The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

Meletios Dimopoulos, M.D., Andrew Spencer, M.D., Michael Attal, M.D., H. Miles Prince, M.D., Jean-Luc Harousseau, M.D., Anna Dmoszynska, M.D., Jesus San Miguel, M.D., Andrzej Hellmann, M.D., Thierry Facon, M.D., Robin Foà, M.D., Alessandro Corso, M.D., Zvenyslava Masliak, M.D., Marta Olesnyckyj, R.N., Zhinuan Yu, Ph.D., John Patin, M.S., Jerome B. Zeldis, M.D., Ph.D., and Robert D. Knight, M.D., for the Multiple Myeloma (010) Study Investigators*

ABSTRACT

BACKGROUND

Lenalidomide is a structural analogue of thalidomide with similar but more potent biologic activity. This phase 3, placebo-controlled trial investigated the efficacy of lenalidomide plus dexamethasone in the treatment of relapsed or refractory multiple myeloma.

METHODS

Of 351 patients who had received at least one previous antimyeloma therapy, 176 were randomly assigned to receive 25 mg of oral lenalidomide and 175 to receive placebo on days 1 to 21 of a 28-day cycle. In addition, all patients received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles and subsequently, after the fourth cycle, only on days 1 to 4. Patients continued in the study until the occurrence of disease progression or unacceptable toxic effects. The primary end point was time to progression.

RESULTS

The time to progression was significantly longer in the patients who received lenalidomide plus dexamethasone (lenalidomide group) than in those who received placebo plus dexamethasone (placebo group) (median, 11.3 months vs. 4.7 months; P<0.001). A complete or partial response occurred in 106 patients in the lenalidomide group (60.2%) and in 42 patients in the placebo group (24.0%, P<0.001), with a complete response in 15.9% and 3.4% of patients, respectively (P<0.001). Overall survival was significantly improved in the lenalidomide group (hazard ratio for death, 0.66; P=0.03). Grade 3 or 4 adverse events that occurred in more than 10% of patients in the lenalidomide group were neutropenia (29.5%, vs. 2.3% in the placebo group), thrombocytopenia (11.4% vs. 5.7%), and venous thromboembolism (11.4% vs. 4.6%).

CONCLUSIONS

Lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in relapsed or refractory multiple myeloma. (ClinicalTrials.gov number, NCT00424047.)

From the University of Athens School of Medicine, Athens (M.D.); Alfred Hospital (A.S.) and Peter MacCallum Cancer Institute (H.M.P.) — both in Melbourne, Australia; Centre Hospitalier Universitaire Purpan, Toulouse, France (M.A.); Centre Hospitalier Hôtel-Dieu, Nantes, France (J.-L.H.); University School of Medicine, Lublin, Poland (A.D.); Hospital Universitario de Salamanca, Salamanca, Spain (J.S.M.); Medical University of Gdansk, Gdansk, Poland (A.H.); Hôpital Claude Huriez, Lille, France (T.F.); University "La Sapienza," Rome (R.F.); Fondazione Istituto Ricovero e Cura a Carattere Scientifico, Policlinico San Matteo, Pavia, Italy (A.C.); Institute of Blood Pathology and Transfusion Medicine, Lviv, Ukraine (Z.M.); and Celgene, Summit, NJ (M.O., Z.Y., J.P., J.B.Z., R.D.K.). Address reprint requests to Dr. Dimopoulos at the University of Athens School of Medicine, Alexandra Hospital, Vas. Sophias 80, Athens 11528, Greece, or at mdimop@med.uoa.gr.

*Other investigators who participated in the Multiple Myeloma (010) Study are listed in the Appendix.

This article (10.1056/NEJMoa070594) was updated on July 29, 2009, at NEJM.org.

N Engl J Med 2007;357:2123-32.

Multiple myeloma, the second most common hematologic cancer, caused more than 19,000 deaths in Europe in 2004.[1] To improve the outcome of treatment, new agents are needed.[2] The immunomodulatory drug thalidomide has activity in about one third of patients with relapsed or refractory multiple myeloma; response rates are increased when thalidomide is combined with dexamethasone or chemotherapy.[3-7] Treatment with thalidomide is associated with sedation, fatigue, constipation, rash, deep-vein thrombosis, and peripheral neuropathy. These toxic effects often require dose reduction and, in some instances, discontinuation of the drug.[8]

Lenalidomide, a derivative of thalidomide, is less toxic and more potent than the parent drug.[9] In patients with relapsed or refractory multiple myeloma, lenalidomide can overcome resistance not only to conventional chemotherapy but also to thalidomide,[10,11] and dexamethasone plus lenalidomide is more effective than either agent alone in refractory multiple myeloma.[11] We report on a randomized, phase 3 trial in which lenalidomide plus dexamethasone was compared with placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.

METHODS

PATIENTS

Patients with multiple myeloma in Europe, Israel, and Australia were eligible to participate in the study if they were at least 18 years of age and had been treated with at least one previous antimyeloma regimen. Patients were excluded if they had had disease progression during previous therapy containing high-dose dexamethasone (total monthly dose, >200 mg). Measurable disease was defined as a level of serum monoclonal protein (M protein) of at least 0.5 g per deciliter or a level of urinary Bence Jones protein of at least 0.2 g per day. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 2 or less, a serum aspartate aminotransferase or alanine aminotransferase level that was no more than three times the upper limit of the normal range, a serum bilirubin level that was no more than two times the upper limit of the normal range, a serum creatinine level of less than 2.5 mg per deciliter (221 μmol per liter), and an absolute neutrophil count of at least 1000 per cubic millimeter. The platelet count needed to be 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 during the study, had a negative pregnancy test before enrollment, and agreed to undergo pregnancy testing every 4 weeks from enrollment until 4 weeks after discontinuation of the assigned study drug. Patients were excluded if they had previously had hypersensitivity to or uncontrollable side effects associated with previous use of thalidomide or dexamethasone. All patients gave written informed consent, and an ethics committee at each study site approved the protocol.

STUDY DESIGN

The primary end point of this multicenter, randomized, placebo-controlled, phase 3 trial was the time to disease progression. Secondary end points included overall survival, the rate of response, and safety.

Patients received either 25 mg of oral lenalidomide or placebo on days 1 to 21 of a 28-day cycle; all patients 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. Patients continued to receive the assigned drug regimen until the occurrence of disease progression or unacceptable toxic effects. Patients were stratified according to the baseline serum β_2-microglobulin level (<2.5 mg per liter or ≥2.5 mg per liter), previous stem-cell transplantation (none or ≥1), and the number of previous antimyeloma regimens (1 or ≥2).

Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 2. For grade 4 adverse events, treatment was withheld and restarted at the next lower dose after resolution of the toxic effects. The dexamethasone dose was modified because of toxic effects at the investigator's discretion as follows: 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). 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 reductions of the lenalidomide dose were 15 mg (dose level, −2), 10 mg (dose level, −3), and 5 mg (dose level, −4), with 5 μg of granulocyte colony-stimulating factor per kilogram daily at the investigator's discretion.

Patients underwent a blood count and physical examination 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 levels of M protein were assessed on day 1 of each cycle and at the end of treatment. Transfusion of platelets and red cells and the administration of neutrophil growth factors and epoetin alfa were allowed as needed. All patients were allowed to receive bisphosphonates. Prophylactic anticoagulation was not recommended.

The study was designed as a collaborative effort by Dr. Dimopoulos, 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. Dimopoulos. All authors had full access to the primary data and the final analysis. Dr. Dimopoulos vouches for the accuracy and completeness of the published results. The first draft was written by Dr. Dimopoulos; subsequent drafts were written by Dr. Dimopoulos with editorial assistance from an employee of the sponsor. All authors had input before submission of both the original and revised manuscripts. An independent data monitoring committee reviewed safety and efficacy data throughout the study.

ASSESSMENTS

The response of patients to treatment was assessed according to the criteria of the European Group for Blood and Marrow Transplantation.[12] The time to progression was measured from randomization to the date of the first assessment showing progression. Progressive disease was defined as any of the following: an absolute increase of more than 500 mg of serum M protein per deciliter, as compared with the nadir value, or an absolute increase of more than 200 mg of urinary M protein in 24 hours; a new bone lesion or plasmacytoma or an increase in the size of such lesions; or the development of hypercalcemia (serum calcium level, >11.5 mg per deciliter [2.9 mmol per liter]). Responses were designated as complete (defined as the absence of M protein in serum and urine, as confirmed by immunofixation in two samples, and <5% marrow plasma cells) or partial (defined as a reduction in the level of M protein in serum of at least 50% and a reduction in urine of at least 90%). Complete and partial responses were confirmed by repeated measurements of M protein in serum and urine after 6 weeks, and progressive disease was confirmed by repeated measurements of M protein in serum and urine after 1 to 3 weeks. Near-complete response, a subcategory of partial response, was defined as a complete response without confirmation of a decrease in marrow plasma cells to less than 5% by bone marrow biopsy, confirmation of the disappearance of M protein in serum or urine by repeat immunofixation, or both.

STATISTICAL ANALYSIS

The accrual goal was the enrollment of 302 patients (151 in each group), which would provide a statistical power of 85% to detect a hazard ratio of 1.5 for the time to progression with the use of a two-sided log-rank test with an overall significance level of 0.05, adjusted for one interim analysis. Full information that was necessary for a log-rank test to have a power of 85% would be achieved when approximately 222 patients had disease progression in the two study groups. For overall survival, the trial had a power of approximately 80% to detect a difference of 50% in median overall survival for an analysis performed when at least 194 patients had died.

An interim analysis of safety and efficacy was planned when disease had progressed in 111 patients. 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 receive lenalidomide at the time of disease 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 time-to-event variables between groups. Both the time to progression and overall survival were estimated with the use of Kaplan–Meier methods. Continuity-corrected Pearson chi-square tests were used to compare the proportions of patients in the two groups who had a response to treatment.

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

Characteristic	Lenalidomide (N=176)	Placebo (N=175)
Age — yr		
Median	63	64
Range	33–84	40–82
Male sex — %	59.1	58.9
Lytic bone lesions — no. (%)	136 (77.3)	140 (80.0)
Time since first diagnosis — yr		
Median	3.4	4.0
Range	0.4–15.7	0.3–26.6
Durie–Salmon stage — no. (%)		
I	11 (6.2)	8 (4.6)
II	50 (28.4)	57 (32.6)
III	115 (65.3)	110 (62.9)
Eastern Cooperative Oncology Group performance status — no. (%)†		
0	78 (44.3)	65 (37.1)
1	72 (40.9)	79 (45.1)
2	23 (13.1)	27 (15.4)
3	0	1 (0.6)
Missing data	3 (1.7)	3 (1.7)
Previous therapy — no. (%)		
No. of therapies		
1	56 (31.8)	57 (32.6)
≥2	120 (68.2)	118 (67.4)
Type of therapy		
Thalidomide	53 (30.1)	67 (38.3)
Bortezomib	8 (4.5)	7 (4.0)
Stem-cell transplantation	97 (55.1)	95 (54.3)
β_2-microglobulin level — no. (%)		
<2.5 mg per liter	51 (29.0)	48 (27.4)
≥2.5 mg per liter	125 (71.0)	127 (72.6)

* There were no significant differences between the two groups according to a pooled t-test for continuous variables (age, time from first pathological diagnosis, percent plasma cells) 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.

RESULTS

PATIENTS AND TREATMENTS

Between September 22, 2003, and September 15, 2004, a total of 351 patients (intention-to-treat population) were enrolled at 41 centers in Europe, 6 centers in Australia, and 3 centers in Israel. Of these patients, 176 were randomly assigned to receive lenalidomide plus dexamethasone (the lenalidomide group) and 175 to receive placebo plus dexamethasone (the placebo group). Baseline characteristics were well balanced between the two groups (Table 1). Previous therapies included stem-cell transplantation, thalidomide, dexamethasone, melphalan, doxorubicin, and bortezomib. Patients in the two groups had received a median of two previous therapies. The average time from initial diagnosis to study entry was more than 4 years. At the time of the analysis, which included all data obtained before unblinding in August 2005, the median follow-up was 16.4 months. Median daily doses of study drugs in the two groups were 25 mg of lenalidomide and 40 mg of dexamethasone. The O'Brien–Fleming boundary for the superiority of lenalidomide had been passed at the time of the interim analysis in September 2004.

EFFICACY

The median time to progression was 11.3 months in the lenalidomide group and 4.7 months in the placebo group (P<0.001) (Fig. 1A). The hazard ratio for time to progression was 2.85 (95% confidence interval [CI], 2.16 to 3.76; P<0.001) in favor of the lenalidomide group. Patients in the lenalidomide group had a significantly longer time to progression than patients in the placebo group in all stratified subgroups. The median time to progression for patients who had undergone one previous therapy was not reached in the lenalidomide group and was 4.7 months in the placebo group. Among patients who had undergone at least two previous therapies, the median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the placebo group (P<0.001).

The median time to progression for patients who had previously undergone treatment with thalidomide (30.1% of the patients in the lenalidomide group and 38.3% of those in the placebo group) was 8.4 months in the lenalidomide group and 4.6 months in the placebo group (P<0.001). Among patients with no previous exposure to thalidomide, the median time to progression was 13.5 months in the lenalidomide group and 4.7 months in the placebo group (P<0.001) (Fig. 1B). In the lenalidomide group, the median time to progression was not significantly related to previous exposure to thalidomide (hazard ratio, 0.65; 95% CI, 0.42 to 1.02; P=0.06). Among patients in whom the disease had progressed during previous thalidomide treatment, the median time to

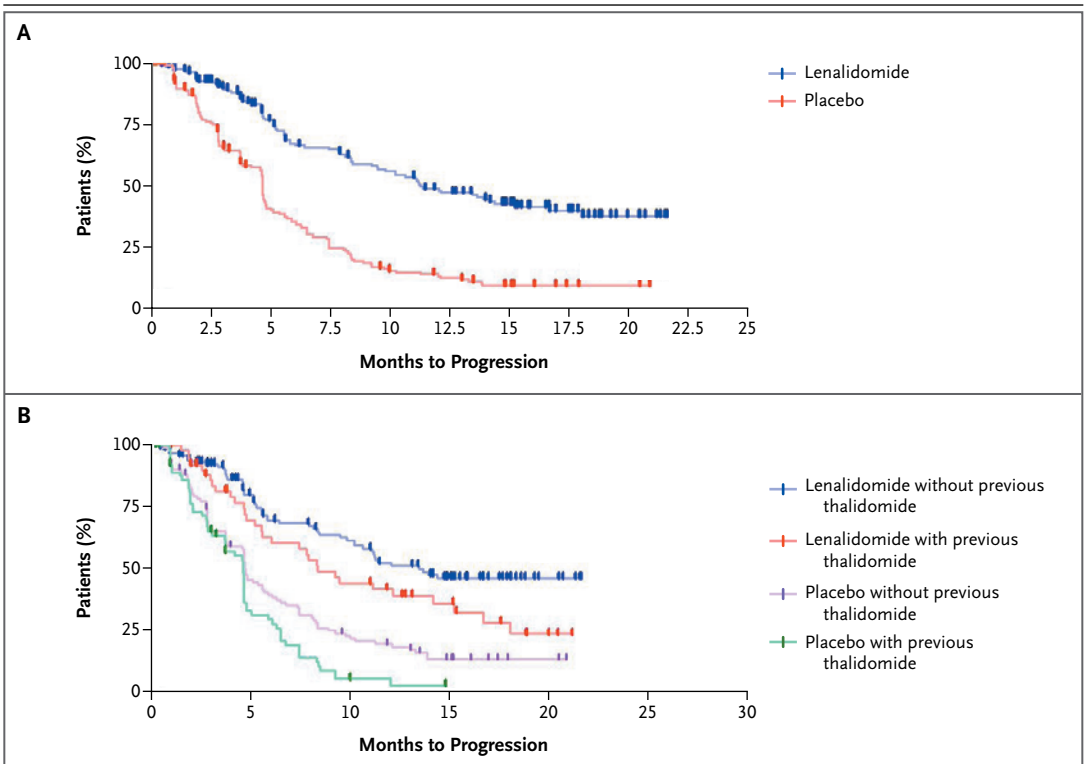

Figure 1. Kaplan–Meier Curves for the Time to Disease Progression among All Patients and in Subgroups with and without Previous Exposure to Thalidomide.

Panel A shows estimates of the median time to disease progression for the intention-to-treat population (11.3 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 median 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, 13.5 months among patients who did not receive thalidomide and 8.4 months among those who did receive thalidomide; in the placebo group, 4.7 months and 4.6 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).

progression was 9.5 months in the lenalidomide group and 3.7 months in the placebo group (P<0.001). The median time to progression was 11.3 months among patients who had undergone stem-cell transplantation and 11.4 months among patients who had not undergone stem-cell transplantation.

A total of 106 patients (60.2%) in the lenalidomide group and 42 patients (24.0%) in the placebo group had at least a partial response (P<0.001); 28 patients (15.9%) in the lenalidomide group and 6 patients (3.4%) in the placebo group had a complete response (P<0.001) (Table 2). The median time to the first response was 2.1 months in the lenalidomide group and 1.6 months in the placebo group. The median time to a complete or near-complete response was 5.1 months in the lenalidomide group and 6.9 months in the placebo group. The median duration of the response was longer in the lenalidomide group (16.5 months) than in the placebo group (7.9 months, P=0.02).

The analysis of overall response rates (complete, near-complete, and partial responses) for each stratification group and for patients with and those without previous thalidomide treatment showed a higher response rate among patients receiving lenalidomide in all the subgroups (Table 2). In the lenalidomide group, the overall response rate was higher in patients who had not received thalidomide than in those who had received thalidomide (65.0% vs. 49.1%, P=0.07).

SURVIVAL

As of May 2006, 47 patients (26.7%) in the lenalidomide group had died (30 from progressive disease), as had 60 patients (34.3%) in the placebo group (49 from progressive disease). At the time of the last analysis, median overall survival had

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