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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N Engl J Med 2005;352:549-57.

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, 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.

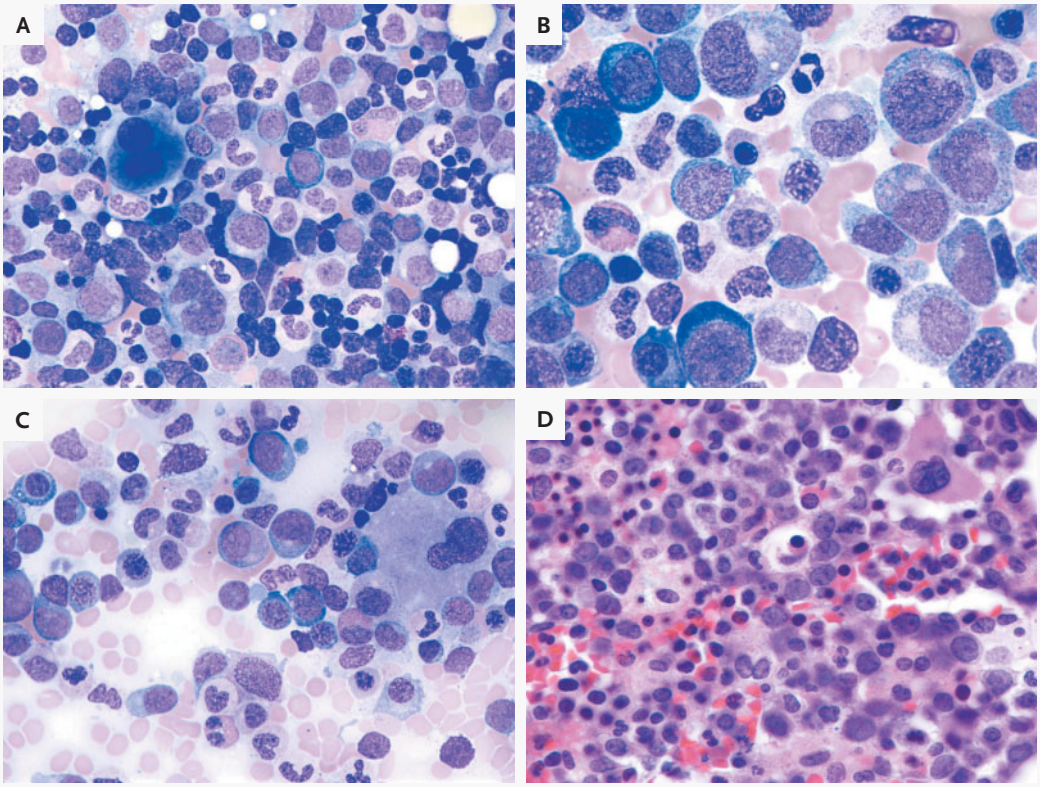

Figure 1. Characteristics of Myelodysplastic Syndromes.

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						*no. of patients (%)*
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

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