ORIGINAL ARTICLE

Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma

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ABSTRACT

BACKGROUND

High-dose chemotherapy with autologous stem-cell transplantation is a standard treatment for young patients with multiple myeloma. Residual disease is almost always present after transplantation and is responsible for relapse. This phase 3, placebo-controlled trial investigated the efficacy of lenalidomide maintenance therapy after transplantation.

METHODS

We randomly assigned 614 patients younger than 65 years of age who had nonprogressive disease after first-line transplantation to maintenance treatment with either lenalidomide (10 mg per day for the first 3 months, increased to 15 mg if tolerated) or placebo until relapse. The primary end point was progression-free survival.

RESULTS

Lenalidomide maintenance therapy improved median progression-free survival (41 months, vs. 23 months with placebo; hazard ratio, 0.50; P<0.001). This benefit was observed across all patient subgroups, including those based on the β_2-microglobulin level, cytogenetic profile, and response after transplantation. With a median follow-up period of 45 months, more than 70% of patients in both groups were alive at 4 years. The rates of grade 3 or 4 peripheral neuropathy were similar in the two groups. The incidence of second primary cancers was 3.1 per 100 patient-years in the lenalidomide group versus 1.2 per 100 patient-years in the placebo group (P=0.002). Median event-free survival (with events that included second primary cancers) was significantly improved with lenalidomide (40 months, vs. 23 months with placebo; P<0.001).

CONCLUSIONS

Lenalidomide maintenance after transplantation significantly prolonged progression-free and event-free survival among patients with multiple myeloma. Four years after randomization, overall survival was similar in the two study groups. (Funded by the Programme Hospitalier de Recherche Clinique and others; ClinicalTrials.gov number, NCT00430365.)

During the past decade, high-dose chemotherapy with autologous stem-cell transplantation has become the standard treatment for newly diagnosed myeloma in patients younger than 65 years of age. However, the median duration of response after this procedure does not exceed 3 years, and few patients remain free of the disease for more than 10 years.[1-4]

Relapses are due to the failure of high-dose chemotherapy to eradicate all myeloma cells. Maintenance treatments have been proposed to control the proliferation of residual malignant cells after transplantation. For many years, interferon with or without glucocorticoids was used,[1,2,5] but this approach was abandoned because of the toxicity of interferon and the negative results of a large, randomized trial.[6] Thalidomide has renewed the interest in maintenance therapy after transplantation. In randomized trials, thalidomide was reported to improve rates of event-free or overall survival[7-11]; however, the long-term use of thalidomide was associated with a high incidence of severe neuropathy. Furthermore, there is no consensus about the benefit of thalidomide for patients with an adverse cytogenetic profile at the time of diagnosis or for those who have already had a complete response after transplantation.[7,8,11] Thus, effective maintenance treatment after transplantation is still needed.

Lenalidomide (Revlimid, Celgene), a derivative of thalidomide, is less toxic and more potent than the parent drug.[12] It is an oral agent that is effective in the treatment of myeloma at the time of diagnosis and at the time of relapse (after conventional-dose chemotherapy or transplantation).[13-15] We report on a randomized, phase 3 trial that compared lenalidomide with placebo for maintenance treatment after transplantation in patients with multiple myeloma.

METHODS

PATIENTS

Patients were eligible if they were less than 65 years of age and presented with multiple myeloma that had not progressed in the interval between first-line autologous stem-cell transplantation (either one or two procedures), performed within the previous 6 months, and randomization. Additional eligibility criteria included 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 35 μmol per liter (2 mg per deciliter), a serum creatinine level of less than 160 μmol per liter (1.8 mg per deciliter), an absolute neutrophil count of at least 1000 per cubic millimeter, and a platelet count of more than 75,000 per cubic millimeter. 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 discontinuation of the study drug. The study was approved by the institutional ethics committee of the coordinating center (Centre Hospitalier Universitaire Purpan, Toulouse, France). All patients gave written informed consent.

STUDY DESIGN AND TREATMENT

The study was a randomized, double-blind, placebo-controlled, phase 3 trial conducted at 77 centers in France, Belgium, and Switzerland. Patients were recruited from July 2006 through August 2008. After undergoing transplantation, patients were randomly assigned in a 1:1 ratio to receive either consolidation treatment with lenalidomide (at a dose of 25 mg per day, on days 1 to 21 of each 28-day cycle, for two cycles), followed by maintenance therapy with lenalidomide (10 mg per day for the first 3 months, increased to 15 mg if tolerated), or the same consolidation treatment with lenalidomide, followed by maintenance therapy with placebo. Before September 2006 (the date of the first amendment introducing the consolidation phase), patients were randomly assigned to the maintenance regimen only (lenalidomide or placebo). Treatment was continued until the patient withdrew consent, the disease progressed, or unacceptable toxic effects occurred. Randomization was stratified according to baseline levels of serum β_2-microglobulin (≤3 mg per liter or >3 mg per liter), the presence or absence of a 13q deletion on the basis of fluorescence in situ hybridization, and response after transplantation achieved at the time of randomization (a complete or very good partial response vs. a partial response or stable disease).

The primary end point was progression-free survival. Secondary end points included the response rate, event-free survival, and overall survival.

Toxic effects were graded according to the World Health Organization toxicity criteria, version 3.0. Serious adverse events were monitored by an

independent data and safety monitoring committee. Dose reductions are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. Thromboprophylaxis was not used.

The senior academic authors designed the trial and wrote the first draft of the manuscript. The sponsor (Toulouse Hospital) collected the data and performed the final analysis in collaboration with the senior academic authors and an independent data and safety monitoring committee. All authors had full access to the primary data and results of the final analysis, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and analyses. Celgene donated the drug and the placebo but played no other role in the study. The study was conducted in accordance with the protocol, which along with the statistical analysis plan, is available at NEJM.org.

ASSESSMENTS

Treatment responses and disease progression were assessed according to the International Uniform Response Criteria for Multiple Myeloma (see the Supplementary Appendix).[16] Complete disappearance of M protein in serum and urine on immunofixation was considered to be a complete response if confirmed by bone marrow evaluation and a very good partial response in the absence of bone marrow evaluation. Blood and 24-hour urine samples were collected every 4 weeks from the time of randomization until disease progression. Follow-up to determine survival status took place every month for patients with disease progression. Investigators provided the sponsor with documentation supporting the treatment responses and diagnosis of progression, which was reviewed by an independent review committee.

STATISTICAL ANALYSIS

The sample size was calculated on the assumption of a 4-year, progression-free survival rate of 37.5% in the placebo group and of 50% in the lenalidomide group. The study had 85% power to detect a significant between-group difference in survival with a hazard ratio of 1.42 by means of a one-sided log-rank test at an overall significance level of 0.025 (adjusted for one interim analysis), with a final alpha level of 0.024. One prespecified interim analysis was to be performed when 180 events (60% of the estimated total number of events) had been recorded, and adjustment for multiple comparisons was taken into account according to the Lan–DeMets method with the use of the O'Brien–Fleming alpha-spending function.

The interim analysis was performed in January 2010 by an independent statistician. The results were submitted to an independent data and safety monitoring committee, which recommended unblinding the study, continuing treatment as assigned (without crossover), and informing patients of the interim results, since the difference in progression-free survival between the two groups had reached the prespecified level of significance for stopping the study ($P<0.004$). No patients in the placebo group received lenalidomide before disease progression. Response, progression-free survival, overall survival, and safety data were analyzed with a data cutoff date of July 7, 2010 (date of study unblinding). In January 2011, an increased incidence of second primary cancers was observed in the lenalidomide group. The independent data and safety monitoring committee recommended stopping lenalidomide maintenance therapy and continuing follow-up each month to determine survival and detect second primary cancers. All patients stopped receiving lenalidomide maintenance therapy. Salvage therapy, second primary cancers, progression-free survival, event-free survival, and overall survival were analyzed, with a data cutoff date of October 1, 2011.

Efficacy analyses were performed according to the intention-to-treat principle. Safety analyses were performed on the treated population. Censoring rules followed Food and Drug Administration instructions regarding end points for cancer trials. Progression-free survival was defined as the time from randomization to the first documentation of progressive disease or to death from any cause. Event-free survival was defined as the time from randomization to progression, occurrence of a second primary cancer, or death from any cause. Overall survival was defined as the time from randomization to death from any cause.

Follow-up time was estimated with the use of the reverse Kaplan–Meier method (the usual method but with an opposite definition of censorship and events).[17] Time-to-event end points were analyzed by the Kaplan–Meier method, with the use of a stratified log-rank test and a Cox proportional-hazards model to estimate the hazard ratio, along with 95% confidence intervals. To examine whether the effect of lenalidomide varied between sub-

groups, Cox models were developed, with terms for study group, subgroup, and the interaction between subgroup and treatment. The interaction terms were evaluated for statistical significance. A comparison of responses before and after consolidation was performed with the use of McNemar's test. Between-group comparisons for the best response during maintenance therapy and for the proportion of patients with adverse events were made with the use of the chi-square test or Fisher's exact test. The incidence rates of second primary cancers were calculated as the ratio of the number of second primary cancers to the number of patient-years at risk and were compared with the use of the binomial exact test. All analyses were predefined in a statistical analysis plan and conducted with the use of Stata software, version 11.0.

RESULTS

PATIENTS AND TREATMENTS

Of the 614 patients who were enrolled, 307 were randomly assigned to lenalidomide maintenance therapy and 307 to placebo. Six patients (1 in the lenalidomide group and 5 in the placebo group) did not receive the assigned study drug. Thirty-seven patients (16 in the lenalidomide group and 21 in the placebo group) did not receive consolidation treatment before maintenance therapy. Table 1 shows the baseline characteristics of the patients. Adverse cytogenetic profiles, including the t(4;14) and the 17p deletion, were more common in the lenalidomide group (P=0.006).

RESPONSE RATES

Lenalidomide consolidation treatment (administered to 577 patients) improved the rate of a complete or very good partial response: 58% before consolidation versus 69% after consolidation (P<0.001) (data not shown). Lenalidomide maintenance therapy improved the rate of a complete or very good partial response, as compared with placebo (P=0.009) (Table 2).

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL AT STUDY UNBLINDING (JULY 2010)

The median follow-up period was 30 months; 264 patients had disease progression (104 in the lenalidomide group and 160 in the placebo group). The median progression-free survival was 41 months in the lenalidomide group, as compared with 23 months in the placebo group (hazard ratio, 0.50; P<0.001). The probability of surviving free of progression for 3 years after randomization was 59% in the lenalidomide group and 35% in the placebo group (Fig. 1). Age, sex, isotype of the monoclonal component, International Staging System stage, induction regimen, or number of transplantations did not modify the progression-free survival benefit with lenalidomide (Fig. 1 in the Supplementary Appendix). The rate of progression-free survival 3 years after randomization was higher in all stratified subgroups of patients who received lenalidomide maintenance therapy, as compared with those who received placebo, including patients who had a very good partial response at the time of randomization (64% vs. 49%, P=0.006) and those who did not (51% vs. 18%, P<0.001), patients with a baseline serum β_2-microglobulin level that was 3 mg per liter or lower (71% vs. 41%, P<0.001) and those with a level that was more than 3 mg per liter (50% vs. 29%, P<0.001), and patients with a 13q deletion (53% vs. 24%, P<0.001) and those without this cytogenetic abnormality (67% vs. 44%, P<0.001). The overall survival 3 years after randomization was similar in the two study groups (80% in the lenalidomide group and 84% in the placebo group; hazard ratio with lenalidomide, 1.25; P=0.29) (Fig. 1). Median survival was not reached in either group.

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL AS OF OCTOBER 2011

The median follow-up was 45 months from the time of randomization and 55 months from the time of diagnosis. The probability of surviving free of disease progression for 4 years after randomization was 43% in the lenalidomide group, as compared with 22% in the placebo group (hazard ratio, 0.50; P<0.001) (Fig. 2 in the Supplementary Appendix); 79 patients (26%) in the lenalidomide group and 73 patients (24%) in the placebo group had died by October 2011 (hazard ratio, 1.06; P=0.70). The overall survival rate 4 years after randomization was similar in the two groups (73% in the lenalidomide group and 75% in the placebo group) (Fig. 2 in the Supplementary Appendix).

SALVAGE THERAPY

As of October 2011, a total of 124 patients in the lenalidomide group had disease progression, and 108 symptomatic patients had received a second-line therapy: lenalidomide (in 16 patients), bortezo-

Table 1. Baseline Characteristics of the Patients.*

Variable	Lenalidomide Group (N=307)	Placebo Group (N=307)
Age — yr		
Mean	55	55
Range	22–67	32–66
Male sex — no. of patients (%)	169 (55)	181 (59)
Type of myeloma — no. (%)		
IgG	192 (63)	169 (55)
IgA	62 (20)	78 (25)
Light-chain	47 (15)	55 (18)
Other	6 (2)	5 (2)
ISS stage — %†		
I	43	49
II	35	36
III	22	15
Serum β_2-microglobulin level — %		
≤3 mg/liter	45	45
>3 mg/liter	55	55
Cytogenetic abnormalities — no. of patients/total no. who could be evaluated‡		
Deletion of chromosome 13§	114/275	116/283
t(4;14) translocation	26/255	12/252
Deletion of chromosome 17	30/265	19/269
t(4;14) or deletion of chromosome 17	52/255	29/253
Type of induction therapy — no. of patients (%)		
Vincristine, doxorubicin, and dexamethasone	141 (46)	157 (51)
Bortezomib and dexamethasone	140 (46)	135 (44)
Other	26 (8)	15 (5)
Induction reinforced with DCEP	79 (26)	74 (24)
Transplantations — no. (%)		
1	243 (79)	243 (79)
2	64 (21)	64 (21)
Time from diagnosis to randomization — mo		
Median	10	10
Range	5–26	5–25
Time from transplantation to randomization — mo		
Median	3	3
Range	1–8	1–7
Response at time of randomization — no. (%)¶		
Complete or very good partial response	192 (63)	176 (57)
Less than very good partial response	115 (37)	131 (43)

* Differences between the two groups were not significant with the exception of t(4;14) ($P<0.05$) and t(4;14) or deletion of chromosome 17 ($P<0.01$). DCEP denotes dexamethasone, cyclophosphamide, etoposide, and cisplatin, and ISS International Staging System.
† The ISS consists of three stages, with higher stages indicating more severe disease.
‡ Data were obtained with the use of fluorescence in situ hybridization.
§ For technical reasons, 56 patients (32 in the lenalidomide group and 24 in the placebo group) could not be evaluated and were not considered to have the 13q deletion.
¶ Responses were based on the assessments by the investigators.

Table 2. Response to Treatment as Assessed by the Independent Review Committee.*

Variable	Lenalidomide Group (N=307)	Placebo Group (N=307)	P Value
Response at randomization			
Response could be evaluated — no. of patients (%)	266 (87)	274 (89)	0.18
Complete response — %	5	8	
VGPR — %†	56	51	
Partial response — %	38	39	
Stable disease — %	1	2	
Complete response or VGPR — %	61	59	0.55
Best response during maintenance			
Response could be evaluated — no. of patients (%)	300 (98)	293 (95)	0.07
Complete response — %	29	27	
VGPR — %‡	55	49	
Partial response — %	15	23	
Stable disease — %	1	1	
Complete response or VGPR — %	84	76	0.009

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. The response could be evaluated if all documentation supporting the response (i.e., results of serum and urine tests at the same time points) was provided to the independent review committee. VGPR denotes very good partial response.
† This group included four patients (2%) in the lenalidomide group who had complete disappearance of M protein on immunofixation but did not undergo bone marrow evaluation and five such patients (2%) in the placebo group.
‡ This group included six patients (2%) in the lenalidomide group who had complete disappearance of M protein on immunofixation but did not undergo bone marrow evaluation and nine such patients (3%) in the placebo group.

mib (in 54), thalidomide (in 5), bortezomib plus thalidomide (in 10), or chemotherapy without new agents (in 23). In the placebo group, 199 patients had disease progression, and 173 symptomatic patients had received a second-line therapy: lenalidomide (in 90 patients), bortezomib (in 30), thalidomide (in 7), bortezomib plus thalidomide (in 27), or chemotherapy without new agents (in 19).

ADVERSE EVENTS

At the time of unblinding (July 2010), 83 patients (27%) in the lenalidomide group and 44 patients (15%) in the placebo group had discontinued the study drug because of adverse events. The median relative dose intensity of the study drug (the administered dose divided by the target dose) was 83% in the lenalidomide group and 94% in the placebo group. Table 3 lists the most common adverse events. The rate of grade 3 or 4 peripheral neuropathy was similar in the two study groups. Thromboembolic events were reported more frequently in the lenalidomide group (6%, vs. 2% in the placebo group; P=0.01), as were grade 3 or 4 hematologic events (58% vs. 23%, P<0.001).

SECOND PRIMARY CANCERS

As of October 2011, an increased incidence of second primary cancers was observed in the lenalidomide group (Table 4, and Fig. 3 in the Supplementary Appendix). Thirty-two second primary cancers in 26 patients were reported in the lenalidomide group versus 12 second primary cancers in 11 patients in the placebo group. The incidence of second primary cancers was 3.1 per 100 patient-years in the lenalidomide group versus 1.2 per 100 patient-years in the placebo group (P=0.002). In the multivariate analysis, the incidence of second primary cancers was significantly related to study-group assignment, age, sex, and International Staging System stage (Table 1 in the Supplementary Appendix). The 4-year event-free survival was 39% in the lenalidomide group and 20% in the placebo group (P<0.001) (Fig. 4 in the Supplementary Appendix).

DISCUSSION

This phase 3 study documents that maintenance therapy with lenalidomide after transplantation is associated with significant improvement in outcomes for patients with newly diagnosed myeloma.

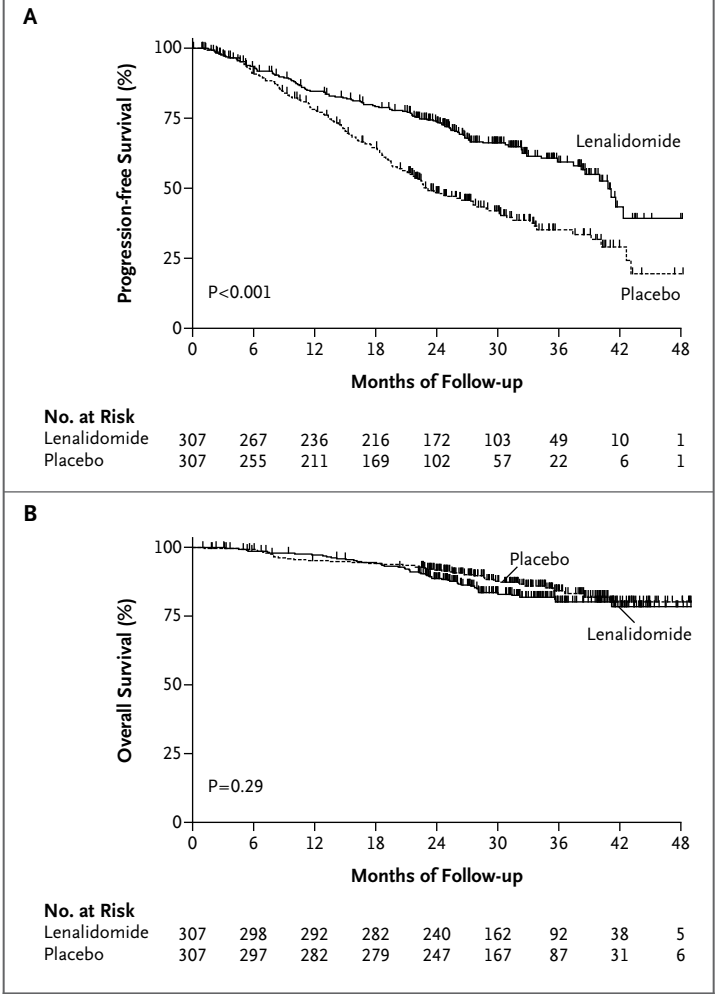

Figure 1. Kaplan–Meier Curves for Progression-free Survival and Overall Survival in the Intention-to-Treat Population, According to Study Group, at Study Unblinding (July 2010).

Panel A shows progression-free survival, with median rates of 41 months in the lenalidomide group as compared with 23 months in the placebo group (hazard ratio, 0.50; P<0.001). Panel B shows overall survival. At 3 years after randomization, overall survival was similar in the two groups (hazard ratio, 1.25; P=0.29).

The probability of surviving free of disease progression (the primary end point) for 3 years after randomization was 59% in the lenalidomide group, as compared with 35% in the placebo group (hazard ratio, 0.50; P<0.001). This benefit was observed across all the patient subgroups, even those with different prognoses based on baseline demographic or disease characteristics, including response at the time of randomization and initial cytogenetic profile.

After a median follow-up of 45 months from the time of randomization (and 55 months from the time of diagnosis), overall survival was similar in the two study groups. Our study was not designed to show an overall survival advantage, and the number of deaths is still low (25% rate of death). The probability of surviving 4 years after randomization was high for both groups. This result might be related to the intensive strategy we used (reinforced induction, a second transplantation in patients who did not have a complete or very good partial response after the first transplantation,[3] and consolidation) and to the activity of new agents that were used to treat relapses.[18] In our study, a longer follow-up is still required to assess the role of lenalidomide maintenance on overall survival. McCarthy et al., who conducted a similar randomized, phase 3 trial that compared lenalidomide with placebo for maintenance therapy after transplantation in myeloma, reported a survival benefit in favor of the lenalidomide group.[19]

The adverse events reported in the lenalidomide group were consistent with established toxicity profiles of lenalidomide.[14,15] The most frequent adverse events were hematologic. Grade 3 or 4 hematologic events were reported in 58% of patients in the lenalidomide group versus 22% in the placebo group (P<0.001). However, these toxic effects were manageable with dose adjustment, without the need for granulocyte colony-stimulating factors or prophylactic antibiotics. Furthermore, the rate of febrile neutropenia was similar in the two study groups. Thromboembolic complications were reported more frequently in the lenalidomide group than in the placebo group (6% vs. 2%, P=0.01). Although thromboembolic events were less frequent in our patients who received lenalidomide maintenance than in patients who received lenalidomide plus dexamethasone for newly diagnosed or relapsed refractory disease,[14,15] our experience justifies the use of prophylactic antithrombotic therapy in future lenalidomide maintenance studies. The rate of grade 3 or 4 peripheral neuropathy was low in both study groups (about 1%). Maintenance with lenalidomide was not associated with the increased risk of peripheral neuropathy observed in studies of thalidomide maintenance therapy.[7-11] Our study shows that lenalidomide maintenance therapy is feasible and that the toxic effects are moderate and manageable.

An increased incidence rate of second primary

Table 3. Adverse Events after Randomization in the Treated Population.*

Event	Lenalidomide Group (N=306)†		Placebo Group (N=302)‡	
	All Events	Grade 3 or 4 Events	All Events	Grade 3 or 4 Events
	number of patients (percent)			
Any event	305 (>99)	225 (74)	297 (98)	130 (43)
Hematologic events	210 (69)	179 (58)	107 (35)	68 (22)
Neutropenia	180 (59)	157 (51)	78 (26)	53 (18)
Febrile neutropenia	6 (2)	4 (1)	1 (<1)	1 (<1)
Anemia	31 (10)	10 (3)	28 (9)	7 (2)
Thrombocytopenia	74 (24)	44 (14)	45 (15)	20 (7)
Gastrointestinal disorders	222 (72)	12 (4)	171 (57)	4 (1)
Nausea and vomiting	48 (16)	1 (<1)	54 (18)	0
Constipation	61 (20)	2 (1)	58 (19)	0
Diarrhea	123 (40)	5 (2)	61 (20)	1 (<1)
General disorders	209 (68)	18 (6)	184 (61)	8 (3)
Fatigue	145 (47)	15 (5)	122 (40)	6 (2)
Pyrexia	62 (20)	1 (<1)	33 (11)	0
Peripheral edema	20 (7)	0	19 (6)	0
Infections	252 (82)	41 (13)	232 (77)	15 (5)
Upper respiratory infection	215 (70)	7 (2)	194 (64)	2 (1)
Pneumonia	35 (11)	11 (4)	14 (5)	5 (2)
Herpes zoster	51 (17)	7 (2)	53 (18)	4 (1)
Vascular disorders	51 (17)	11 (4)	44 (15)	8 (3)
Deep-vein thrombosis	14 (5)	7 (2)	6 (2)	3 (1)
Pulmonary embolism	5 (2)	4 (1)	0	0
Nervous system disorders	156 (51)	9 (3)	130 (43)	12 (4)
Ischemic stroke	2 (1)	2 (1)	0	0
Headache	35 (11)	0	31 (10)	1 (<1)
Dizziness	22 (7)	0	31 (10)	1 (<1)
Tremor	4 (1)	0	5 (2)	0
Peripheral neuropathy	71 (23)	4 (1)	49 (16)	3 (1)
Skin disorders	176 (57)	21 (7)	146 (48)	11 (4)
Rash	61 (20)	10 (3)	51 (17)	6 (2)
Other conditions				
Decreased appetite	18 (6)	0	12 (4)	1 (<1)
Insomnia	27 (9)	0	23 (8)	0
Dyspnea	20 (6)	1 (<1)	13 (4)	0
Back pain	80 (26)	4 (1)	83 (27)	4 (1)
Arthralgia	49 (16)	2 (1)	52 (17)	5 (2)
Muscle spasms	119 (39)	2 (1)	70 (23)	1 (<1)

* In the lenalidomide group, 1 patient did not receive the study drug (as consolidation and maintenance therapy) owing to grade 4 thrombocytopenia; in the placebo group, 5 patients did not receive the study drug: 3 because of disease progression and 2 because consent was withdrawn.

† In the lenalidomide group, treatment was discontinued in 83 patients (27.1%) for the following reasons: blood disorders (10), gastrointestinal disorders (13), general disorders (13), neoplasms (8), nervous system disorders (11), skin and subcutaneous tissue disorders (12), vascular disorders (6), infections (4), or other events (17). A patient could have more than one adverse event.

‡ In the placebo group, treatment was discontinued in 44 patients (14.6%) for the following reasons: blood disorders (7), gastrointestinal disorders (3), general disorders (3), neoplasms (2), nervous system disorders (6), skin and subcutaneous tissue disorders (8), vascular disorders (3), infections (4), or other events (17). A patient could have more than one adverse event.

Table 4. Types of Lesions in Patients with at Least One Second Primary Cancer.*

Type of Lesion	Lenalidomide Group (N=306)	Placebo Group (N=302)	Total (N=608)
	number of patients (percent)		
Hematologic cancers	13 (4)	5 (2)	18 (3)
AML or MDS	5	4	
ALL	3	0	
Hodgkin's lymphoma	4	0	
Non-Hodgkin's lymphoma	1	1	
Solid tumors	10 (3)	4 (1)	14 (2)
Esophageal	1	0	
Colon	3	0	
Prostate	2	1	
Breast	2	0	
Lung	0	1	
Sinus	1	0	
Kidney	1	1	
Melanoma	0	1	
Nonmelanoma skin cancers	5 (2)	3 (1)	8 (1)
Total	26 (8)	11 (4)	37 (6)

* There were 32 second primary cancers in the lenalidomide group and 12 in the placebo group. ALL denotes acute lymphoblastic leukemia, AML acute myeloblastic leukemia, and MDS myelodysplastic syndrome.

cancers was observed in the lenalidomide group. Similar trials of lenalidomide maintenance have confirmed this risk.[19,20] Second primary cancers (especially acute myeloblastic leukemia or the myelodysplastic syndrome) are part of the natural history of myeloma and its treatment.[21] In our study, there were seven cases of acute lymphoblastic leukemia or Hodgkin's disease among patients who had received induction therapy with dexamethasone, cyclophosphamide, etoposide, and cisplatin or had undergone two transplantations and had received lenalidomide maintenance therapy for at least 2 years. An increased risk of acute lymphoblastic leukemia or Hodgkin's disease has not previously been reported among patients with myeloma.[21] Currently, the beneficial effect of lenalidomide maintenance therapy on event-free survival suggests that more patients receive benefit than are harmed; however, the risk of second primary cancers is serious, and longer follow-up periods will be necessary to accurately quantify the risk.

In conclusion, this study shows that lenalidomide maintenance therapy after transplantation significantly improves progression-free and event-free survival (with second primary cancers included as events) in patients with multiple myeloma, without improvement in overall survival. Its use is associated with increased myelotoxicity and increased risks of thromboembolism and second primary cancers. Together with the findings reported by McCarthy et al.,[19] our data support the use of lenalidomide maintenance therapy after high-dose chemotherapy and autologous hematopoietic stem-cell transplantation in patients with myeloma, but the impressive benefits must be weighed against the increased risks.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335:91-7.
2. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348:1875-83.
3. Attal M, Harousseau J-L, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495-502. [Erratum, N Engl J Med 2004;350:2628.]
4. Barlogie B, Tricot GJ, van Rhee F, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. Br J Haematol 2006;135:158-64.
5. Cunningham D, Powles R, Malpas J, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. Br J Haematol 1998; 102:495-502.
6. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006; 24:929-36.
7. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006;108:3289-94.
8. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 2006;354:1021-30.
9. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 2009;27:1788-93.
10. Lokhorst HM, van der Holt B, Zweegman S, et al. A randomized phase 3 study on the effect of thalidomide combined

with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood 2010;115:1113-20.
11. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC myeloma IX results and meta-analysis. Blood 2012;119:7-15.
12. Marriott JB, Clarke IA, Dredge K, Muller G, Stirling D, Dalgleish AG. Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2 during costimulation of both CD4(+) and CD8(+) T cells. Clin Exp Immunol 2002;130:75-84.
13. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005; 106:4050-3.
14. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32. [Erratum, N Engl J Med 2009;361:544.]
15. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.
16. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73. [Errata, Leukemia 2006; 20:2220, 2007;21:1134.]
17. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-6.
18. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-20.
19. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1770-81.
20. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759-69.
21. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer 2001;85: 997-1005.