



Linda Holmes. *Marsh 1* (detail). Oil on canvas, 24" × 18". Private collection.

*Lenalidomide promotes
erythropoiesis in lower-risk
myelodysplastic syndromes
with del(5q).*

Lenalidomide: Targeted Anemia Therapy for Myelodysplastic Syndromes

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Lenalidomide, an IMiD[®] drug (a novel type of immunomodulating drug) was recently approved by the US Food and Drug Administration for the treatment of transfusion-dependent anemia in patients with myelodysplastic syndromes (MDS) and interstitial deletions of chromosome 5q [del(5q)]. This review examines the clinical experience from the MDS-001 and MDS-003 clinical trials that led to this approval, the results of biological correlates supporting the targets of drug action, and the results from a non-del(5q) multicenter study (MDS-002). Lenalidomide treatment resulted in both erythroid and cytogenetic responses in the majority of patients with del(5q), accompanied by reductions in inflammatory cytokine generation and marrow microvessel density and improvement in primitive hematopoietic progenitor recovery. Central pathology review showed that resolution of cytologic dysplasia was common in patients with del(5q) but was infrequent in erythroid-responding patients without the chromosome 5 deletion. These findings indicate that lenalidomide promotes erythropoiesis in lower-risk MDS, with two apparently distinct mechanisms of action: suppression of the ineffective del(5q) clone and promotion of effective erythropoiesis in non-del(5q) MDS progenitors. These studies identified lenalidomide as a highly active erythropoietic- and cytogenetic-remitting agent in lower-risk MDS patients who otherwise would not be expected to benefit from recombinant erythropoietin therapy. The most common adverse reactions include dose-dependent neutropenia and thrombocytopenia that are more pronounced in patients with del(5q) in whom early suppression of the clone is expected.

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Abbreviations used in this paper: IMiD[®] = immunomodulating drug, EPO = erythropoietin, GM-CSF = granulocyte-macrophage colony-stimulating factor, VEGF = vascular endothelial growth factor, ITT = intention-to-treat, MER = major erythroid response, NR = non-responders

Introduction

Myelodysplastic syndromes (MDS) encompass a spectrum of hematopoietic stem cell malignancies characterized by ineffective hematopoiesis that derives from disordered regulation of proliferation, differentiation, and apoptosis in hematopoietic progenitors and their progeny.¹ Clinically, MDS is characterized by one or more peripheral cytopenias in the presence of normo- or hypercellular bone marrow.² Patients with lower-risk MDS (ie, low- or intermediate-1-risk groups according to the International Prognostic Scoring System [IPSS]) account for approximately 70% of patients with the disease.³ Over time, the vast majority of these patients will develop anemia that is symptomatic and/or dependent on red blood cell transfusions.⁴

Treatment of anemia in individuals with lower-risk MDS has been limited to the use of recombinant erythropoietin (EPO) alpha (Procrit®, Ortho-Biotech, Bridgewater, NJ; Epogen®, Amgen, Thousand Oaks, Calif), or darbepoetin alfa (Aranesp®, Amgen, Thousand Oaks, Calif), alone or combined with growth factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) to potentiate response. Unfortunately, less than 30% of lower-risk MDS patients are appropriate candidates for hematopoietic growth factor therapy, based on potential response profile.⁴ Indeed, a meta-analysis evaluating EPO treatment results in patients with MDS showed that only 16% responded to treatment.⁵

With the advent of improved understanding of the pathobiology of MDS, IMiDs®, a proprietary group of immunomodulatory drugs, have emerged as effective therapeutic alternatives for patients who have either not responded to or are unlikely to benefit from recombinant EPO treatment. The identification of increased microvessel density in the bone marrow of patients with MDS provided the initial insight into the role that medullary angiogenesis plays in the pathobiology of MDS. Indeed, myelomonocytic precursors in MDS produce vascular endothelial growth factor (VEGF) and display one or more of the cognate receptors that serve to promote myeloblast self-renewal and amplify ineffective erythropoiesis through paracrine induction of proapoptotic cytokines.⁶ Thalidomide, a first-generation IMiD®, was the first agent with antiangiogenic properties to be studied in MDS. Responses were largely restricted to the erythroid series in less than 20% of patients. However, the majority of responses were robust, with relatively long-lasting transfusion independence. These data and encouraging results in multiple myeloma led to the investigation of structural analogs, including lenalidomide.⁷ Lenalidomide (CC-5013; Revlimid®, Celgene Corp, Summit, NJ) an amino-substituted thalidomide derivative, possesses a number of biologic and pharmacologic properties that are potentially beneficial in the manage-

ment of anemia in MDS. Lenalidomide lacks the toxicologic profile of thalidomide (ie, neuropathy, somnolence, constipation), yet it retains the ability to modify ligand-induced cellular responses such as suppression of inflammatory cytokine release (eg, TNF- α), suppression of angiogenic response, and enhancement of EPO receptor signaling.⁸

In December 2005, the US Food and Drug Administration approved lenalidomide for the management of anemia in lower-risk MDS patients with an interstitial deletion involving the long arm of chromosome 5 [del(5q)]. This approval marks a new milestone in the development of targeted therapy for MDS and the hope that the cytogenetic-remitting activity of lenalidomide will impact the natural history of disease in patients with greater karyotype complexity.

The del(5q) population, which accounts for approximately 15% of the MDS population,^{1,9} is composed of three karyotypically defined subsets: isolated del(5q), including patients with the 5q- (minus) syndrome, del(5q) with one additional chromosome abnormality, and del(5q) with two or more cytogenetic abnormalities (ie, a complex karyotype). Overall survival decreases with increasing karyotype complexity; median survival is less than 6 months in patients with a complex karyotype regardless of marrow myeloblast percentage.^{1,10}

The MDS-001 Clinical Study

MDS-001 was the initial phase I-II open-label, single-center clinical study that evaluated the safety and efficacy of lenalidomide in 43 MDS patients with symptomatic anemia.¹¹ Patients received one of three oral lenalidomide dosing schedules: 25 mg daily, 10 mg daily, and 10 mg per day administered for 21 days of every 28-day cycle. Among the 43 subjects enrolled in

Table 1. — Key Clinical Findings Summarized From the MDS-001 Study

| Variable | Outcome |
|---|--------------------------------|
| Sample size | 43 |
| Patients with normal karyotype | 23 |
| Patients with abnormal karyotype | 20 |
| Patients with del(5)(q31.1) | 12 |
| Overall erythroid response | 24 (56%) |
| Major | 21 (49%) |
| Minor | 3 (7%) |
| Median time to response | 9–11.5 weeks |
| Erythroid response by karyotype | |
| Del(5)(q31.1) only | 10 (83%) |
| Normal karyotype | 13 (57%) |
| Overall cytogenetic response | 11 (55%) |
| Overall cytogenetic response in del(5)(q31.1) | 10 (83%) |
| Complete response | 9 (75%) |
| Median time to response | 8 weeks (range: 8–24 weeks) |

the study, 74% were transfusion-dependent, and all had either not responded to prior treatment with EPO (77%) or had a low probability of EPO response based on high transfusion burden and serum EPO concentration (23%). Overall, 30% had not responded to thalidomide therapy. An abnormal karyotype was present in 46%, including del(5q) in 12 patients either alone or with additional chromosome abnormalities.

Table 1 summarizes the results of the MDS-001 study. Of the 43 participating subjects, 24 (56%) experienced an erythroid response according to International Working Group criteria in an intention-to-treat (ITT) analysis.¹² Twenty-one of the responders (49% of all subjects) achieved a major erythroid response (MER)

characterized as transfusion-independent for 8 weeks or longer, or, in patients not transfusion-dependent, a rise in hemoglobin of ≥ 2 g/dL sustained for 8 weeks or more. Median time to response was dose-related and ranged from 9 to 11.5 weeks, with the shortest interval observed in patients receiving the 25-mg dose. The observed erythroid responses were durable, with the median duration of major response not reached after a median follow-up of 81 weeks. Seven patients, or a third of the major responders, have remained transfusion-free for over 4 years. Interestingly, erythroid response rate was karyotype-dependent. Overall, 10 (83%) of 12 patients with a del(5q) had an erythroid response compared to 13 (57%) of patients with a nor-

Table 2. — Change in Bone Marrow Plasma Cytokine Concentration After Lenalidomide Treatment

| Cytokine or Protein* | Erythroid Response | Posttreatment | | Week 16 | | P Value |
|----------------------|--------------------|---------------|--------------------|--------------|--------------------|---------|
| | | Mean (pg/mL) | Standard Deviation | Mean (pg/mL) | Standard Deviation | |
| IL-1 β | NR | 70.11 | 42.54 | 77.82 | 17.28 | .0070 |
| | R | 71.65 | 27.14 | 50.76 | 15.74 | |
| IL-2 | NR | 148.62 | 96.69 | 145.24 | 48.69 | .0192 |
| | R | 165.18 | 56.55 | 97.58 | 47.03 | |
| IL-6 | NR | 23.07 | 19.87 | 22.60 | 3.91 | .0831 |
| | R | 25.56 | 11.91 | 13.00 | 7.34 | |
| IL-8 | NR | 37.88 | 22.66 | 43.09 | 33.80 | .4505 |
| | R | 34.15 | 16.98 | 29.90 | 11.15 | |
| IL-10 | NR | 36.90 | 46.33 | 40.64 | 49.44 | .1517 |
| | R | 29.18 | 33.82 | 8.07 | 4.97 | |
| IFN- α | NR | 101.81 | 75.04 | 123.00 | 9.57 | .0093 |
| | R | 176.36 | 223.86 | 103.52 | 101.19 | |
| IFN- γ | NR | 116.56 | 75.48 | 129.96 | 53.23 | .0093 |
| | R | 109.13 | 45.60 | 81.55 | 37.01 | |
| TNF- α | NR | 398.91 | 255.98 | 406.99 | 127.31 | .0117 |
| | R | 426.89 | 213.92 | 299.26 | 149.06 | |
| GM-CSF | NR | 519.27 | 128.87 | 545.90 | 369.92 | .23 |
| | R | 468.88 | 104.75 | 408.43 | 74.64 | |
| bFGF | NR | 56.75 | 107.24 | 68.59 | 33.68 | .3430 |
| | R | 126.84 | 297.15 | 337.12 | 428.31 | |
| HGF | NR | 2105.18 | 2439.92 | 1448.81 | 248.55 | .2698 |
| | R | 1676.98 | 952.68 | 996.36 | 310.95 | |
| TIMP-1 | NR | 19234.63 | 7951.24 | 26499.30 | 8836.68 | .0536 |
| | R | 20264.06 | 9272.93 | 18448.48 | 8622.29 | |
| TIMP-2 | NR | 83561.43 | 13207.13 | 85246.84 | 11666.67 | .1065 |
| | R | 81817.57 | 30229.64 | 65468.43 | 21688.00 | |
| MIP1- α | NR | 570.92 | 119.62 | 566.15 | 75.34 | .4855 |
| | R | 514.89 | 107.05 | 482.81 | 130.22 | |
| SDF1 β | NR | 1326.23 | 898.73 | 1362.77 | 301.67 | .0106 |
| | R | 2238.69 | 2644.06 | 1474.00 | 1955.23 | |
| VEGF | NR | 6.58 | 7.31 | 6.27 | 8.35 | .5 |
| | R | 11.12 | 21.13 | 5.62 | 6.58 | |

* Bone marrow plasma was isolated by centrifugation at 900 g for 20 minutes interleukin (IL)-2 (IL-2), IL-6), IL-8, IL-10, interferon-alpha (IFN- α), interferon-gamma (IFN- γ), GM-CSF, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinase-1 (TIMP-1), TIMP-2, macrophage inflammatory protein-1 alpha (MIP-1 α), and stromal cell-derived factor-1 beta (SDF-1 β) were determined using a multiplex enzyme-linked immunosorbent assay (ELISA) (SearchLight, Pierce Biotechnology, Boston, Mass). VEGF was measured using an R & D Systems ELISA that recognizes 2 secreted isoforms (121 kd and 165 kd). Differences in cytokine concentration were evaluated by student's *t* test.

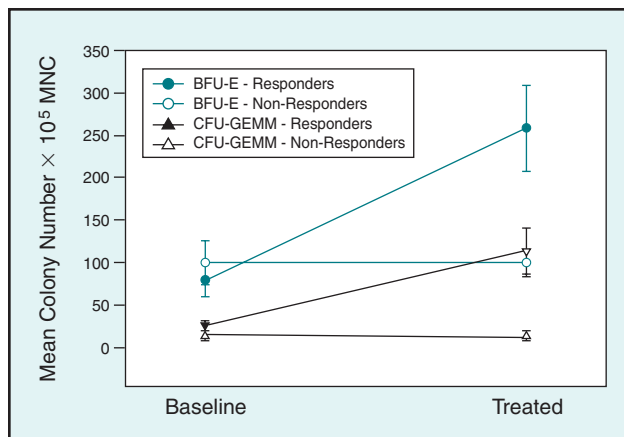


Fig 1. — Change in bone marrow progenitor recovery after lenalidomide treatment. Bone marrow progenitor colony-forming assays were performed as previously described.⁶ Growth of CFU-GEMM, BFU-E, and colony-forming unit granulocyte-macrophage (CFU-GM) was scored after 14 days incubation. Mean BFU-E and CFU-GEMM increased significantly in erythroid responders and reached the normal range, whereas there were no significant changes in hematologic nonresponders.

mal karyotype and 1 (12%) of patients with other cytogenetic abnormalities ($P=.007$).

Cytogenetic response, defined as a 50% or greater reduction in the number of abnormal metaphases, was observed in 11 (55%) of the 20 informative patients, including complete cytogenetic responses in 10 patients, among whom 9 had del(5q). Cytogenetic response was rapid and was reached at a median of 8 weeks (range: 8 to 24 weeks), the first date of scheduled marrow evaluation.

Correlative biologic studies have confirmed changes in pharmacologic targets believed to be relevant to disease-specific response. Analysis of bone marrow plasma concentration of 16 cytokines or bioactive peptides

showed no differences between responders and non-responders prior to study treatment. However, mean marrow plasma concentration of six inflammatory or proapoptotic cytokines, including TNF- α , IL-1 β , IFN- α , IFN- γ , SDF-1 β , and IL-2, significantly declined after 16 weeks of lenalidomide treatment in erythroid responders (Table 2). Corresponding improvement in erythroid burst (BFU-E; $P=.002$) and multipotent progenitor (CFU-GEMM; $P=.011$) recovery was restricted to erythroid responders, without discernible change in myeloid progenitor recovery (Fig 1). Immunohistochemical staining of trephine biopsies showed that MERs had a significantly greater reduction in medullary microvessel density compared to minor and nonresponders (NR) (-43% vs -13% NR; $P=.02$) (Fig 2), whereas increases in proliferation and apoptotic indices in MER patients were not significant (Figs 3 and 4). Although sample size is limiting, comparison by cytogenetic pattern provides important insight into lenalidomide's contrasting karyotype-dependent mechanism of action. MER patients with del(5q) showed a trend toward a greater reduction in marrow microvessel density compared to non-del(5q) MERs (-50% vs -39% non-del5q vs -13% NR; $P=.06$) accompanied by a marked rise in apoptotic index (207% vs 48% non-del5q MERs vs 65% NR), whereas reduction in proliferation index was limited to non-del(5q) MERs (-76% vs -9% del5q vs -13% NR). These findings provide a biological rationale for the pattern of hematologic and cytogenetic response observed in the MDS-001 study. In patients with del(5q), lenalidomide appears cytotoxic, thereby leading to apoptosis and sustained suppression of the MDS clone, whereas in non-del(5q) erythroid responders in whom cytologic dysplasia persists, lenalidomide promotes the arrest of proliferating cells to restore effective erythropoiesis.

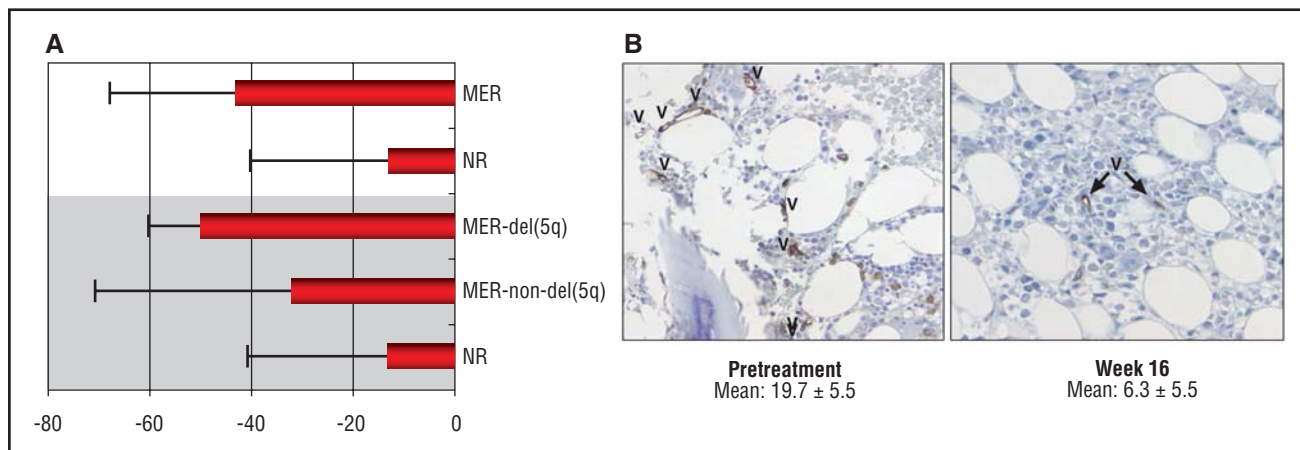


Fig 2. — Change in bone marrow microvessel density (MVD) according to erythroid response and cytogenetic category. Bone marrow MVD was assessed by immunohistochemistry in trephine biopsy specimens from 18 study patients before and after lenalidomide treatment as previously described.⁶ Vessels were identified based on endothelial staining for CD-31 and morphology. Branched structures were counted as one vessel. Vascularized areas were counted at 200 \times (each field represents an area of 0.74 mm²). Three to five areas were counted per sample and the mean number of vessels per unit area determined. All samples were coded to eliminate potential observer bias in counting. (A) Median MVD was significantly reduced in major erythroid responders (MER, -43%, $n = 8$) compared to nonresponders and minor responders (NR, -13%, $n = 10$) ($P=.02$). There was a trend favoring a greater reduction in median MVD in MER with del(5q) (-50%, $n = 3$) compared to non del(5q) (-39%, $n = 5$) and NR. Two-group comparisons were made by Wilcoxon Sum Rank test, and heterogeneity among cytogenetic and response groups by Kruskal-Wallis analysis. (B) Comparison of median MVD before and after 16 weeks of lenalidomide treatment in a patient with del(5q). Median MVD decreased from 19.7 ± 5.5 to $6.3 \pm 5.5/0.74$ mm².

The MDS-003 Clinical Study

The MDS-003 trial was the pivotal multicenter phase II study that evaluated lenalidomide treatment response in 148 patients with del(5q) with or without other chromosome abnormalities.¹³ Eligible patients had lower-risk IPSS categories (ie, low or intermediate-1-risk disease) and were red blood cell transfusion-dependent with a minimum of 2 units of packed red blood cells in the 8 weeks preceding study registration. Lenalidomide was initially administered at a dose

of 10 mg per day for 21 days of every 28-day cycle. However, the treatment schedule was later amended to administer 10 mg daily, a decision made after final analysis of the MDS-001 study that showed a shorter time to response with continuous dosing. The primary end-point for the study was the frequency of transfusion independence after 24 weeks of lenalidomide treatment, with secondary analyses including duration of transfusion independence, frequency of minor erythroid response, cytogenetic and pathologic response, and safety of lenalidomide. The vast majority of partic-

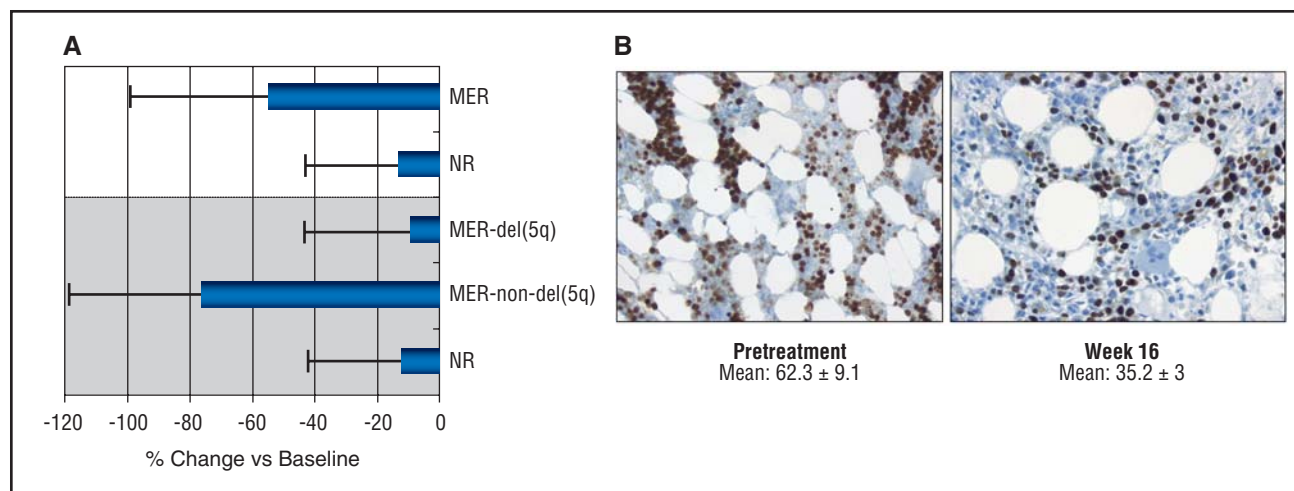


Fig 3. — Change in marrow proliferation index according to erythroid response and cytogenetic category. Proliferation index was assessed by immunohistochemical staining of trephine biopsy specimens for the Ki67 proliferation antigen that recognizes cells in G₁, S, G₂, and M phases of the cell cycle as previously described.¹⁶ (A) MERs had a greater reduction in median proliferation index compared to NRs (MER, -53.5% vs NR, -13%; $P = .29$). Comparison according to cytogenetic category showed that non-del(5q) MERs had a greater reduction in proliferation index compared to del(5q) MERs (-76% vs -9%) and NR (-13%; $P = .15$). Statistical comparisons were performed as described in Fig 2. (B) Comparison of Ki67 staining before and after 16 weeks of lenalidomide treatment in a non-del(5q) patient. Median Ki67 index decreased from 62.3 ± 9.1% to 35.2 ± 3%/high-powered field (HPF).

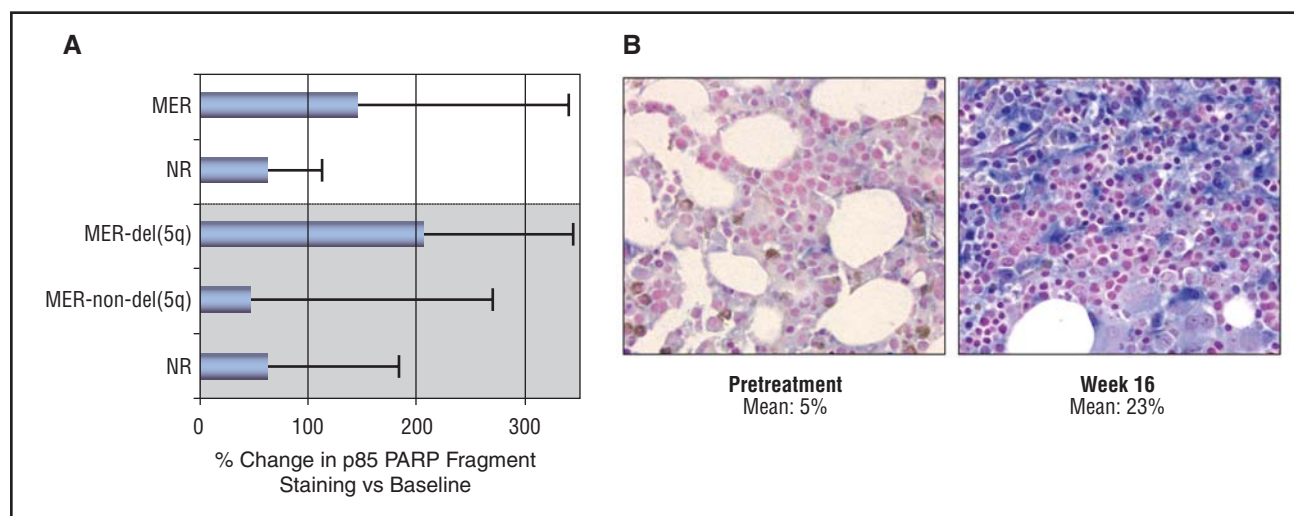


Fig 4. — Change in apoptotic index according to erythroid response and cytogenetic category. Apoptosis was assessed by detection of the p85 fragment of poly (ADP-ribose) polymerase (PARP) in trephine biopsy specimens. Activated caspase-3 cleaves PARP into at least two fragments, p85 and p25, which can be detected by immunohistochemistry (IHC). Following antigen retrieval using citrate buffer pH 6.0, an anti-PARP p85 fragment antibody (Promega Corp, Madison, Wisc) was used to detect apoptotic cells. IHC was carried out as previously described.⁶ Positively staining cells, denoted by the blue staining, indicate apoptotic cells. Apoptotic index was calculated by the number of p85-positive cells in a field of 250 cells. When possible, at least three high-power fields were used to calculate the apoptotic index. (A) Median apoptotic index was higher after lenalidomide treatment in MERs compared to NRs (MER, 146.5% vs NR, 65.5%; $P = .37$). Comparison by karyotype showed a >4-fold increase in apoptosis in del(5q) MERs vs non-del(5q) responders (207% vs 48%; $P = .33$). Statistical comparisons were performed as described in Fig 2. (B) Comparison of p85 staining before and after 16 weeks of lenalidomide treatment in a del(5q) patient. Median apoptosis index increased from 5% to 23%/HPF after lenalidomide treatment.

ipants had failed prior treatment with EPO (73%) and had a heavy transfusion burden (2 units or more, 71%); 37% of patients were receiving iron chelation therapy. Overall, 74% of patients had an isolated del(5q), including 27% with the 5q- syndrome, 17% had one additional abnormality, and 8% had a complex karyotype.

The final results of MDS-003 were analyzed in July 2005 and are summarized in Table 3. Using an ITT analysis, 112 patients (76%) achieved a transfusion response characterized by a 50% or greater reduction in transfusions, among whom 99 (67%) achieved transfusion independence with a rise in hemoglobin of 1 g/dL or more. Response to treatment was rapid and occurred in a median of 4.6 weeks (range: 1 to 49 weeks). As in the MDS-001 study, the erythroid response was durable. With a median follow-up of 2 years, the median duration of transfusion independence was not reached, with 61 of the 99 transfusion-independent responders remaining transfusion-free at 1 year. Achievement of transfusion independence was associated with a rise in hemoglobin to the normal or near normal range. Median hemoglobin at the time of maximum response was 13.4 g/dL, with a corresponding median rise in hemoglobin compared to pre-study nadir of 5.4 g/dL.

Cytogenetic response closely correlated with transfusion-response, with 62 (73%) of 85 evaluable patients experiencing a 50% or greater reduction in the number of abnormal metaphases and 45% of patients achieving a complete cytogenetic remission. All cytogenetic responders achieved transfusion inde-

Table 4. — Summary of Adverse Reactions in Patients Prescribed Lenalidomide

| Event | MDS-001 | MDS-002 | MDS-003 |
|--------------------|----------|---------|---------|
| Neutropenia | | | |
| Total (all grades) | 28 (65%) | 27% | 57% |
| Grade 3 or 4 | 28 (65%) | 24% | 55% |
| Thrombocytopenia | | | |
| Total (all grades) | 32 (74%) | 25% | 58% |
| Grade 3 or 4 | 23 (53%) | 19% | 44% |

pendence. Despite the known unfavorable natural history in del(5q) patients with additional chromosome abnormalities, there is no significant difference in the frequency of either transfusion independence or cytogenetic response according to karyotype complexity (Table 3), therefore suggesting that lenalidomide may possibly extend survival in patients with higher-risk del(5q) karyotypes. Moreover, central pathology review showed that 36% of patients achieved a complete histological response by week 24, all of whom were cytogenetic complete responders. Multivariate analysis revealed that pretreatment thrombocytopenia was the most important variable limiting cytogenetic and transfusion response rate, directly correlating with reduced cumulative drug delivery and duration of drug administration. Taken together, the compelling results of the MDS-001 and MDS-003 studies led to the approval of lenalidomide in December 2005 for the treatment of transfusion-dependent anemia in MDS patients with chromosome del(5q).

Table 3. — Key Clinical Findings Summarized From the MDS-003 Study

| Variable | Outcome |
|--|----------------------------------|
| Sample size | 148 |
| Karyotype * | |
| Del(5q) | 110 (74%) |
| Del(5q) + 1 or more | 37 (25%) |
| Overall erythroid response | 112 (76%) |
| Transfusion independence (TI) | 99 (67%) |
| TI frequency by karyotype complexity | |
| Isolated del(5q) | 79 (72%) |
| Del(5q) + 1 additional | 12 (48%) |
| Complex (≥ 30) | 8 (67%) |
| Median time to response | 4.6 weeks (range: 1–49 weeks) |
| Overall cytogenetic response | 62/85 (73%) |
| Complete response | 38/85 (45%) |
| Cytogenetic response by karyotype complexity | 85 |
| Del(5q) (n = 64) | 49 (77%) |
| Del(5q) + 1 (n = 15) | 10 (67%) |
| Complex karyotype (n = 6) | 3 (50%) |
| * Del(5q) was confirmed by fluorescent in situ hybridization in one patient without analyzable metaphases. | |

The MDS-002 Clinical Study

A second multicenter phase II trial, using the MDS-003 lenalidomide dose and schedule, investigated the frequency of transfusion response in lower-risk, transfusion-dependent MDS patients without the chromosome 5q31.1 deletion (MDS-002).¹⁴ Among 215 patients enrolled in the MDS-002 study, 44% of patients achieved a 50% or greater reduction in red blood cell transfusions in an ITT analysis performed March 31, 2005, and 27% of these patients achieved transfusion independence. Among 166 eligible patients with low- or intermediate-1-risk disease, 33% achieved transfusion independence by week 24, with an overall transfusion response rate of 51%. These responses were observed after a median of 4.5 weeks (range: 0.3 to 39.1 weeks). The duration of transfusion independence was not as robust as the results observed in patients with del(5q). With a median follow-up of 58 weeks, the median duration of transfusion independence was 43 weeks, with a corresponding rise in non-transfused hemoglobin of 3.3 g/dL. The results of this study indicate that lenalidomide has significant ery-

thropoietic activity in lower-risk MDS patients without deletion 5q who otherwise would not benefit from erythropoietin therapy. Moreover, the MDS-002 and MDS-003 studies complement and confirm the initial observations that the remitting activity of lenalidomide in MDS is karyotype-dependent.

Clinical Safety of Lenalidomide

In each of the three clinical studies performed to date, myelosuppression was the most common adverse event (Table 4). In the MDS-001 clinical study, moderate to severe myelosuppression was dose-dependent (25 mg, 77%; 10 mg continuous, 62%; and 10 mg × 21 days, 45%). Other adverse effects were largely mild and infrequent and included pruritus (28%), loose stools (21%), fatigue (7%), and thyroid dysfunction (5%).

As in the MDS-001 trial, neutropenia and thrombocytopenia were the most common grade 3 or greater adverse effects in the MDS-003 del(5q) study, occurring in 55% and 44% of patients, respectively, and managed by treatment interruption and dose reduction. Consistent with lenalidomide's rapid suppression of the del(5q) clone, the majority (62%) of serious neutropenic or thrombocytopenic events occurred within the first 8 weeks of treatment. For this reason, patients should be monitored with a complete blood count weekly in the first 8 weeks of lenalidomide treatment.¹⁰ In contrast, corresponding event rates on the MDS-002 non-del(5q) study were much lower, with limiting neutropenia or thrombocytopenia reported in only 24% and 19% of patients, respectively. Other adverse events in the multicenter studies were infrequent and generally of mild severity and included urticaria, diarrhea, and fatigue.

Table 5. — Recommended Lenalidomide Dose Adjustment in Patients With Treatment-Related Thrombocytopenia

| Time to Thrombocytopenia | Baseline Value | When Platelets | Recommend Course |
|--|----------------|---|--|
| Within 4 weeks of starting therapy with 10 mg daily | ≥100,000/μL | Fall to <50,000/μL Return to ≥ 50,000/μL | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg daily |
| | <100,000/μL | Fall to 50% of baseline If baseline ≥60,000/μL and returns to ≥50,000 μL If baseline <60,000/μL and returns to ≥30,000/μL | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg daily Resume lenalidomide at 5 mg daily |
| After 4 weeks of starting treatment with 10 mg daily | | <30,000/μL or <50,000/μL and platelet transfusions Return to ≥30,000/μL (without hemostatic failure) | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg daily |
| | | <30,000/μL or <50,000/μL and platelet transfusions Return to ≥30,000/μL (without hemostatic failure) | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg every other day |

Table 6. — Recommended Lenalidomide Dose Adjustment in Patients With Treatment-Related Neutropenia

| Time to Neutropenia | Baseline ANC | When Neutrophils | Recommend Course |
|--|--------------|--|---|
| Within 4 weeks of starting therapy with 10 mg daily | ≥1,000/μL | Fall to <750/μL Return to ≥1,000/μL | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg daily |
| | <1,000/μL | Fall to <500/μL Return to ≥500/μL | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg daily |
| After 4 weeks of starting treatment with 10 mg daily | | <500/μL for ≥7 days or <500/μL associated with fever (38.5°C) Return to ≥500/μL | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg daily |
| | | <500/μL for ≥7 days or <500/μL associated with fever (38.5°C) Return to ≥500/μL | Interrupt lenalidomide therapy Resume lenalidomide at 5 mg every other day |

The results of the MDS-003 study showed that thrombocytopenia was the most important variable impacting transfusion response with lenalidomide treatment owing to a significantly reduced number of consecutive days of drug treatment. This observation suggests that the duration of time on study drug is a critical variable impacting the potential for clonal suppression and consequent hematologic improvement in patients with del(5q). Although myeloid growth factors were used infrequently in the MDS-003 study, experience from the pilot study shows that neutropenia should not be limiting and can be mitigated with the introduction of growth factor support when the neutrophil count declines below a 1,000/ μ L threshold.

Specific recommendations by the US Food and Drug Administration for the management of neutropenia and thrombocytopenia during lenalidomide administration are summarized in Tables 5 and 6 and are included in the Revlimid[®] package insert.¹⁵ In the absence of growth factor support, management of myelosuppression involves withholding lenalidomide administration and reintroduction at a 5-mg dose upon appropriate neutrophil or platelet recovery.

Conclusions

Lenalidomide has unprecedented erythropoietic remitting activity in lower-risk MDS patients who either have not responded to treatment with EPO or otherwise are unlikely to benefit from cytokine therapy. Activity is greatest in patients with chromosome 5 deletion. Unlike treatment with recombinant erythropoietic stimulators, lenalidomide has dual biological effects, ie, direct cytotoxicity to and suppression of del(5q) MDS progenitors with a corresponding high frequency of cytogenetic response that is complemented by the promotion of effective erythropoiesis in non-del(5q) MDS clones. These effects translate into robust erythroid responses that restore hemoglobin production to the normal range and consequently allow termination of iron chelation with the introduction of phlebotomy therapy at a considerable cost savings. Since myelosuppression is common and consistent with the agent's mechanism of action in patients with del(5q), close clinical monitoring in the initial months of therapy is essential. Given the broad remitting activity in patients with del(5q) unrelated to karyotype complexity, it is anticipated that current randomized trials will show that lenalidomide may impact the natural history of disease in patients with greater karyotype complexity. Moreover, the EPO dependence of lenalidomide's erythropoietic-promoting activity in non-del(5q) MDS suggests that combination treatment strategies incorporating recombinant EPO may improve the rate of transfusion response.

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