The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America

Donna M. Weber, M.D., Christine Chen, M.D., Ruben Niesvizky, M.D., Michael Wang, M.D., Andrew Belch, M.D., Edward A. Stadtmauer, M.D., David Siegel, M.D., Ivan Borrello, M.D., S. Vincent Rajkumar, M.D., Asher Alban Chanan-Khan, M.D., Sagar Lonial, M.D., Zhinuan Yu, Ph.D., John Patin, M.S., Marta Olesnyckyj, R.N., Jerome B. Zeldis, M.D., Ph.D., and Robert D. Knight, M.D., for the Multiple Myeloma (009) Study Investigators*

ABSTRACT

BACKGROUND

Lenalidomide, an oral immunomodulatory drug that is similar to thalidomide but has a different safety profile, has clinical activity in relapsed or refractory multiple myeloma.

METHODS

Patients in the United States and Canada who had received at least one previous therapy for multiple myeloma but who required additional treatment were randomly assigned to receive either 25 mg of lenalidomide or placebo on days 1 to 21 of a 28-day cycle. Both groups also received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles. After the fourth cycle, 40 mg of dexamethasone was administered only on days 1 to 4. Safety, clinical response, time to progression, and overall survival were assessed.

RESULTS

We assigned 177 patients to the lenalidomide group and 176 to the placebo group. Complete, near-complete, or partial responses occurred in 108 patients (61.0%) in the lenalidomide group and in 35 patients (19.9%) in the placebo group (P<0.001); complete responses occurred in 14.1% and 0.6%, respectively (P<0.001). The median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the placebo group (P<0.001). Median overall survival times in the two groups were 29.6 months and 20.2 months, respectively (P<0.001). Grade 3 or 4 adverse events were reported in 85.3% of the lenalidomide group and in 73.1% of the placebo group; these events resulted in study discontinuation in 19.8% and 10.2%, respectively. Grade 3 or 4 neutropenia and venous thromboembolism were more common in the lenalidomide group than in the placebo group (41.2% vs. 4.6% and 14.7% vs. 3.4%, respectively; P<0.001 for both comparisons).

CONCLUSIONS

Lenalidomide plus dexamethasone is superior to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma. (ClinicalTrials.gov number, NCT00056160.)

From the M.D. Anderson Cancer Center, Houston (D.M.W., M.W.); Princess Margaret Hospital, Toronto (C.C.); Weill Cornell Medical College, New York (R.N.); Cross Cancer Institute, Edmonton, AB, Canada (A.B.); University of Pennsylvania Cancer Center, Philadelphia (E.A.S.); the Cancer Center at Hackensack University Medical Center, Hackensack, NJ (D.S.); Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore (I.B.); Mayo Clinic Cancer Center, Rochester, MN (S.V.R.); Roswell Park Cancer Institute, Buffalo, NY (A.A.C.-K.); Emory University, Atlanta (S.L.); and Celgene, Summit, NJ (Z.Y., J.P., M.O., J.B.Z., R.D.K.). Address reprint requests to Dr. Weber at the Department of Lymphoma and Myeloma, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 429, Houston, TX 77030, or at dmweber@mdanderson.org.

*Other investigators in the Multiple Myeloma (009) Study are listed in the Appendix.

N Engl J Med 2007;357:2133-42.

Multiple myeloma causes nearly 11,000 deaths annually in the United States.[1] Treatment with the immunomodulatory agent thalidomide or the proteasome inhibitor bortezomib has improved response rates, time to progression, and survival, but the side effects of fatigue, neuropathy, constipation, and thrombotic events remain a concern.[2-6] In nearly all patients who receive these drugs or other chemotherapy, the disease eventually relapses and is subsequently resistant to treatment.

Lenalidomide is a thalidomide derivative that down-regulates interleukin-6 and nuclear factor κ-B and activates caspase 8 in vitro. The drug is up to 50,000 times as potent as its parent molecule in inhibiting tumor necrosis factor α.[7] Phase 1 and 2 trials of lenalidomide in patients with treatment-refractory multiple myeloma showed a partial-response rate of 24 to 29%.[8-10] Moreover, an additional 29% of patients who had not had a response to lenalidomide alone had a partial remission after the addition of pulsed doses of dexamethasone.[10] We report here on a randomized, phase 3 trial that compared lenalidomide plus dexamethasone with placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.

METHODS

PATIENTS

Patients were eligible for the study if they were at least 18 years of age, had progressive multiple myeloma after at least one previous treatment, and had measurable disease that was not resistant to dexamethasone. Patients were considered to have disease that was resistant to dexamethasone if they had had progression during previous therapy containing high-dose dexamethasone (total monthly dose, >200 mg). Measurable disease was defined as a serum monoclonal protein (M protein) level of at least 0.5 g per deciliter or a urinary Bence Jones protein level of at least 0.2 g per day. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of no more than 2, a serum aspartate aminotransferase or alanine aminotransferase level that was no more than 3 times the upper limit of the normal range, a serum bilirubin level that was no more than 2 times the upper limit of the normal range, a serum creatinine level of less than 2.5 mg per deciliter (221 μmol per liter), an absolute neutrophil count of at least 1000 per cubic millimeter, and a platelet count of more than 75,000 per cubic millimeter for patients with less than 50% bone marrow plasma cells and more than 30,000 per cubic millimeter for patients with 50% or more bone marrow plasma cells. Women of childbearing potential were eligible if they agreed to use contraception, had a negative pregnancy test before enrollment, and agreed to undergo monthly pregnancy testing until 4 weeks after the discontinuation of the study drug.

STUDY DESIGN

In this multicenter, double-blind, placebo-controlled, randomized, phase 3 trial, patients received 25 mg of daily oral lenalidomide or placebo on days 1 to 21 of each 28-day cycle. All patients also received 40 mg of daily oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20. After the fourth cycle, 40 mg of dexamethasone was administered only on days 1 to 4. Treatment was continued until the occurrence of disease progression or unacceptable toxic effects. Central randomization was performed with a block size of 4 and the use of an integrated voice-response system. The assignment of patients was stratified according to the level of serum β_2-microglobulin (<2.5 mg per liter vs. ≥2.5 mg per liter), previous stem-cell transplantation (none vs. ≥1), and the number of previous antimyeloma therapies (1 vs. ≥2).

The primary end point was the time to disease progression. Secondary end points included overall survival and the response rate.

Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.[11] In the case of a grade 3 or 4 adverse event, treatment was withheld and restarted at the next lower daily dose. The dose of lenalidomide was modified as follows: 15 mg (dose level, –1), 10 mg (dose level, –2), or 5 mg (dose level, –3). For grade 3 or 4 neutropenia without other toxic effects, the first dose-modification step was dose level –1 (daily subcutaneous injection of 5 μg of granulocyte colony-stimulating factor per kilogram of body weight and 25 mg of lenalidomide); sequential dose reductions of lenalidomide were 15 mg (dose level, –2), 10 mg (dose level, –3), and 5 mg (dose level, –4) plus the daily administration of 5 μg per kilogram of granulocyte colony-stimulating factor at the investigator's discretion. Thromboprophylaxis was not required, although it was used on an individual basis. Modifications in the dose of dexamethasone because of toxic effects were 40 mg daily for 4 days

every 2 weeks (dose level, –1) or every 4 weeks (dose level, –2) or 20 mg daily for 4 days every 4 weeks (dose level, –3).

Blood counts and physical examination were performed on days 1 and 15 (and day 8 of cycle 1) during cycles 1 to 3 and on day 1 of each cycle thereafter. Serum and urinary protein electrophoresis studies were performed on day 1 of each cycle and at the end of treatment. Survival status was determined every 6 months after the discontinuation of treatment.

The study was designed as a collaborative effort by Dr. Weber, the coinvestigators, and the sponsor, Celgene. The sponsor collected the data and performed the final analysis in collaboration with an independent data monitoring committee and Dr. Weber. All authors had full access to the primary data and the final analysis. Dr. Weber wrote the first draft of the manuscript and vouches for the completeness and accuracy of the clinical results and the reporting of adverse events. An independent data and safety monitoring committee reviewed ongoing safety and efficacy data throughout the study.

RESPONSE CRITERIA

The response of patients was assessed according to the criteria of the European Group for Blood and Marrow Transplantation.[12] A partial response was defined as a reduction of M protein by at least 50% in serum, 90% in urine, or both, as confirmed by at least two electrophoretic measurements. A complete response was defined as the complete disappearance of M protein in serum and urine by immunofixation, as confirmed by two measurements, and the presence of less than 5% marrow plasma cells; the criteria for near-complete remission were identical to those for complete remission but without confirmation of marrow plasmacytosis of less than 5% or the disappearance of M protein.

The time to progression was measured from randomization to the date of the first assessment showing disease progression. Progressive disease was defined as an increase of at least 25% in M protein from nadir; an absolute increase in serum M protein of more than 500 mg per deciliter, as compared with the nadir value; an absolute increase in urinary M protein of more than 200 mg per 24-hour period; or either a new bone lesion or plasmacytoma (or an increase in the size of such lesions), or a serum calcium level of more than 11.5 mg per deciliter (2.9 mmol per liter).

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Lenalidomide (N=177)	Placebo (N=176)
Age — yr		
Median	64	62
Range	36–86	37–85
Male sex — %	59.9	59.1
Time since diagnosis — yr		
Median	3.1	3.1
Range	0.5–14.7	0–19.7
Durie–Salmon stage — no. (%)		
I	6 (3.4)	5 (2.8)
II	56 (31.6)	55 (31.2)
III	114 (64.4)	116 (65.9)
Missing data	1 (0.6)	0
Eastern Cooperative Oncology Group performance status — no. (%)†		
0	74 (41.8)	83 (47.2)
1	83 (46.9)	80 (45.5)
2	14 (7.9)	6 (3.4)
Missing data	6 (3.4)	7 (4.0)
Previous therapy — no. (%)		
No. of therapies		
1	68 (38.4)	67 (38.1)
≥2	109 (61.6)	109 (61.9)
Type of therapy		
Thalidomide	74 (41.8)	80 (45.5)
Bortezomib	19 (10.7)	20 (11.4)
Stem-cell transplantation	109 (61.6)	108 (61.4)
β_2-microglobulin level — no. (%)		
<2.5 mg per liter	52 (29.4)	51 (29.0)
≥2.5 mg per liter	125 (70.6)	125 (71.0)

* There were no significant differences between the two groups according to a pooled t-test for continuous variables (age and time since first pathological diagnosis) and Fisher's exact test for categorical variables (all other variables in the table) (P>0.05). Percentages may not total 100 because of rounding.
† Lower numbers indicate better performance.

Data for patients who died before there was evidence of disease progression were censored at the time of the last evaluation for assessment of time to progression. Overall survival was calculated as the time from randomization until death from any cause or the date of the last visit.

STATISTICAL ANALYSIS

The number of patients was calculated so that a one-sided log-rank test at the 0.025 level, allowing

Table 2. Response among Patients in the Intention-to-Treat Population and in Selected Subgroups.

Variable	Lenalidomide (N=177)	Placebo (N=176)	P Value*
Response in the intention-to-treat population — no. (%)			
Overall response	108 (61.0)	35 (19.9)	<0.001
Complete response	25 (14.1)	1 (0.6)	<0.001
Near-complete response	18 (10.2)	2 (1.1)	
Partial response	65 (36.7)	32 (18.2)	
Stable disease	54 (30.5)	102 (58.0)	
Progressive disease	5 (2.8)	25 (14.2)	
Response could not be evaluated	10 (5.6)	14 (8.0)	
Overall response in selected subgroups — no./total no. (%)†			
Previous use of thalidomide			
Yes	42/74 (56.8)	10/80 (12.5)	<0.001
No	66/103 (64.1)	25/96 (26.0)	<0.001
Previous use of bortezomib			
Yes	13/19 (68.4)	2/20 (10.0)	<0.001
No	95/158 (60.1)	33/156 (21.2)	<0.001
β_2-microglobulin level			
<2.5 mg per liter	39/52 (75.0)	14/51 (27.5)	<0.001
≥2.5 mg per liter	69/125 (55.2)	21/125 (16.8)	<0.001
Previous no. of therapies			
1	44/68 (64.7)	15/67 (22.4)	<0.001
≥2	64/109 (58.7)	20/109 (18.3)	<0.001
Previous stem-cell transplantation			
Yes	72/109 (66.1)	21/108 (19.4)	<0.001
No	36/68 (52.9)	14/68 (20.6)	<0.001

* P values were calculated with the use of a continuity-corrected Pearson chi-square test.

† There was no stratum-by-treatment interaction for response rates with the use of the Breslow–Day test for homogeneity. Percentages are for the rate of overall response among patients within selected subgroups of the intention-to-treat population.

for one interim analysis, would have a statistical power of 85% to detect a difference between the time to progression for each group with a constant hazard ratio of 1.5, reflecting an increase of 50% in the median time to progression. The number of events required was 222. On the basis of the planned accrual rate, a log-rank test of overall survival that was performed 18 months after the last patient had been enrolled, when 194 deaths were expected, would have a power of 80% to detect a hazard ratio for death of 0.67. An interim analysis to evaluate safety and efficacy was planned when 111 patients had disease progression; if the predetermined O'Brien–Fleming boundary for the superiority of lenalidomide over placebo was crossed, the study would be unblinded and patients would be allowed to cross over to open-label administration of lenalidomide at progression or at the investigator's discretion.

All primary analyses were based on the intention-to-treat population, and subgroup analyses were planned on the basis of stratification variables. An unstratified log-rank test was used to compare the time-to-event variables between the two study groups. Both the time to progression and overall survival were estimated by Kaplan–Meier methods, and a Cox proportional-hazards regression model was used to assess the effect of demographic and prognostic variables on differences in treatment responses between the two study groups. Exact tests were used to compare response rates. All reported P values are two-sided.

RESULTS

PATIENTS

From February 27, 2003, to April 14, 2004, a total of 353 patients were enrolled at 44 centers in the United States and 4 in Canada. Of those patients, 177 were assigned to receive lenalidomide plus dexamethasone (lenalidomide group) and 176 to receive placebo plus dexamethasone (placebo group). Baseline characteristics were well balanced between the two groups (Table 1). Previous treatments included radiotherapy, myeloablative therapy with stem-cell transplantation, and various combinations of dexamethasone, melphalan, doxorubicin, thalidomide, bortezomib, and other chemotherapy agents.

Because the O'Brien–Fleming boundary for the superiority of lenalidomide over placebo was crossed at the interim analysis, the data and safety monitoring committee recommended that the study be unblinded. The results presented here for response and time to progression are based on data obtained before unblinding, and the results for safety are based on data obtained before December 31, 2005. Median follow-up was 17.6 months.

RESPONSE RATE

Among 177 patients in the lenalidomide group, 108 (61.0%) had a response (complete, near-complete, or partial), as compared with 35 of 176 patients (19.9%) in the placebo group (P<0.001)

(Table 2). A complete response occurred in 25 patients (14.1%) in the lenalidomide group and in 1 patient (0.6%) in the placebo group (P<0.001); a near-complete response occurred in 18 patients (10.2%) in the lenalidomide group and in 2 patients (1.1%) in the placebo group (P<0.001). The median time to a response was similar in the two groups, but the median duration of the response was significantly longer in the lenalidomide group than for those in the placebo group (15.8 months vs. 5.1 months, P<0.001). The overall response rate was higher for patients who received lenalidomide, regardless of the stratification group (Table 2). In addition, previous treatment with thalidomide did not affect the response to lenalidomide; 56.8% of patients who had received thalidomide had a complete, near-complete, or partial response, as compared with 64.1% who had not received thalidomide (P=0.33). Similarly, previous treatment with bortezomib did not affect the response to lenalidomide (Table 2).

TIME TO PROGRESSION

The median time to progression was significantly longer in the lenalidomide group (11.1 months) than in the placebo group (4.7 months), with a hazard ratio of 0.35 (95% confidence interval [CI], 0.27 to 0.47; P<0.001) (Fig. 1A). The median time to progression was significantly larger in all subgroups of patients who received lenalidomide, as compared with those who received placebo (P<0.001 for all comparisons), including patients who had received one previous therapy (median time not reached vs. 5.1 months) or two or more previous therapies (10.2 months vs. 4.6 months).

Among the 154 patients who had been ex-

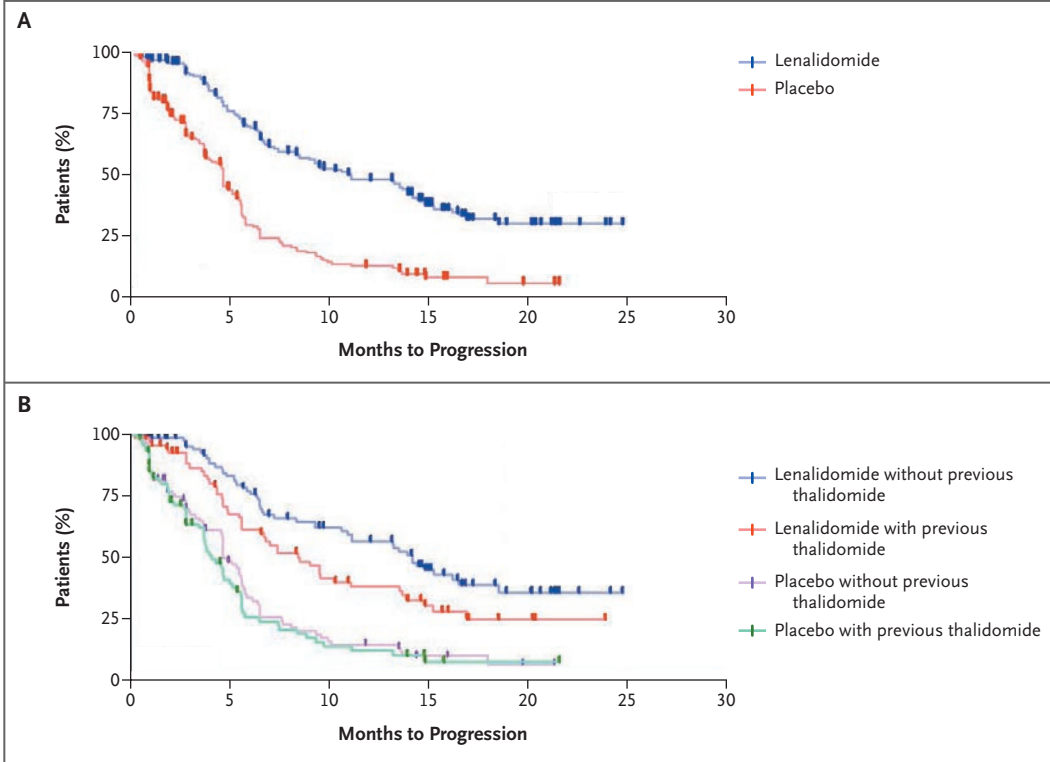

Figure 1. Kaplan–Meier Curves for the Time to Disease Progression among All Patients and in Subgroups with and without Previous Exposure to Thalidomide.

Panel A shows the curves for time to progression for the intention-to-treat population (a median of 11.1 months in the lenalidomide group and 4.7 months in the placebo group, P<0.001 by the log-rank test). Panel B shows the time to disease progression among patients in the two study groups who received thalidomide before study entry and those who did not receive thalidomide. In the lenalidomide group, the median time was 14.2 months among patients who did not receive thalidomide and 8.5 months among those who received thalidomide; in the placebo group, the median time was 4.7 months and 4.1 months, respectively (P<0.001 by the log-rank test for both between-group comparisons of patients who did and those who did not receive thalidomide).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.