ORIGINAL ARTICLE

Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

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ABSTRACT

BACKGROUND

Severe, often refractory anemia is characteristic of the myelodysplastic syndrome associated with chromosome 5q31 deletion. We investigated whether lenalidomide (CC5013) could reduce the transfusion requirement and suppress the abnormal 5q31– clone in patients with this disorder.

METHODS

One hundred forty-eight patients received 10 mg of lenalidomide for 21 days every 4 weeks or daily. Hematologic, bone marrow, and cytogenetic changes were assessed after 24 weeks of treatment by an intention-to-treat analysis.

RESULTS

Among the 148 patients, 112 had a reduced need for transfusions (76%; 95% confidence interval [CI], 68 to 82) and 99 patients (67%; 95% CI, 59 to 74) no longer required transfusions, regardless of the karyotype complexity. The response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1 to 49) and sustained; the median duration of transfusion independence had not been reached after a median of 104 weeks of follow-up. The maximum hemoglobin concentration reached a median of 13.4 g per deciliter (range, 9.2 to 18.6), with a corresponding median rise of 5.4 g per deciliter (range, 1.1 to 11.4), as compared with the baseline nadir value before transfusion. Among 85 patients who could be evaluated, 62 had cytogenetic improvement, and 38 of the 62 had a complete cytogenetic remission. There was complete resolution of cytologic abnormalities in 38 of 106 patients whose serial bone marrow samples could be evaluated. Moderate-to-severe neutropenia (in 55% of patients) and thrombocytopenia (in 44%) were the most common reasons for interrupting treatment or adjusting the dose of lenalidomide.

CONCLUSIONS

Lenalidomide can reduce transfusion requirements and reverse cytologic and cytogenetic abnormalities in patients who have the myelodysplastic syndrome with the 5q31 deletion. (ClinicalTrials.gov number, NCT00065156.)

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Interstitial deletions involving the long arm of chromosome 5 are among the most common cytogenetic abnormalities identified in patients with the myelodysplastic syndrome, with frequencies ranging from 16 to 28%.[1,2] Although the size of the interstitial deletions varies, deletion mapping has shown that the common deleted region involves a 1.5-Mb segment extending from bands 5q31 to 5q32.[3] A tumor-suppressor gene is postulated to reside in this region, but no specific gene with pathogenetic relevance has been identified. Patients with the 5q deletion have distinct clinical and pathological features that include a hypoproliferative anemia and dysplastic megakaryocytes in the bone marrow. Endogenous erythropoietin production is generally elevated, and most patients become dependent on red-cell transfusions.[1]

The World Health Organization recognizes a distinct syndrome associated with the 5q deletion that was first described by Van den Berghe and colleagues in 1974.[4,5] In patients with this syndrome, a minor subgroup of patients with the 5q deletion, there is an isolated 5q31 deletion accompanied by severe hypoplastic anemia, a normal or elevated platelet count, atypical marrow megakaryocytes with less than 5% myeloblasts in the bone marrow, and a relatively indolent clinical course.

In a preliminary study of lenalidomide (CC-5013, Revlimid; Celgene) involving patients with the myelodysplastic syndrome who did not have a response to treatment with recombinant erythropoietin, 10 of 12 patients with the 5q deletion no longer needed red-cell transfusions and had a complete or partial cytogenetic response, whereas only 14 of 31 patients with other karyotypes no longer required transfusion, and few of them had a cytogenetic response.[6] We performed a multicenter international study to determine the frequency of erythroid and cytogenetic responses to lenalidomide therapy in transfusion-dependent patients with the myelodysplastic syndrome and the 5q31 deletion.

METHODS

PATIENTS

Eligible patients had a confirmed histologic diagnosis of primary myelodysplastic syndrome according to French–American–British (FAB) criteria; a chromosome 5q31 deletion that was either isolated or accompanied by additional cytogenetic abnormalities; a disease of low or intermediate-1 risk, according to the International Prognostic Scoring System (IPSS); and transfusion-dependent anemia, defined as anemia requiring a transfusion of at least 2 units of red cells within the 8 weeks before enrollment.[7,8] Transfusion frequency and pretransfusion hemoglobin values within the 8 weeks preceding study treatment served as the reference values for assessment of the response. Patients were excluded if they had severe neutropenia (defined as fewer than 500 polymorphonuclear neutrophils per cubic millimeter), severe thrombocytopenia (defined as fewer than 50,000 platelets per cubic millimeter), proliferative chronic myelomonocytic leukemia (defined as more than 12,000 leukocytes per cubic millimeter), treatment-related myelodysplastic syndrome, known hypersensitivity to thalidomide, or clinically significant coexisting illnesses.

STUDY DESIGN

All patients gave written informed consent before enrollment. The trial was designed, monitored, and analyzed by the principal investigator along with the cytogenetic and pathology reviewers in consultation with Celgene Corporation. The manuscript was written by Dr. List, and editorial revisions were made by the coauthors, without limitations from the sponsor. The principal investigator and coauthors had unrestricted access to trial data collected by the sponsor for outcome and safety analyses. Dr. List vouches for the accuracy and completeness of the data.

Lenalidomide was supplied in 5-mg capsules and was initially administered at a daily dose of 10 mg for 21 days of every 28-day cycle. The study was initiated on July 21, 2003, and the treatment schedule was subsequently amended so that the 10-mg dose was given every day because of the shorter interval between initiation of treatment and a response in the pilot study. Treatment was interrupted for adverse effects of grade 3 or more and resumed at a dose of 5 mg per day or 5 mg every other day, according to tolerance, after the adverse effects had been resolved. Complete blood counts were obtained weekly during the first 8 weeks and every 2 weeks thereafter. Bone marrow aspiration, biopsy, and cytogenetic examination were repeated after 24 weeks of treatment.

Patients with a response continued to receive treatment with lenalidomide until disease progression, treatment failure, or treatment-limiting adverse effects occurred. Transfusions were administered according to the following guidelines, which were determined before the initiation of the study: 2 units for patients with a hematocrit of 24 to 21%, 3 units for patients with a hematocrit of 20 to 18%, and 4 units for patients with a hematocrit of less than 18%. Myeloid growth factors were the only cytokines permitted for the management of neutropenia.

ASSESSMENT OF RESPONSE AND TOXICITY

The primary end point of the study was the proportion of patients who no longer needed transfusions (hematologic response). The secondary end points were the duration of transfusion independence; the frequency of minor erythroid, cytogenetic, and pathological responses; and the safety of lenalidomide. Hematologic response was assessed according to modified criteria of an international working group, which defined a response as a sustained improvement for at least 8 consecutive weeks.[9] Transfusion independence was defined as a period of at least 56 consecutive days during which no transfusions were given and the hemoglobin concentration rose by at least 1 g per deciliter. A minor response was defined as a reduction of at least 50% in the number of transfusions as compared with baseline requirements. The rise in the hemoglobin concentration in patients who no longer required transfusions was calculated as the difference between the maximum hemoglobin concentration and the minimum pretransfusion value during the 8 weeks before enrollment in the study.

Classification of the cytogenetic response was determined by standard metaphase analysis before and after treatment in patients with at least 20 cells in metaphase that could be evaluated in sequential specimens. Deletion of a Y chromosome in men was not considered abnormal. A complete cytogenetic remission was defined as the absence of cells in metaphase containing any abnormal clone. A partial cytogenetic response was defined as a reduction of at least 50% in the proportion of abnormal cells in metaphase after treatment. Patients with cytogenetic results based on the examination of less than 20 cells in metaphase before or after treatment could not be evaluated for a cytogenetic response. Cytogenetic progression was defined by the appearance of a new clonal chromosomal abnormality.

Initial study eligibility was determined according to the pathological and cytogenetic assessment of the local institution. Before treatment and at week 24, bone marrow was examined pathologically for assignment of a FAB category, and karyotypes were reviewed to identify a cytogenetic pattern. Adverse events were graded according to the Common Toxicity Criteria of the National Cancer Institute, version 2.0.[10]

STATISTICAL ANALYSIS

A one-stage, response-focused trial design required 30 patients; however, the target enrollment was extended to more than 90 patients in order to provide sufficient safety data and improve the precision of response estimates. Extension of the total enrollment to 148 patients was permitted after interim analysis by the data and safety monitoring committee showed favorable efficacy and safety results. All analyses of response and adverse effects include the 148 registered patients, regardless of final eligibility, and reflect data collected from visits through July 15, 2005.

The time to the beginning of transfusion independence was defined as the number of days from the initiation of study treatment to the day after the date of the last transfusion preceding the first 8-week response period. The duration of transfusion independence was calculated as the period from the day after the date of the last transfusion until 1 day before the date of the next transfusion. The duration of survival according to karyotype complexity was calculated as the period from the date of diagnosis of the myelodysplastic syndrome until death. The median survival adjusted for time under study observation and the duration of transfusion independence were estimated by the Kaplan–Meier method.[11] The homogeneity of survival curves according to stratification variables was tested by the Cox proportional-hazards model. Univariate comparisons were performed with the use of Fisher's exact test, a two-sample independent t-test, or a Wilcoxon rank-sum test. All reported P values are two-sided. Summary statistics (number of patients, standard deviation, median, and minimum and maximum values) are reported as appropriate. Multivariate analysis of response variables was performed with

logistic-regression techniques. The estimated frequencies of efficacy end points are reported with exact 95% confidence intervals (CIs).

RESULTS

Between July 21, 2003, and May 21, 2004, 148 patients were enrolled and received lenalidomide. Of these 148 patients, 46 were treated on the 21-day schedule and 102 received continuous daily dosing. Ninety-five patients (64%) had either refractory anemia or refractory anemia with ringed sideroblasts, and 120 (81%) were at low or intermediate-1 risk according to the IPSS scores (Table 1). In 20 patients, the IPSS category could not be assigned because the bone marrow specimen was inadequate to confirm the FAB category, the diagnosis was other than the myelodysplastic syndrome, or there were not enough cells in metaphase to permit estimation of karyotype complexity. The median number of units of red cells transfused in the 8 weeks before a patient entered the study was 6 (range, 0 to 18), with 105 patients (71%) receiving 4 or more units. One hundred eight patients (73%) had received prior erythropoietin treatment, 58 (39%) had received cytotoxic chemotherapy, and 55 (37%) were receiving iron-chelation therapy. Forty-four patients (30%) had moderate-to-severe neutropenia, and 28 patients (19%) had thrombocytopenia. All patients had a chromosome 5q31 deletion identified by either standard metaphase analysis (147 patients) or fluorescence in situ hybridization (1 patient) (see Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). An isolated 5q deletion was found in 110 patients (74%), whereas only 40 patients (27%) met the criteria for the diagnosis of the 5q− syndrome. Thirty-seven patients (25%) had one or more cytogenetic abnormalities in addition to del(5q).

Table 1. Clinical and Hematologic Characteristics of the 148 Patients.

Characteristic	Value
Age — yr	
Median	71
Range	37–95
Sex — no. (%)	
Male	51 (34)
Female	97 (66)
Duration of the myelodysplastic syndrome — yr	
Median	2.5
Range	0.1–20.7
Red cells transfused in previous 8 wk — units	
Median	6
Range	0–18
≥2 Units of red cells transfused/mo — no. (%)	105 (71)
IPSS risk category — no. (%)	
Low	55 (37)
Intermediate 1	65 (44)
Intermediate 2 or high	8 (5)
Unclassified	20 (14)
FAB type — no. (%)	
Refractory anemia	77 (52)
Refractory anemia with ringed sideroblasts	18 (12)
Refractory anemia with excess blasts	30 (20)
Chronic myelomonocytic leukemia	3 (2)
Acute myeloid leukemia	1 (1)
Atypical chronic myeloid leukemia	3 (2)
Inadequate specimen	16 (11)
Neutropenia — no. (%)*	44 (30)
Thrombocytopenia — no. (%)†	28 (19)

* Neutropenia was defined as fewer than 1500 polymorphonuclear neutrophils per cubic millimeter.
† Thrombocytopenia was defined as fewer than 100,000 platelets per cubic millimeter.

HEMATOLOGIC RESPONSE

Of the 148 patients who received lenalidomide, 112 (76%) had a response to the treatment (Table 2). Among these 148 patients, 99 (67%) no longer needed transfusions by week 24; the remaining 13 patients had a reduction of 50% or greater in the number of transfusions required. There was no significant difference in response rate between the two treatment schedules (P=0.26). The median time to transfusion independence was 4.6 weeks (range, 1 to 49). The median peak hemoglobin concentration among transfusion-independent patients was 13.4 g per deciliter (range, 9.2 to 18.6), with a corresponding median rise from baseline of 5.4 g per deciliter (range, 1.1 to 11.4). Erythrocytosis, with hemoglobin values exceeding 17 g per deciliter, developed in four patients who had a response to lenalidomide.

With a median of 104 weeks of follow-up, 53

Table 2. Erythroid Response to Lenalidomide.

Variable	Continuous Daily Dosing (N=102)*	21-Day Dosing (N=46)*	All Patients (N=148)
Erythroid response — no. (%)			
Transfusion independence	71 (70)	28 (61)	99 (67)
95% CI			59–74
≥50% decrease in no. of transfusions	8 (8)	5 (11)	13 (9)
95% CI			5–15
Total transfusion response	79 (77)	33 (72)	112 (76)
95% CI			68–82
Time to response — wk			
Median	4.7	4.3	4.6
Range	1–34	1–49	1–49
Hemoglobin — g/dl			
Baseline†			
Median	7.7	8.0	7.8
Range	5.3–10.4	5.6–10.3	5.3–10.4
Response‡			
Median	13.4	13.5	13.4
Range	9.2–18.6	9.3–16.9	9.2–18.6
Increase			
Median	5.4	5.4	5.4
Range	2.2–11.4	1.1–9.1	1.1–11.4

* The daily dose was 10 mg.
† The baseline hemoglobin concentration was the minimum value during the baseline period.
‡ The response hemoglobin concentration was the maximum value during the transfusion-independent response period.

patients who had a response remained transfusion-free; none were lost to follow-up. As a result, the Kaplan–Meier estimate of the median duration of transfusion independence could not be determined (range, 8.6 to 89.0 or more weeks) (Fig. 1). Transfusion independence was maintained for at least one year in 61 of 99 patients who had a response to treatment (62%). The response rate was not significantly influenced by age, sex, FAB type, IPSS, or cytogenetic pattern (Table 2 in the Supplementary Appendix). The rate of transfusion independence was significantly lower among patients with baseline thrombocytopenia than among patients with platelet counts of more than 100,000 per cubic millimeter at baseline (39% vs. 73%, P=0.001). The 28 patients with thrombocytopenia received treatment with the study drug for a shorter period than the remaining 120 patients (median, 22 weeks vs. 63 weeks; P=0.004). Multivariate analysis showed that the hematologic response to lenalidomide was adversely affected by only two of the above variables: thrombocytopenia (odds ratio for the comparison with the absence of thrombocytopenia, 4.53; P=0.003) and a high requirement for transfusion (odds ratio for the comparison with a requirement of less than 4 units, 3.59; P=0.01).

CYTOGENETIC RESPONSE

Of 85 patients who had at least 20 cells in metaphase that could be analyzed at baseline and at week 24 and who could be evaluated for a cytogenetic response, 38 (45%) had a complete cytogenetic remission (95% CI, 34 to 56) and 24 patients (28%) had a partial cytogenetic response (95% CI, 19 to 39). For an additional seven patients with fewer than 20 cells in metaphase that could be analyzed at baseline, at least 20 cells in metaphase were analyzed at follow-up, and no abnormal cells in metaphase were detected (Table 3 in the Supplementary Appendix). A partial or complete remission was confirmed in 15 patients by

fluorescence in situ hybridization. The cytogenetic responses closely correlated with the hematologic response: 61 of 62 patients with partial or complete cytogenetic responses no longer required transfusions.

There was no significant association between karyotype complexity and the frequency of a cytogenetic response (P=0.27) or the frequency of complete cytogenetic remission (P=0.93) (Table 3). Seventy-seven percent of patients with an isolated 5q deletion had a cytogenetic response, as compared with 67% of patients with the 5q deletion and one other chromosomal abnormality and 50% of patients with the 5q deletion and two or more other chromosomal abnormalities. Multivariate analysis showed that only two variables were associated with a lower probability of a cytogenetic response: thrombocytopenia (odds ratio, 4.78; P=0.02) and an age of 60 years or less (odds ratio, 2.99; P=0.07). In 119 patients, it was possible to evaluate cytogenetic progression. Among the 62 patients with a cytogenetic response, the initial cytogenetic pattern returned in 17 (27%), the proportion of abnormal cells in metaphase increased in 14 patients (9 with a complete response and 5 with a partial response), and 4 patients had a new clonal chromosomal abnormality accompanying the 5q deletion. Six additional patients had cytogenetic progression characterized by the appearance of a new clone in the absence of the 5q deletion. With a median follow-up from the diagnosis of the myelodysplastic syndrome of 3.8 years, the estimated median survival was 7.6 years for patients with an isolated 5q deletion and 5.6 years for patients with one or more cytogenetic abnormalities (P=0.64) (Fig. 1 of the Supplementary Appendix).

New chromosomal abnormalities occurred in 24 patients during treatment; 13 of these patients did not have a cytogenetic response. The baseline karyotype in patients with cytogenetic evolution included an isolated 5q deletion in 13 patients, an independent clone without the 5q deletion in 1 patient, one additional abnormality in 6 patients, and a complex karyotype in 4 patients. In two patients the new abnormality emerged coincidentally with complete suppression of the 5q-deletion clone; one of these patients had an isolated 5q deletion, and the other had a discordant clone at baseline. Acquired chromosomal abnormalities varied widely and no one type was observed in more than one patient; structural or numerical abnormalities involving chromosome 7 were detected in only one patient.

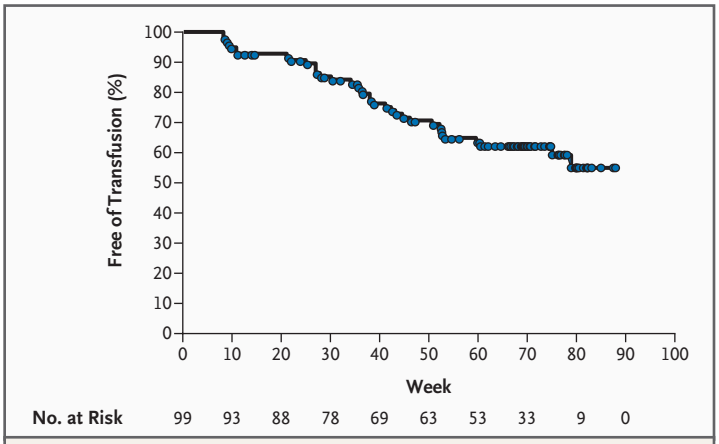

Figure 1. Kaplan–Meier Estimate of the Duration of Independence from Red-Cell Transfusion.

Circles represent censored data from patients who remained transfusion-free at the time of data cutoff (July 15, 2005) or at the time of study discontinuation. On the x axis, 0 indicates the day after the patient's last transfusion preceding a response to treatment. After a median follow-up of 104 weeks, the median duration of transfusion independence could not be estimated.

BONE MARROW CHANGES

Sequential marrow specimens that were adequate for central pathology review were obtained from 106 patients, 82% of whom had become transfusion-independent (Table 3 in the Supplementary Appendix). After 24 weeks of treatment, there was complete resolution of cytologic dysplasia in all hematopoietic lineages in 38 of the 106 patients (36%). The proportion of myeloblasts in the marrow returned to less than 5% in 74% of patients with excess myeloblasts (median at baseline, 7.0±2.4% [range, 5 to 14]; median at week 24, 1.0±1.8% [range, 0 to 3]), as did the proportion of ringed sideroblasts in 64% of patients who had refractory anemia with ringed sideroblasts and who could be evaluated (median at baseline, 40±10% [range, 30 to 50]; median at week 24, 0±2.8% [range, 0 to 3]). Sixteen patients had progression to a more advanced FAB type of the myelodysplastic syndrome (eight patients) or acute myeloid leukemia (eight patients) (Table 3 in the Supplementary Appendix). Multivariate analysis of prognostic variables, including the proportion of myoblasts (≥5% vs. <5%), karyotypic complexity, the duration of disease, the lactate dehydrogenase level, and the presence or absence of neutropenia, thrombocytopenia, 5q– syndrome, transfusion

Table 3. Frequency of Cytogenetic Response According to Karyotype Complexity.

Complexity	Patients Who Could Be Evaluated*	Cytogenetic Response	Complete Cytogenetic Remission
Isolated 5q deletion — no. (%)	64	49 (77)	29 (45)
5q deletion + 1 additional abnormality — no. (%)	15	10 (67)	6 (40)
Complex (≥3 abnormalities) — no. (%)	6	3 (50)	3 (50)
P value		0.27	0.93

* Patients who could be evaluated were those with at least 20 analyzable cells in metaphase at baseline and at least one follow-up assessment. P values are for the association between karyotypic complexity and a cytogenic response or complete cytogenetic remission.

response, and cytogenetic response, showed that progression of disease was associated only with a lower frequency of cytogenetic response (13% vs. 45%, P=0.05).

ADVERSE EFFECTS AND DOSE ADJUSTMENT

Neutropenia and thrombocytopenia were the most common treatment-associated adverse events (Table 4). National Cancer Institute Common Toxicity Criteria grade 3 or 4 neutropenia (fewer than 1000 polymorphonuclear neutrophils per cubic millimeter) and thrombocytopenia (fewer than 50,000 platelets per cubic millimeter) were reported in 54.7% and 43.9% of patients, respectively, and were the most common reasons for dose adjustment. Grade 4 neutropenia (fewer than 500 polymorphonuclear neutrophils per cubic millimeter) was more common among patients receiving continuous daily dosing than among those receiving 21-day dosing (44.1% vs. 17.4%, P<0.001), whereas grade 4 thrombocytopenia (fewer than 10,000 platelets per cubic millimeter) was less common among those receiving continuous daily dosing than among those receiving 21-day dosing (6.9% vs. 15.2%, P=0.05). Severe myelosuppression generally occurred early in the course of treatment, with 62% of grade 3 or 4 hematologic adverse events occurring within the initial 8 weeks of treatment. Neutropenia was accompanied by fever in only 4.1% of patients. Most other adverse events were of low or moderate severity; they included pruritus, rash, diarrhea, and fatigue.

Eleven patients died while receiving treatment or within 30 days after the last dose of lenalidomide; three deaths attributed to neutropenic infection were judged to be possibly treatment-related by the treating physician. All other deaths were considered to be unrelated to treatment. There were three deaths from congestive heart failure, one death from ischemic colitis, one death from acute myeloid leukemia, one death from procedure-associated intestinal perforation, one death from subarachnoid hemorrhage, and one sudden death. The subarachnoid hemorrhage was caused by trauma and occurred in a patient with a response to treatment who had a stable platelet count (more than 75,000 per cubic millimeter, with a baseline mean value of 99,000 per cubic millimeter) during a 2-week hiatus in study treatment because of unexplained dyspnea.

Adjustment of the lenalidomide dose was required in 124 patients (84%), including 93 (91%) of those receiving continuous daily dosing and 31 (67%) of those receiving 21-day dosing. At week 24, 32% of patients were receiving 10 mg of lenalidomide daily, 44% were receiving 5 mg daily, and 24% were receiving 5 mg every other day. The median interval to dose adjustment was 22 days (range, 2 to 468). Thirty patients (20%) discontinued lenalidomide treatment prematurely because of adverse events, including 18 (18%) of those initially assigned to the continuous regimen and 12 (26%) of those assigned to the 21-day regimen. Of these patients, 10 had thrombocytopenia or neutropenia, 5 had rash, 3 had acute myeloid leukemia, and 1 patient each had anemia, facial edema, congestive heart failure, urticaria, diarrhea, weight loss, renal insufficiency, cerebrovascular accident, dementia, dyspnea, pyrexia, and pneumonia.

DISCUSSION

In patients with the myelodysplastic syndrome, chronic anemia adversely affects the quality of life and the clinical course of the disease. Hemodynamic compensation contributes to hypertrophic cardiac remodeling over time, the risk of which

Table 4. Grade 3 and 4 Treatment-Related Adverse Events.

Adverse Event	Grade 3		Grade 4		Grade 3 or 4
	Continuous Daily Dosing* (N=102)	21-Day Dosing* (N=46)	Continuous Daily Dosing* (N=102)	21-Day Dosing* (N=46)	Both Schedules (N=148)
	number of patients (percent)				
Neutropenia	20 (20)	8 (17)	45 (44)	8 (17)	81 (55)
Thrombocytopenia	37 (36)	14 (30)	7 (7)	7 (15)	65 (44)
Anemia (not otherwise specified)	4 (4)	2 (4)	4 (4)	0	10 (7)
Leukopenia (not otherwise specified)	3 (3)	2 (4)	4 (4)	0	9 (6)
Rash	5 (5)	4 (9)	0	0	9 (6)
Febrile neutropenia	2 (2)	1 (2)	2 (2)	1 (2)	1 (1)
Pruritus	2 (2)	2 (4)	0	0	4 (3)
Fatigue	2 (2)	2 (4)	0	0	4 (3)
Muscle cramp	3 (3)	0	0	0	3 (2)
Pneumonia	1 (1)	2 (4)	1 (1)	0	4 (3)
Nausea	3 (3)	1 (2)	0	0	4 (3)
Diarrhea	4 (4)	0	0	0	4 (3)
Deep-vein thrombosis	3 (3)	1 (2)	0	0	4 (3)
Hemorrhage	1 (1)	2 (4)	1 (1)	1 (2)	4 (3)
Hypokalemia	1 (1)	1 (2)	0	0	2 (1)
Pyrexia	1 (1)	0	0	0	1 (1)

* The daily dose was 10 mg.

is reduced with each graded sustained elevation in hemoglobin.[12] Dependence on transfusions, in particular, is associated with reduced survival in lower-risk patients with the myelodysplastic syndrome as a result of iron loading, cardiac failure, and progression to acute myeloid leukemia.[13] These observations suggest that sustained improvement in erythropoiesis might improve the outcome of the disease.[13]

In this study of transfusion-dependent patients with the myelodysplastic syndrome and chromosome 5q deletion, most patients had had no response to treatment with recombinant erythropoietin and had a substantial need for transfusions, with a median of 3 units per month. Seventy-six percent of the patients who were given lenalidomide needed fewer transfusions than they did before entering the study, and 67% became transfusion-independent, with a rise in hemoglobin to a nearly normal range (Table 2). The response to treatment was rapid (median interval between initiation of treatment and response, 4.6 weeks) and durable; 61 patients (62%) who had a response to treatment remained transfusion-free for at least 1 year, and the median duration of transfusion independence had not been reached after a median follow-up of 2 years (Fig. 1).

Our results confirm initial observations that lenalidomide suppresses the 5q-deletion clone.[6] After 24 weeks of therapy, 73% of the 148 patients we studied had a cytogenetic response, and 45% had a complete cytogenetic remission in association with sustained transfusion independence and improvement in bone marrow morphologic features (Tables 5 and 6 of the Supplementary Appendix). Bone marrow morphologic features returned to normal in 36% of patients who could be evaluated. Among most patients with an excess of bone marrow myeloblasts or ringed sideroblasts, the number of these cells returned to normal. These findings are consistent with preclinical observations that lenalidomide is selectively cytotoxic to 5q-deletion clones and restores red-cell production in part by suppressing the myelodysplastic clone (unpublished data). In a recently completed multicenter study evaluating the he-

matologic response to lenalidomide in 215 transfusion-dependent patients who had lower-risk myelodysplastic syndrome without the 5q deletion, only 26% of patients no longer required transfusions, indicating that the efficacy of lenalidomide in the myelodysplastic syndrome is associated with the 5q deletion.[14]

Thrombocytopenia was the most important variable associated with a reduced probability of transfusion independence (P=0.003) or having a cytogenetic response (P=0.02). The number of consecutive days of drug treatment was significantly lower among patients with baseline thrombocytopenia (P=0.004) because of the repeated interruption of treatment for myelosuppression. This observation suggests that the duration of lenalidomide treatment is a determinant of the potential for clonal suppression and hematologic improvement. We found no significant differences in the frequency of transfusions or cytogenetic responses among patients with different degrees of karyotype complexity, or among patients with an isolated 5q deletion, either with or without the 5q– syndrome. Among patients who have the myelodysplastic syndrome with a 5q deletion, the presence of one or more additional chromosomal abnormalities is associated with an aggressive clinical course and considerably poorer overall survival, as compared with the 5q deletion.[1,2,15] Our finding that survival was similar among patients with additional chromosomal abnormalities and patients with an isolated 5q deletion suggests that lenalidomide may extend survival in higher-risk patients with the myelodysplastic syndrome (Fig. 1 in the Supplementary Appendix). The finding that the additional chromosome abnormalities and the cytologic abnormalities disappear in patients with karyotype complexity who have a cytogenetic response to lenalidomide is consistent with the model proposed by Pedersen-Bjergaard and colleagues, in which the 5q deletion represents an initiating event responsible for clonal propagation, whereas acquisition of additional aberrations is secondary.[16] The mechanisms of resistance that allow recurrence of the initial clone remain undefined, but they may be related to emergence of target mutations or amplification, analogous to the action of imatinib on the *BCR–ABL* gene in chronic myeloid leukemia.[17]

Myelosuppression, manifested by moderate-to-severe neutropenia and thrombocytopenia, occurred regularly and usually early in the course of treatment (Table 7 in the Supplementary Appendix), a finding that is consistent with the suppressive effect of lenalidomide on the 5q-deletion clone. Three patients died of neutropenic infection, which emphasized the need for close laboratory monitoring and consideration of myeloid growth factors during the initial weeks of treatment. Nonetheless, infectious complications were infrequent during the initial period of clonal suppression. There were no significant differences in the rate of response or in adverse effects between patients receiving continuous daily dosing and those receiving 21-day dosing.

We conclude that lenalidomide is effective in lower-risk, transfusion-dependent patients with the myelodysplastic syndrome and a 5q deletion.

Sponsored by Celgene.

Drs. Wride, Zeldis, and Knight; Mr. Patin; and Ms. Schmidt report being employees of Celgene, the sponsor of this study, and owning equity in Celgene. Drs. Bennett, Raza, Feldman, Powell, and Greenberg report having received grant support from Celgene; Drs. Bennett, Raza, Greenberg, Thomas, Stone, and Giagounidis consulting fees from Celgene; and Drs. Bennett, Greenberg, Thomas, Zeldis, Knight, and Giagounidis lecture fees from Celgene. No other potential conflict of interest relevant to this article was reported.

APPENDIX

In addition to the authors, the following investigators participated in the Myelodysplastic Syndrome-003 Study: M. Baer, Roswell Park Cancer Institute, Buffalo, NY; P. Curtin, Oregon Health and Science University, Portland; H.J. Deeg, Fred Hutchinson Cancer Research Center, Seattle; L. Dreisbach, Desert Hematology Oncology, Rancho Mirage, CA; G. Fonseca, Cancer and Blood Disease Center, Lecanto, FL; Michael Gordon, Arizona Cancer Center, Scottsdale, AZ; S. Gore, Johns Hopkins School of Medicine, Baltimore; J. Gotlib, Stanford Cancer Center, Stanford, CA; R. Hermann, Northwest Georgia Oncology, Marietta, GA; J. Ifthikharuddin, James P. Wilmot Cancer Center, Rochester, NY; R. Larson, University of Chicago Medical Center, Chicago; E. Lian, Sylvester Cancer Center, Miami; L. Maness, University of Nebraska Medical Center, Omaha; A. Moreno, Mayo Clinic, Jacksonville, FL; S. Nimer, Memorial Sloan-Kettering Cancer Center, New York; M. Sekeres, Cleveland Clinic Foundation, Cleveland; R. Shadduck, Western Pennsylvania Cancer Institute, Pittsburgh; J. Shammo, Rush–Presbyterian–St. Luke's Medical Center, Chicago; L. Silverman, Mt. Sinai Medical Center, New York; A. Tefferi, Mayo Clinic, Rochester, MN.

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