ORIGINAL ARTICLE

Efficacy of Lenalidomide in Myelodysplastic Syndromes

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ABSTRACT

BACKGROUND

Ineffective erythropoiesis is the hallmark of myelodysplastic syndromes. Management of the anemia caused by ineffective erythropoiesis is difficult. In patients with myelodysplastic syndromes and symptomatic anemia, we evaluated the safety and hematologic activity of lenalidomide, a novel analogue of thalidomide.

METHODS

Forty-three patients with transfusion-dependent or symptomatic anemia received lenalidomide at doses of 25 or 10 mg per day or of 10 mg per day for 21 days of every 28-day cycle. All patients either had had no response to recombinant erythropoietin or had a high endogenous erythropoietin level with a low probability of benefit from such therapy. The response to treatment was assessed after 16 weeks.

RESULTS

Neutropenia and thrombocytopenia, the most common adverse events, with respective frequencies of 65 percent and 74 percent, necessitated the interruption of treatment or a dose reduction in 25 patients (58 percent). Other adverse events were mild and infrequent. Twenty-four patients had a response (56 percent): 20 had sustained independence from transfusion, 1 had an increase in the hemoglobin level of more than 2 g per deciliter, and 3 had more than a 50 percent reduction in the need for transfusions. The response rate was highest among patients with a clonal interstitial deletion involving chromosome 5q31.1 (83 percent, as compared with 57 percent among those with a normal karyotype and 12 percent among those with other karyotypic abnormalities; P=0.007) and patients with lower prognostic risk. Of 20 patients with karyotypic abnormalities, 11 had at least a 50 percent reduction in abnormal cells in metaphase, including 10 (50 percent) with a complete cytogenetic remission. After a median follow-up of 81 weeks, the median duration of transfusion independence had not been reached and the median hemoglobin level was 13.2 g per deciliter (range, 11.5 to 15.8).

CONCLUSIONS

Lenalidomide has hematologic activity in patients with low-risk myelodysplastic syndromes who have no response to erythropoietin or who are unlikely to benefit from conventional therapy.

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Refractory anemia resulting from ineffective hematopoiesis is the principal therapeutic challenge for patients with myelodysplastic syndromes.[1] Recombinant erythropoietin alone or in combination with myeloid growth factors ameliorates anemia in some patients but is generally ineffective in patients who require two or more red-cell transfusions per month; its use rarely induces cytogenetic remissions.[2,3]

Hematopoietic precursors in patients with myelodysplastic syndromes have an accelerated cell-cycle transition and impaired responsiveness to cytokine stimulation.[1,4] Survival signals from the microenvironment are compromised, owing in part to the presence of angiogenic molecules, disruption of the medullary architecture, and excess production of inflammatory cytokines.[5-10] Thalidomide, a multifunctional inhibitor of angiogenesis and an immune modulator, restores erythropoiesis and reduces transfusion dependence in approximately 18 percent of patients who have no response to recombinant erythropoietin.[11-14] However, long-term treatment and dose escalation are limited by the drug's sedative and neurologic effects. Lenalidomide is a novel 4-amino-glutarimide analogue of thalidomide that is more potent but does not have the neurotoxic and teratogenic effects of thalidomide.[15-17] We report the results of a safety and efficacy study of lenalidomide in patients with myelodysplastic syndromes.

METHODS

PATIENTS

Eligible patients had received a histologically confirmed diagnosis of a primary myelodysplastic syndrome according to French–American–British (FAB) criteria (Fig. 1)[18] more than three months before enrollment and a diagnosis of either symptomatic anemia (defined by a hemoglobin level of less than 10.0 g per deciliter) or transfusion-dependent anemia (defined by the need for at least 4 units of red cells within eight weeks before enrollment). Hematologic values obtained during the eight weeks preceding study treatment served as a reference for the assessment of response. Patients either had had no response to treatment with recombinant erythropoietin or had an endogenous serum level of more than 500 mU per milliliter. Patients with severe neutropenia (defined by an absolute neutrophil count of less than 500 per cubic millimeter), severe thrombocytopenia (defined by a platelet count of less than 10,000 per cubic millimeter), treatment-related myelodysplastic syndromes, or clinically significant coexisting medical illnesses were excluded.

STUDY DESIGN

This open-label, single-center trial evaluated the safety and efficacy of lenalidomide in patients with myelodysplastic syndromes who had symptomatic anemia. All patients gave written informed consent, and the study was approved by the institutional review board of the University of Arizona. The principal investigator designed and conducted the study, analyzed the data, and wrote the article in consultation with Celgene. Lenalidomide (Revlimid) was supplied by Celgene as 5-mg or 25-mg capsules. Three oral dosing schedules were sequentially evaluated: 25 mg daily, 10 mg daily, and 10 mg daily for 21 days of every 28-day cycle. Treatment was interrupted in the event of adverse events of grade 3 or higher according to the Common Toxicity Criteria of the National Cancer Institute and resumed at the next lower dose after the resolution of these effects.[19] Sequential dose reductions were as follows: 10 mg per day, 10 mg per day for 21 days, 5 mg per day for 21 days, and 5 mg every other day.

Complete blood counts were obtained every two weeks, with the response to treatment and adverse events assessed every four weeks. Bone marrow aspiration, biopsy, and cytogenetic analysis were repeated every eight weeks. The final response was assessed after 16 weeks of therapy. Patients with a response continued taking lenalidomide until disease progression, treatment failure, or dose-limiting adverse events occurred. Patients with hematologic improvement that did not qualify as a protocol-defined response after 16 weeks could receive 8 additional weeks of treatment before the final assessment of response, whereas patients without a response who had been following the 21-day treatment schedule were offered continual dosing. Red-cell transfusions were administered according to prestudy clinical indicators with the following guidelines: 2 units were given to patients with a hematocrit of less than 25 percent, 3 units to those with a hematocrit of less than 21 percent, and 4 units to those with a hematocrit of less than 18 percent. Myeloid growth factors for the management of an exacerbation of neutropenia were the only cytokines permitted.

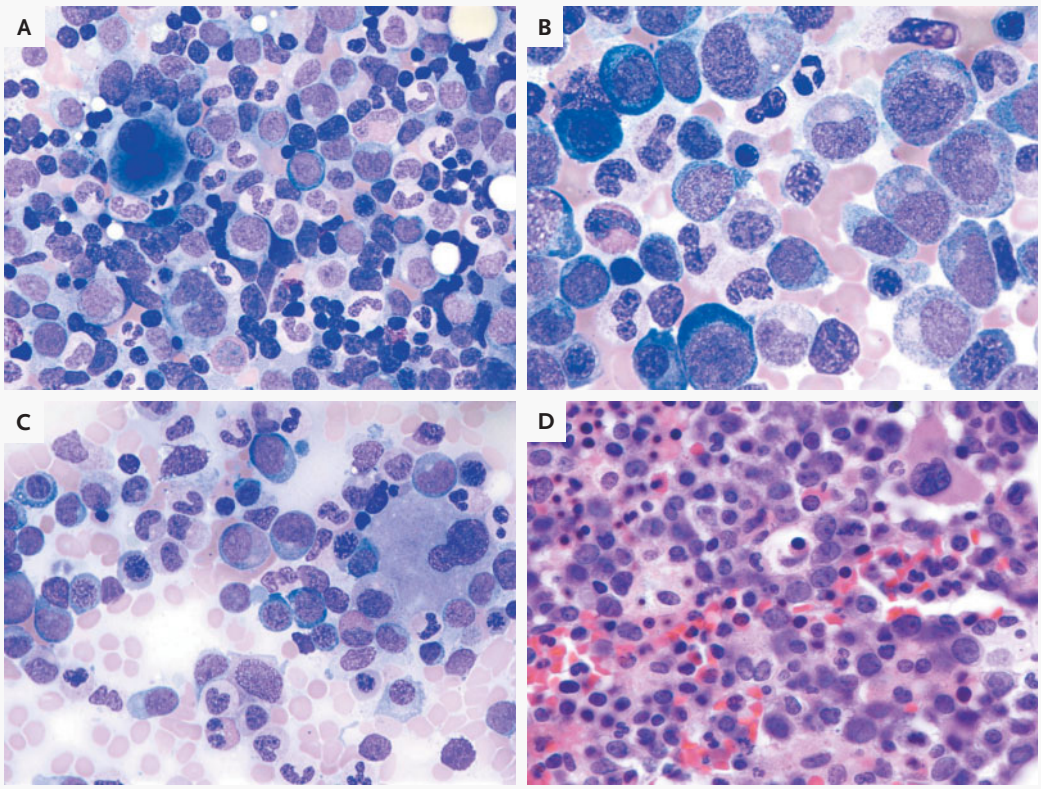

Figure 1. Characteristics of Myelodysplastic Syndromes.

The bone marrow aspirate in patients with myelodysplasia is hypercellular, reflecting trilineal dysplasia (Panel A; Wright–Giemsa stain). In this specimen, hypolobated megakaryocytes and hyposegmented neutrophils are prominent. Myeloid maturation is shifted to the left, and myeloblasts may be increased, as shown in Panel B in a patient with refractory anemia with excess blasts (Wright–Giemsa stain). Dyserythropoiesis accompanies the hypolobated megakaryocytes and hyposegmented neutrophils. There may be a left-sided shift in erythroid maturation, nuclear budding, megaloblastic changes, and as shown in Panel C, a decrease in the number of erythroid precursors (Wright–Giemsa stain). The cellularity of a core-biopsy specimen can approach 100 percent, with readily apparent dysplasia (Panel D; hematoxylin and eosin). (Provided by Lynn Moscinski, M.D., H. Lee Moffitt Cancer Center and Research Institute, Tampa, Fla.)

ASSESSMENT OF RESPONSE AND ADVERSE EVENTS

The hematologic response was assessed according to the modified criteria of the International Working Group, with the requirement that an improvement had to be sustained for at least eight consecutive weeks.[20] A major erythroid response was defined as freedom from the need for transfusion or an increase in the hemoglobin level of more than 2 g per deciliter in patients with transfusion-independent anemia. A minor response was defined as at least a 50 percent reduction in transfusions or a sustained elevation in the hemoglobin level of 1 to 2 g per deciliter. A major cytogenetic response was defined by the absence of the pretreatment cytogenetic abnormality on standard metaphase analysis (e.g., at least 20 cells in metaphase), and a minor response by a reduction in the number of abnormal cells in metaphase of at least 50 percent. Cytogenetic progression was defined as the sustained acquisition of a new chromosomal abnormality.

Responses were compared by means of the International Prognostic Scoring System (IPSS), which assesses the percentage of blasts in bone marrow, the karyotype, and the number of cytopenias.[21] Blinded review of bone marrow specimens was performed by two investigators. Immunohistochemical staining of biopsy specimens and clot sections used monoclonal antibodies against IgG2a (Ventana Medical Systems) recognizing CD3 (PSI clone) and CD20 (L26 clone) antigens. Cytologic dysplasia was graded with the use of a 10 percent threshold. Adverse events were graded with the use of the

Common Toxicity Criteria of the National Cancer Institute.[19]

STATISTICAL ANALYSIS

The duration of transfusion independence was calculated from the date of the last red-cell transfusion to the resumption of transfusion through April 1, 2004, according to the method of Kaplan and Meier.[22] The duration of major responses in transfusion-independent patients was recorded from the initial date of the sustained elevation in hemoglobin levels of more than 2 g per deciliter. The analyses of adverse events and response were carried out according to the intention-to-treat principle. Univariate comparisons were performed with the use of Fisher's exact test, a two-sample independent t-test, or a Wilcoxon rank-sum test. The duration of transfusion independence was compared among the groups by means of the log-rank test. All reported P values are two-sided. Data are reported as medians ±SD.

RESULTS

From March 2002 to August 2003, 55 candidates were screened and 43 were enrolled. Thirty-three patients (77 percent) had refractory anemia or refractory anemia with ringed sideroblasts, and 38 (88 percent) had IPSS risk scores of low or intermediate 1 (Table 1). Overall, 74 percent were transfusion-dependent, 33 (77 percent) had had no response to treatment with erythropoietin, and 13 (30 percent) had had no response to treatment with thalidomide. None had received cytotoxic therapy. The median number of prior nontransfusion treatments was 1.7 (range, 0 to 5). Moderate-to-severe neutropenia was present in 28 percent of patients, and moderate-to-severe thrombocytopenia in 23 percent of patients; 37 percent had at least two cytopenias. Twenty patients (46 percent) had clonal karyotypic abnormalities (defined by the presence of at least two abnormal cells in metaphase), including interstitial deletions of chromosome 5q31.1 alone (11 patients) or in association with trisomy 21 (1), an interstitial deletion of chromosome 20q11.2 (2), a complex karyotype (1), and other abnormalities (5).

ADVERSE EVENTS

Neutropenia and thrombocytopenia were the most common adverse events (Table 2). Severe myelosuppression (grade 3 or higher) was dose-depen-

Table 1. Clinical and Hematologic Characteristics of the 43 Patients.*

Characteristic	Value
Age — yr	
Median	72
Range	28–85
Sex — no. (%)	
Male	25 (58)
Female	18 (42)
FAB class — no. (%)	
Refractory anemia	20 (47)
Refractory anemia with ringed sideroblasts	13 (30)
Refractory anemia with excess blasts	8 (19)
Refractory anemia with excess blasts in transformation	1 (2)
Chronic myelomonocytic leukemia	1 (2)
IPSS risk category — no. (%)	
Low	22 (51)
Intermediate 1	16 (37)
Intermediate 2	4 (9)
High	1 (2)
Transfusion dependence	
No. (%)	32 (74)
Median no. of red-cell units transfused/mo	3
Range	2–6
Pretransfusion hemoglobin level — g/dl	
Transfusion-dependent patients	
Median	8.0
Range	6.7–8.6
Other	
Median	8.3
Range	7.0–8.5
Duration of disease — mo	
Median	29
Range	3–169
Neutropenia — no. (%)†	12 (28)
Thrombocytopenia — no. (%)‡	10 (23)
Karyotype — no. (%)	
Normal	23 (53)
Abnormal	20 (47)

* FAB denotes French–American–British, and IPSS International Prognostic Scoring System.
† Neutropenia was defined by an absolute neutrophil count of less than 1500 per cubic millimeter.
‡ Thrombocytopenia was defined by a platelet count of less than 100,000 per cubic millimeter.

Table 2. Treatment-Associated Adverse Events.

Adverse Event	Lenalidomide, 25 mg/day (N=13)		Lenalidomide, 10 mg/day (N=13)		Lenalidomide, 10 mg/day for 21 days (N=17)		All Patients, Any Grade (N=43)
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	
	number of patients (percent)						
Neutropenia	0	10	0	8	0	10	28 (65)
Thrombocytopenia	2	7	4	7	3	9	32 (74)
Pruritus	5	0	4	0	3	0	12 (28)
Diarrhea	0	0	2	1	6	0	9 (21)
Urticaria	0	0	4	0	2	0	6 (14)
Fatigue	0	1	1	1	0	0	3 (7)
Bone pain	1	0	1	0	2	0	4 (9)
Pneumonia	0	1	0	2	0	0	3 (7)
Edema	0	0	0	0	2	0	2 (5)
Hypothyroidism	0	0	2	0	0	0	2 (5)
Hypogonadism	1	0	1	0	0	0	2 (5)
Myalgias	1	0	0	0	0	0	1 (2)
Autoimmune hemolytic anemia	1	0	0	0	0	0	1 (2)

dent and necessitated treatment interruption or dose reduction in 25 patients (58 percent). Treatment was interrupted because of myelosuppression in 77 percent of patients in the 25-mg group after a median of 4.6 weeks (range, 3 to 9), as compared with 62 percent of those who were receiving 10 mg daily (median, 8.5 weeks; range, 2 to 20) and 47 percent of those who were receiving 10 mg daily for 21 days (median, 6 weeks; range, 1 to 11) ($P=0.62$). The median interval between the first interruption of treatment and the resumption of treatment was 22 days in each cohort (range, 9 to 55).

At week 8, marrow cellularity was reduced by 75 percent among patients who were receiving 25 mg of lenalidomide per day, as compared with a reduction of 12 percent in both 10-mg cohorts. Pneumonia developed in three patients, one of whom had worsening of preexisting neutropenia. One patient was removed from the study on day 5 because of autoimmune hemolytic anemia with escalating transfusion requirements that preceded enrollment in the study. There were three deaths, none of which were thought to be treatment-related: one was due to cholecystitis with rupture (day 8), one to splenic infarct in a patient with massive splenomegaly (day 5) and a history of such events, and one to pneumonia without neutropenia (week 20). All other adverse events were either minor or of moderate severity.

Pruritus, generally self-limited and restricted to the scalp, was reported by 28 percent of patients during the first week of treatment. Isolated and transient urticaria was reported by 14 percent of patients, whereas a systemic rash with an urticarial component developed in one patient and resolved after treatment was interrupted. Diarrhea occurred in 21 percent of patients after prolonged treatment (more than three months) but was manageable with the use of either medication for diarrhea or the interruption of treatment with lenalidomide. Four patients required hormone replacement — two for hypothyroidism, and two for gonadal dysfunction. Seven patients discontinued lenalidomide prematurely (before 28 days) because of withdrawal of consent by three patients, autoimmune hemolytic anemia in one, early myelosuppression in one, and early death in two.

HEMATOLOGIC RESPONSE

Twenty-four patients (56 percent) had a response (Table 3); 20 of 32 transfusion-dependent patients (63 percent) achieved independence from transfusion. Of 11 patients who required no transfusions, 1 had an increase in the hemoglobin level of more

Table 3. Erythroid Responses.

Lenalidomide Dose	No. of Patients	Erythroid Response			Weeks to Response	
		Major	Minor	Total	Median ±SD	Range
		number (percent)				
25 mg/day	13	6	0	6 (46)	9.0±5.8	2.5–18.5
10 mg/day	13	6	1	7 (54)	10.5±6.4	2–17.5
10 mg/day for 21 days	17	9	2	11 (65)	11.5±10.3	6–24
Total	43	21 (49)	3 (7)	24 (56)	—	—

Table 4. Relation between Clinical and Biologic Features and Erythroid Response.*

Variable	No. of Patients	Erythroid Response	P Value†
		no. (%)	
Sex			0.35
Male	25	12 (48)	
Female	18	12 (67)	
Race‡			0.68
White	37	20 (54)	
Other	6	4 (67)	
Prior recombinant erythropoietin			0.15
Yes	33	16 (48)	
No	10	8 (80)	
Prior thalidomide			0.51
Yes	13	6 (46)	
No	30	18 (60)	
FAB class			0.07
Refractory anemia	20	15 (75)	
Refractory anemia with ringed sideroblasts	13	6 (46)	
Refractory anemia with excess blasts, with or without transformation	9	3 (33)	
Chronic myelomonocytic leukemia	1	0	
IPSS risk category			0.14
Low	22	15 (68)	
Intermediate 1	16	8 (50)	
Intermediate 2 or high	5	1 (20)	
Karyotype			0.007
Del(5)(q31.1)	12	10 (83)	
Normal	23	13 (57)	
Other	8	1 (12)	
≥ Grade 3 myelosuppression			1.0
Yes	25	14 (56)	
No	18	10 (56)	

* FAB denotes French–American–British, and IPSS International Prognostic Scoring System.
† Fisher's exact test was used for univariate comparisons.
‡ Race was determined from patient registration forms.

than 2 g per deciliter. The median time to a response increased from 9 weeks in the 25-mg cohort to 11.5 weeks in the cohort given 10 mg per day for 21 days. Patients with a major response reached a median hemoglobin level of 13.2±1.4 g per deciliter (range, 11.5 to 15.8), with a corresponding median increase in hemoglobin from baseline of 5.3 g per deciliter (range, 4.4 to 8.7). After a median follow-up of 81 weeks (range, 42 to 110), the median duration of the major response had not been reached (more than 48 weeks; range, more than 13 to more than 101). Among the 21 patients with a major response, anemia recurred in 4, with the resumption of transfusions after intervals of 12, 19, 56, and 74 weeks. In one of these patients, treatment failure was associated with karyotypic evolution and subsequent progression to leukemia.

Of 10 patients with moderate-to-severe thrombocytopenia, 1 had a sustained improvement in the platelet count (i.e., an increase of more than 30,000 per cubic millimeter). Of the 12 patients with neutropenia, 2 had a sustained increase in the neutrophil count of more than 500 per cubic millimeter.

CYTOGENETIC FINDINGS

The cytogenetic pattern correlated significantly with the hematologic response: 83 percent of patients with a deletion of 5q31.1 had a response, as compared with 57 percent of those with a normal karyotype and 12 percent of those with other cytogenetic abnormalities (P=0.007) (Table 4). The FAB category had no significant correlation with response (P=0.07), nor did the IPSS risk category, age, duration of disease, or number of prior treatments (Table 4). The median time to a response was more rapid in patients with a deletion of 5q31.1 (8.0±4.4 weeks; range, 2.5 to 16.0) than in patients with a normal karyotype or other karyotypic abnormalities (11.2±6.7 weeks; range, 2.0 to 26.0; P=0.029).

Among 20 patients with clonal cytogenetic abnormalities, 11 had cytogenetic responses, including 10 with a complete cytogenetic remission (Table 5). Of these 10 patients, 9 had del(5)(q31.1) and 1 had t(1;22)(q21p11.2). All cytogenetic responses occurred in patients who also had a hematologic response. Overall, 10 of 12 patients (83 percent) with a 5q31.1 deletion had a cytogenetic response. Fluorescence in situ hybridization with the use of the 5q31 (EGR1X2)-specific probe (Vysis) confirmed the absence of the 5q31.1 deletion among 200 cells in interphase in each of five patients who

had a complete response and who were evaluated by means of standard metaphase analysis.

The median time to a cytogenetic response was 8 weeks (range, 8 to 24). Of 10 patients with a 5q31.1 deletion, 9 had a cytogenetic response after 8 weeks, whereas 1 patient had a response at 16 weeks. Four patients had transient emergence of karyotypically unrelated clones, including trisomy 8 (in two), a reciprocal translocation [t(12;16)(p13;p13.3)], and monosomy 7. Sustained acquisition of karyotypically discordant clones occurred in four patients: three patients with remitting disease and a 5q31.1 deletion had translocations involving the long arm of chromosome 7 [t(7;11)(q22;q12), t(7;8)(q22;p21), and t(7;21)(q31q11.1)] and one patient with a normal karyotype before treatment had deletion 20 (q21q13.1). Only one of these four patients had an exacerbation of anemia coincident with the appearance of the new abnormality and subsequent evolution to acute leukemia. All others remained free of the need for transfusion.

Table 5. Cytogenetic Responses According to Chromosomal Abnormality.

Chromosomal Abnormality	No. of Patients	≥50% Decrease in Abnormal Cells in Metaphase	Complete Cytogenetic Response
		number of patients (percent)	
Del(5)(q31.1)	12	10 (83)	9 (75)
Isolated	11	9	8
With trisomy 21	1	1	1
Del(20)(q11.2)	2	0	0
t(1;22)(q21p11.2)	1	1	1
Other*	5	0	0
Total	20	11 (55)	10 (50)

* Other chromosomal abnormalities were as follows: +19, t(3;3)(q21;q26.3), +8, –X, and complex.

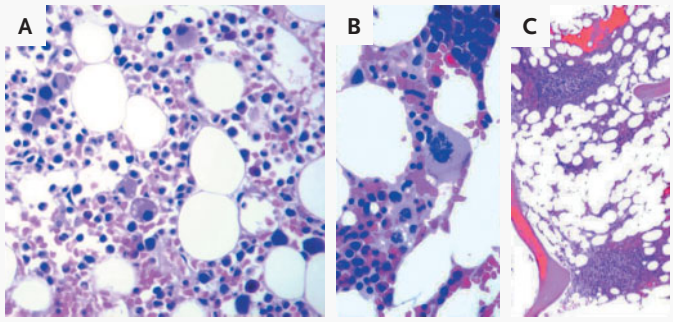

Figure 2. Morphologic Changes in a Bone Marrow Specimen from a Patient with a 5q31.1 Deletion.

Numerous small, mononuclear megakaryocytes are readily identified in the bone marrow specimen obtained by trephine biopsy before treatment (Panel A, hematoxylin and eosin). After 16 weeks of lenalidomide therapy, megakaryocytes appear normal in size and have multiple nuclei (Panel B, hematoxylin and eosin), and multiple aggregates of benign-appearing lymphocytes are apparent (Panel C, hematoxylin and eosin).

PATHOLOGICAL RESPONSES AND MORPHOLOGIC FINDINGS

Among six patients with excess myeloblasts (at least 5 percent; range, 6 to 21 percent) who could be evaluated, three had more than a 50 percent reduction in blasts, with a return to the normal range. The percentage of ringed sideroblasts was reduced from 36 percent to 11 percent in 1 of 10 patients with refractory anemia with ringed sideroblasts who could be evaluated. All reductions in myeloblasts and sideroblasts occurred in patients with a hematologic response. Only one patient with refractory anemia with ringed sideroblasts had an increase in blasts during lenalidomide treatment, and this patient was removed from the study after 16 weeks.

Serial marrow preparations from 28 patients were suitable for a detailed assessment of dysplasia and architecture. The morphologic characteristics of megakaryocytes became normal after treatment with lenalidomide in 14 of 22 patients (64 percent) with pretreatment dysplasia, including 12 patients with a response; 10 of these 12 patients had a 5q31.1 deletion (Fig. 2). Lymphoid aggregates, often multiple and not paratrabecular, were detected in 10 of 28 patients (36 percent) after lenalidomide treatment (including 5 patients with a 5q31.1 deletion) and corresponded with a hematologic response in 7. Lymphoid aggregates were composed of polytypic B cells and T cells. Dysplastic erythroid elements and myeloid elements were common (present in 22 and 11 patients, respectively), whereas resolution of cytologic atypia was infrequent (occurring in 2) and unrelated to hematologic response. Reticulin fibrosis resolved after lenalidomide treatment in one of two patients with extensive fiber deposition in the pretreatment trephine-biopsy specimen, concordant with a hematologic response. Marrow or peripheral-blood eosinophilia or both (7.5 percent to 14 percent) developed in three patients, including two with a hematologic response.

DISCUSSION

In this study, lenalidomide had substantial activity in patients with myelodysplastic syndromes who had had no response to treatment with erythropoietin or who had high endogenous erythropoietin levels and therefore a low probability of benefit from erythropoietin treatment. Overall, 56 percent of patients had a response, with most having sustained independence from the need for transfusion and restoration of hemoglobin to levels within or near the normal range. Cytogenetic remissions, which occur rarely with erythropoietin therapy, were observed in 55 percent of patients. The high rate of complete cytogenetic response in patients with a 5q31.1 deletion (75 percent), which was confirmed by more sensitive fluorescence in situ hybridization probes, indicates that this subtype of myelodysplastic syndrome is especially sensitive to lenalidomide treatment. Indeed, the time to response was more rapid in patients with the 5q31.1 deletion, and response was associated with the disappearance of dysplastic megakaryocytes, the morphologic hallmark of the 5q– syndrome.[23] These findings suggest that lenalidomide restores red-cell production in part by eliminating ineffective myelodysplastic clones but does not extinguish the myelodysplastic syndrome–initiating stem cell.

The persistence of ringed sideroblasts in patients with refractory anemia with ringed sideroblasts who had a response, however, indicates that clonal suppression is selective and complemented by the restoration of erythropoiesis in susceptible myelodysplastic syndrome progenitors. This notion is supported by the transient emergence of karyotypically distinct and unrelated clones, which mirrors the experience reported with imatinib treatment in patients with chronic myeloid leukemia.[24,25] In addition, three patients with a 5q31.1 deletion acquired new translocations involving chromosome 7 despite the complete suppression of the initial karyotypic abnormality. Despite its unfavorable prognostic implication in primary myelodysplastic syndromes, the clinical significance of the acquired translocations is unclear. Only one of these patients had cytogenetic and disease progression, whereas the others had a sustained hematologic response. Further observation is necessary before the clinical significance of these findings can be determined.

Several effects of lenalidomide may contribute to its activity in myelodysplastic syndromes. It suppresses the production of tumor necrosis factor α (TNF-α), but selective antagonists of TNF-α have minimal clinical activity in myelodysplastic syndromes.[26-28] Lenalidomide affects a broad range of ligand-induced responses that may be integral to its activity in myelodysplastic syndromes, including angiogenesis, inflammation, cell adhesion, and the immune response. Indeed, vascular endothelial growth factor (VEGF) is an autocrine growth factor elaborated by myeloid precursors in myelodysplastic syndromes that contributes to their self-renewal while exacerbating ineffective erythropoiesis in erythroid progenitors, which lack VEGF receptors.[9,29] Lenalidomide enhances cell-mediated immunity by potentiating the production of interleukin-2 and interferon-γ and increasing the responses of cytolytic T cells and natural killer cells in experiments in animals.[15,16] Of particular interest in our study was the appearance of multiple lymphoid aggregates composed of a mixture of B cells and T cells in the trephine-biopsy specimens from patients with a response. Whether this finding represents an immune response against the ineffective clone is unknown. Furthermore, lenalidomide sensitizes erythroid progenitors to the trophic effects of recombinant erythropoietin (unpublished data).

The promising activity of lenalidomide in myelodysplastic syndromes must be balanced against its potential to cause clinically significant myelosuppression, which necessitates close laboratory monitoring during the initial weeks of treatment. Neutropenia or thrombocytopenia developed in more than half the patients and was not limited to patients with preexisting lineage deficits. The extent of myelosuppression varied according to the dose and cumulative exposure to lenalidomide and was reversed by the interruption of treatment or a reduction in the dose. Although early exacerbation of cytopenias may be expected with an agent that selectively suppresses myelodysplastic clones that dominate steady-state hematopoiesis, many patients did not have myelosuppression despite prolonged lenalidomide treatment. A reduction in marrow cellularity coincided with myelosuppression in patients treated with 25 mg daily, indicating that lenalidomide suppresses myelopoiesis at higher doses. At lower doses, however, this effect was not apparent. Other adverse events were uncommon and generally mild in severity. Hypothyroidism or gonadal dysfunction developed in four patients, raising the possibility that the action of lenalidomide on ligand-induced responses may extend to hypophyseal hormones.

We conclude that lenalidomide has substantial activity in patients with low-risk myelodysplastic syndromes who would otherwise not benefit from growth-factor therapy. Ongoing phase 2, multicenter trials will estimate the clinical benefits of lenalidomide in a larger number of patients.

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