sup>7</sup> Therefore, patients with this karyotypic abnormality represent a substantial proportion of the overall MDS population.

Three cytogenetically distinct subpopulations of del(5q) with varied prognosis are discernible:

1. **Isolated del(5q):** Patients with del(5q) have a hypoproliferative anemia with dysplastic bone marrow megakaryocytes. Affected individuals typically have

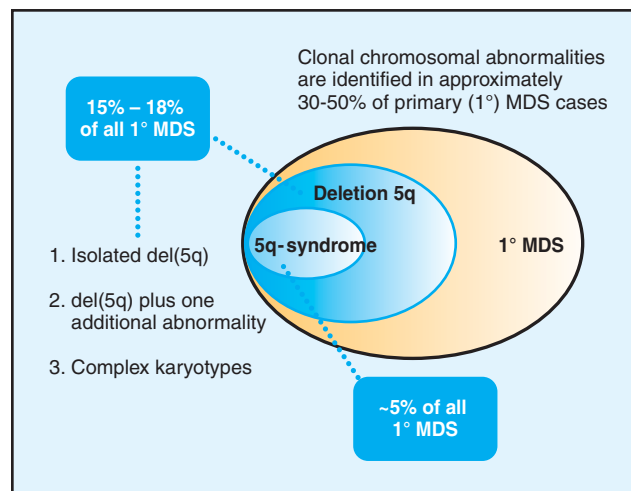


Fig 2. — Estimated size of various populations of cytogenetic abnormalities in individuals with MDS.

**Table 1. — Major Erythroid Response to Lenalidomide in MDS Patients With del(5q)**

| Variable                              | MDS-001 <sup>16</sup> | MDS-003 <sup>17</sup> |
|---------------------------------------|-----------------------|-----------------------|
| Frequency of major erythroid response | 83%                   | 67%                   |
| Time to erythroid response (median)   | 9.0–11.5 weeks        | 4.4 weeks             |
| Cytogenetic response                  | 83%                   | 73%                   |
| Time to cytogenetic response (median) | 8 weeks               | 24 weeks              |

high endogenous serum EPO levels and have become RBC transfusion-dependent. Only a small fraction of such patients who have the clinical and pathological features of the so-called 5q- syndrome display the most favorable prognosis with a long natural history and relatively low frequency of transformation to AML.

**2. del(5q) With One Additional Cytogenetic Abnormality:** Patients in whom del(5q) is accompanied by an additional chromosome abnormality have an intermediate course with a historical median survival ranging from 36 to 47 months with supportive care alone.<sup>10,13</sup> In those patients with a medullary blast count above 5%, the median survival is further reduced, approximating 24 months.

**3. Complex Karyotype Including del(5q):** Individuals with a complex karyotype involving del(5q) have an especially poor prognosis. Regardless of marrow blast percentage, the majority of patients succumb to their disease within only 7 to 8 months of diagnosis.<sup>12</sup>

The 5q- (minus) syndrome is a specific subset within the karyotypically defined group of isolated interstitial deletion of chromosome 5q (group #1 above). These patients have a constellation of clinical and morphologic features that include refractory macrocytic anemia, normal or elevated platelet count, normal marrow myeloblast percentage, mononuclear megakaryocytes, and mild leukopenia.<sup>10,15</sup> Patients with 5q- syndrome account for approximately 4% to 5% of all primary cases of MDS. The most common interstitial deletion segment in patients with the 5q- syndrome is del(5)(q13-q33) and uniformly involves the 5q31 region.<sup>12,13</sup> Prognosis for MDS patients with 5q- syndrome is the most favorable, with a median survival ranging from 7 to 9 years and a low frequency of AML progression.<sup>14,15</sup>

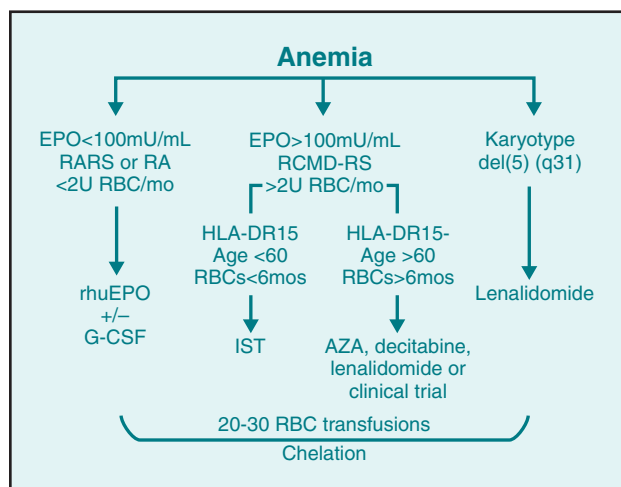
With the recent FDA approval of lenalidomide, patients with interstitial deletions of chromosome 5 are directed to arm 3 of the treatment algorithm, regardless of the complexity of the cytogenetic abnormality. As summarized in Table 1, lenalidomide has compound beneficial effects in MDS patients with del(5q).<sup>16,17</sup> First, lenalidomide suppresses the del(5q) clone to restore effective erythropoiesis; in the majority of patients this translates into a decrease in the number of transfusions, and in approximately two thirds or more of patients, it yields sustained transfusion independence. These findings directly benefit patients not only through expected improvement

in quality of life, but also — for many — the elimination of the need for chronic iron chelation by introducing more efficient iron storage reduction by phlebotomy. Finally, the cytogenetic remitting activity of lenalidomide in del(5q) raises the possibility that this agent may affect the natural history of disease and perhaps extend survival in patients with higher-risk cytogenetic patterns. In the latter patients in particular, only thrombocytopenia rather than neutropenia should be limited by obviating its myelosuppressive properties through the coadministration of myeloid growth factors. The cytogenetic remitting activity of lenalidomide is unique to this agent, which is not observed with cytokine therapy.

Lower-risk MDS patients with interstitial deletions of chromosome 5q who fail to respond to lenalidomide are redirected to either arm 1 or arm 2 of the current NCCN treatment algorithm. Treatment selection is guided by the magnitude of endogenous serum EPO response to anemia, which influences the potential for recombinant EPO responsiveness.

## Lenalidomide and the Evolving Treatment Algorithm

While the NCCN has been quick to modify its treatment algorithm in response to the FDA approval of lenalidomide, there is sufficient information from clinical investigations to warrant further refinement to the algorithm. Fig 3 illustrates a modified treatment algorithm that considers lenalidomide in other lower-risk IPSS disease subsets, particularly in individuals with a normal karyotype or with non-del(5q) chromosomal abnormalities. As summarized in Table 2, sustainable erythroid responses were achieved in a significant per-



**Fig 3. — Alternate treatment algorithm for the management of low- and intermediate-1-risk MDS based on current NCCN treatment guidelines and clinical research trials.** EPO = erythropoietin, RA = refractory anemia, RARS = refractory anemia with ringed sideroblasts, RBC = red blood cell, rhuEPO = human recombinant EPO, RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts, IST = immunosuppressive therapy.

**Table 2. — Erythroid Response to Lenalidomide in MDS Patients With a Non-del5q Karyotype**

| Variable                        | MDS-001 <sup>16</sup> | MDS-002 <sup>18</sup>          |
|---------------------------------|-----------------------|--------------------------------|
| Frequency of erythroid response | 45%                   | 43%                            |
| Major                           | 39%                   | 26%                            |
| Minor                           | 6%                    | 17%                            |
| Mean time to response           | Not reported          | 4.5 weeks<br>(range: 0.3–39.1) |

centage of patients with del(5q) in two separate clinical trials (MDS-001 and MDS-003) in which the majority of patients had a heavy transfusion burden and had failed prior treatment with recombinant EPO.<sup>16-18</sup> While the erythroid response rate is not as high as in the del(5q) population, the results are encouraging, given that nearly half of these patients experienced erythroid improvement with lenalidomide administration. Therefore, both lenalidomide and azacitidine represent reasonable treatment alternatives for the management of anemia in patients with a low EPO response profile and cytogenetic pattern other than del(5q).

Additional refinements in the modified algorithm in Fig 3 include a lower serum EPO threshold of 100 mU/mL for recombinant EPO administration.<sup>19</sup> In the model generated by the Nordic MDS Study Group, the lower serum EPO concentration provided much greater predictive power for response to recombinant EPO. Second, morphologic characterization (using the World Health Organization [WHO] classification system) and transfusion burden are additional features that complement the Nordic EPO response model.<sup>20</sup> Those patients who are RBC transfusion-dependent and require two units or more of RBC transfusions per month have a low probability of EPO response, as do those with refractory anemia with ringed sideroblasts (RARS) with multilineage dysplasia (RCMD-RS in the WHO classification). Finally, selection criteria to identify patients who are potentially responsive to immunosuppressive therapy (arm 2) can be refined by consideration of age and duration of transfusion dependence, features identified in a model generated and validated by investigators at the National Institutes of Health.<sup>21,22</sup> Therefore, individuals who lack the HLA-DR15 class II antigen phenotype or who are older than 60 years of age and have been transfusion-dependent for longer than 6 months should be directed to arm 2b. Recommended treatment options among this subset of MDS patients include administration of lenalidomide or azacitidine.

## Future Therapeutic Alternatives For Lower-Risk MDS With Lenalidomide

Lenalidomide represents a breakthrough in the development of the first targeted drug therapy for the manage-

ment of anemia in patients with low- and intermediate-1-risk MDS. Additional trials are underway to optimize the dose and schedule of lenalidomide in MDS and explore the potential to improve erythroid response rate by combination therapy. One such trial, the MDS-004 trial, is a phase III randomized, double-blind, placebo-controlled trial involving transfusion-dependent patients with del(5q). This trial is evaluating response and safety of two daily doses of lenalidomide (5 mg and 10 mg) compared with a placebo. It will provide insight as to the dose-related response dynamics and the potential to impact progression of disease in higher-risk cytogenetic categories.

It is anticipated that combination drug therapy will build on responses observed with monotherapies that are becoming the standard of care for MDS management. Such approaches may lessen toxicities such as myelosuppression and potentially increase cumulative drug administration to augment response to lenalidomide treatment. Indeed, new trials are underway evaluating the potential benefit of combined treatment with thrombopoietin mimetic agents to ameliorate thrombocytopenia that is often cumulative dose limiting. Combinations involving lenalidomide and recombinant EPO and darbepoetin are under investigation in lower-risk MDS patients without del(5q) to possibly exploit the action of lenalidomide to improve EPO receptor signaling and augment erythroid response. Other combination strategies include phase I studies with histone deacetylase inhibitors and DNA methyltransferase inhibitors. The evolution of lenalidomide administration, either alone or in combination with other agents such as those above, is likely to significantly modify the MDS treatment algorithm in the not-so-distant future.

## Conclusions

In response to the FDA's approval of lenalidomide for the management of anemia in MDS patients with del(5q), the NCCN modified its treatment recommendations and promptly released an updated algorithm. Lenalidomide has proven itself as the lead therapeutic in a new strategy for the MDS armamentarium as the first disease-selected targeted drug. As more is learned about lenalidomide and other applications are approved for the use of lenalidomide in various subgroups of MDS, either alone or in combination, it is anticipated that the NCCN treatment algorithm will continue to evolve to reflect the heterogeneity of the disease itself.

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