# Maintenance therapy with thalidomide improves survival in patients with multiple myeloma

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**Newer chemotherapeutic protocols as well as high-dose chemotherapy have increased the response rate in myeloma. However, these treatments are not curative. Effective maintenance strategies are now required to prolong the duration of response. We conducted a randomized trial of maintenance treatment with thalidomide and pamidronate. Two months after high-dose therapy, 597 patients younger than age 65 years were randomly assigned to receive no maintenance (arm A), pamidronate (arm B), or pamidronate plus thalidomide (arm C). A complete or very good partial response was achieved by 55% of patients in arm A, 57% in arm B, and 67% in arm C ($P = .03$). The 3-year postrandomization probability of event-free survival was 36% in arm A, 37% in arm B, and 52% in arm C ($P < .009$). The 4-year postdiagnosis probability of survival was 77% in arm A, 74% in arm B, and 87% in arm C ($P < .04$). The proportion of patients who had skeletal events was 24% in arm A, 21% in arm B, and 18% in arm C ($P = .4$). Thalidomide is an effective maintenance therapy in patients with multiple myeloma. Maintenance treatment with pamidronate does not decrease the incidence of bone events. (Blood. 2006;108:3289-3294)**



## Introduction

During the past 10 years, major advances in the treatment have improved the outlook in myeloma. The antitumor activity of thalidomide,[1] bortezomib,[2] and lenalidomide[3] has been discovered, and the combination of these new drugs with conventional cytotoxic agents has been reported to induce a high complete response rate.[4-8] High-dose therapy followed by autologous stem cell transplantation (ASCT) has been shown to improve response rate,[9-13] event-free survival,[9-11,13] and overall survival[9,10,13] as compared with conventional chemotherapy. ASCT is now recommended for young patients as part of the initial therapy or at time of the disease progression.[14] However, the median duration of response after the newer chemotherapeutic protocols and ASCT does not exceed 3 years, and almost all patients relapse.

To prolong the duration of response, maintenance therapy was a logical approach. Maintenance therapy might prolong response and survival by inhibiting proliferation and inducing apoptosis of malignant cells that have not been eliminated by chemotherapy. However, this hypothesis is not supported by controlled trials, and the role of maintenance therapy in myeloma remains controversial. Maintenance chemotherapy has failed to demonstrate any benefit.[15,16] Most randomized studies and meta-analyses evaluating maintenance interferon showed a modest increase in progression-free survival without any, or with minimal, survival benefit after conventional or high-dose therapy.[17-19] Corticosteroid maintenance was found to prolong the duration of response; however, the effect on survival was controversial.[20,21]

Thalidomide is an agent with immunomodulatory and antiangiogenic properties. In 1999, Singhal et al[1] reported that thalidomide induced responses in one third of patients with refractory disease. Several studies confirmed the activity of this oral agent among patients who had failed high-dose therapy, with doses as low as 50 mg, without myelosuppressive toxicity.[22,23] Thus, thalidomide was an attractive candidate for use in maintenance situations, particularly after high-dose therapy. Biphosphonates inhibit osteoclastic activity and are effective in the treatment of cancer-associated hypercalcemia.[24] Pamidronate, a second-generation biphosphonate, was found to decrease the incidence of osteolytic bone lesion

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Submitted May 25, 2006; accepted July 6, 2006. Prepublished online as *Blood* First Edition Paper, July 27, 2006; DOI 10.1182/blood-2006-05-022962.

A complete list of the members of the Inter-Groupe Francophone du Myélome appears in the "Appendix."

Supported by a major grant from the Programme Hospitalier de Recherche Clinique and by the Swiss Group for Clinical Cancer Research (SAKK).

The authors declare no competing financial interests.

M.A., J.-L.H., S.L., C.D., C.H., L.B., I.Y.A., J.-H.B., L.G., B.P., C.D., M.R., L.V., C.B., G.M., M.M., D.C., B.G., H.A.-L., P.M., and T.F. participated in designing and performing the research; M.A. analyzed the data and wrote the paper; and all authors checked the final version of the manuscript.

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in myeloma, when added to conventional chemotherapy.[25] However, the efficacy of pamidronate in reducing skeletal events has never been evaluated when used as maintenance treatment after conventional or high-dose therapy. In 1999, the Intergroupe Francophone du Myélome (IFM) initiated the first randomized trial designed to evaluate the role of thalidomide and pamidronate as maintenance treatment.

## Patients, materials, and methods

### Requirements for patient enrollment

Patients younger than 65 years of age were eligible for the IFM 99 trials. Patients with 2 adverse prognostic factors (β-2 microglobulin > 3 mg/L and deletion of chromosome 13 by fluorescence in situ hybridization [FISH] analysis) were enrolled in the IFM 99 03-04 trials (reported elsewhere). Patients without or with only 1 adverse prognostic factor were enrolled in the present IFM 99 02 protocol. The criteria for exclusion were prior treatment for myeloma, another malignancy, abnormal cardiac function (systolic ejection fraction < 50%), chronic respiratory disease (vital capacity or carbon monoxide diffusion < 50% of normal), abnormal liver function (serum bilirubin > 35 μM or ALAT, ASAT > 4 times normal), psychiatric disease. Between April 2000 and October 2003, 1019 patients from 74 centers were registered in the IFM 99 trials. Two hundred thirty-nine patients (23%) were enrolled in the IFM 99 03-04 trials and 780 patients (77%) were enrolled in the present IFM 99 02 protocol. The study was approved by the institutional ethics committees of Purpan Hospital (Toulouse, France), and the patients gave written informed consent in accordance with the Declaration of Helsinki.

### Study protocol

***Initial enrollment.*** Patients were registered by the coordinating center (Toulouse), and a centralized analysis of β-2 microglobulin and deletion of chromosome 13 were performed (Nantes).

***Initial chemotherapy.*** Patients were initially treated with a continuous intravenous infusion of 0.4 mg vincristine/$m^2$ body surface area and 9 mg doxorubicin/$m^2$ over a 24-hour period for 4 days, with 40 mg oral dexamethasone/day on days 1 through 4 (the VAD regimen). Three to 4 cycles of VAD were administered at 3-week intervals.

***Stem-cell transplantation.*** After initial chemotherapy, patients with a performance status below World Health Organization grade 3 and a serum creatinine level less than 150 μM underwent blood stem-cell collection. Double ASCT was performed. Melphalan alone was given before each ASCT (140 mg/$m^2$ before the first transplantation and 200 mg/$m^2$ before the second).

***Randomization.*** Two months after the second ASCT, patients without progressive disease were randomly assigned to receive one of the following treatment arms until disease progression: arm A, no maintenance treatment; arm B, maintenance treatment with pamidronate (intravenous infusion of 90 mg pamidronate at 4-week intervals); arm C, maintenance treatment with pamidronate and thalidomide (400 mg orally, dose reduction to a minimum dose of 50 mg was allowed for treatment-related toxicity). Patients enrolled in arm C did not receive any prophylaxis of thromboembolic complications. The sequence of randomization was determined by the coordinating center (Toulouse), which made the treatment assignment by Fax after each patient's eligibility was confirmed.

### Assessments

The response criteria of the European Group for Blood and Marrow Transplantation[26] proposed in 1998 were not used in this study submitted to the French authorities in 1998. A complete remission was defined as the lack of detectable paraprotein by serum and urine electrophoresis and 5% or fewer plasma cells with normal morphology in a bone marrow aspirate. A very good partial response was defined as a decrease of 90% in the serum paraprotein level, a partial response as a decrease of 50% in the serum paraprotein level or a 90% decrease in the level of Bence Jones protein (including patients with Bence Jones protein only) or both, a minimal response as a decrease of 25% in the serum paraprotein level, stable disease as no change in the paraprotein level, progressive disease as an increase of 25% in the serum paraprotein level after 2 cycles of the initial chemotherapy, and a relapse as the reappearance of the paraprotein and/or the recurrence of bone marrow infiltration in a patient with a complete response and a 50% increase in paraprotein above the "plateau" level in 2 samples obtained 4 weeks apart in a patient with a response. A skeletal event was defined as a bone lesion requiring a specific therapy (chemotherapy, irradiation, or surgery).

### Statistical analysis

The proportions of patients with a given characteristic were compared by chi-square test or Fisher exact test. Differences in the means of continuous measurements were tested by Student *t* test and checked with the use of the Mann-Whitney *U* test. All tests were 2-tailed. The duration of event-free survival was calculated for patients randomly assigned from the date of random assignment to the time of progression, relapse, or death. The duration of relapse-free survival was calculated for patients achieving at least a minimal response, from the date of random assignment to the date of progression. The time to skeletal event was calculated from the date of random assignment to the date of the first occurrence of a skeletal event. Kaplan-Meier curves for event-free survival, relapse-free survival, time to skeletal event, and overall survival were compared by the use of the log-rank test. Prognostic factors for event-free survival were determined by means of the Cox proportional hazard model for covariate analysis. The objectives were to compare the arm A and arm B with respect to the 3-year risk of skeletal events, and to compare the arm B and arm C with respect to the 3-year risk of events. Two hundred patients were required in each group to ensure a significance level of 5% and a power of 95% if the true 3-year risk of skeletal events were 25% in arm A and 10% in arm B, and if the true 3-year risk of events were 50% in arm B and 38% in arm C. The study was completed after 597 patients had been randomly assigned.

## Results

### Patient flow

Seven hundred eighty patients were enrolled. Five hundred ninety-seven patients (77%) were randomly assigned: 200 in arm A, 196 in arm B, and 201 in arm C. The median time from enrollment to randomization was 9 months (range, 6-21 months). One hundred eighty-three patients were not randomly assigned: 40 because of protocol violation, 26 because of early death, 40 because of early progression, and 77 because they did not undergo double transplantation.

### Baseline characteristics

The baseline characteristics of the 597 patients randomly assigned is shown in Table 1. No significant differences were found between the treatment groups.

### Response rate

The response rate at each step of the study is shown in Table 2. Thalidomide was found to improve the best response achieved after randomization ($P < .001$). Sixty-seven percent of the patients enrolled in arm C had a complete or a very good partial response, as compared with 55% in arm A and 57% in arm B ($P = .03$).

### Event-free, relapse-free, and overall survival

In arm A, the median follow-up was 40 months (range, 28-63 months) from the time of enrollment and 30 months (range,

**Table 1. Baseline characteristics of the patients**

| | Arm A; n = 200 | Arm B; n = 196 | Arm C; n = 201 |
|---|---|---|---|
| Sex, M/F, no. of patients | 110/90 | 109/87 | 112/89 |
| Age, y | 59 ± 8* | 59 ± 8 | 58 ± 8 |
| DS stage I/II/III, no. of patients | 19/50/131 | 16/34/146 | 16/42/143 |
| **M component, no. of patients** | | | |
| IgG | 124 | 129 | 119 |
| IgA | 47 | 32 | 52 |
| Bence Jones | 24 | 30 | 28 |
| IgD | 5 | 5 | 2 |
| Hemoglobin, g/dL | 11.3 ± 2 | 11.2 ± 2 | 11.1 ± 2 |
| Serum calcium, μM | 2.4 ± 0.2 | 2.4 ± 0.3 | 2.4 ± 0.4 |
| Serum albumin, g/L | 40 ± 7 | 40 ± 8 | 39 ± 7 |
| Lactate dehydrogenase, IU | 321 ± 146 | 336 ± 146 | 311 ± 143 |
| Serum creatinine, μM | 101 ± 64 | 101 ± 67 | 101 ± 57 |
| Bone marrow plasmocytosis, % of cells | 30 ± 24 | 34 ± 24 | 31 ± 25 |
| Serum β-2 microglobulin, mg/L | 3.4 ± 3 | 3.3 ± 2.5 | 3.7 ± 5 |
| C reactive protein, mg/L | 10 ± 16 | 10 ± 18 | 11 ± 23 |
| **Chromosome 13, no. of patients** | | | |
| No deletion | 134 | 136 | 142 |
| Deletion | 60 | 56 | 55 |
| Unknown | 6 | 4 | 4 |

*All such values are means ± SD.

18-50 months) from the time of randomization. The 3-year probabilities of event-free and relapse-free survival after randomization were 36% and 38%, respectively. The probability of overall survival 4 years after enrollment was 77%.

In arm B, the median follow-up was 39 months (range, 29-64 months) from the time of enrollment and 29 months (range, 19-52 months) from the time of randomization. The 3-year probabilities of event-free and relapse-free survival after randomization were 37% and 39%, respectively. The probability of overall survival 4 years after enrollment was 74%.

In arm C, the median follow-up was 39 months (range, 30-63 months) from the time of enrollment and 29 months (range, 20-53 months) from the time of randomization. The 3-year probabilities of event-free and relapse-free survival after randomization were 52% and 51%, respectively. The probability of overall survival 4 years after enrollment was 87%.

The event-free survival ($P < .009$), relapse-free survival ($P < .008$), and overall survival ($P < .04$) were significantly different between the 3 treatment arms. The event-free survival ($P = .6$), relapse-free survival ($P = .7$), and overall survival ($P = .7$) of patients randomly assigned to arms A and B were similar (without thalidomide). The event-free survival ($P < .01$), relapse-free survival ($P < 0.01$), and overall survival ($P < 0.03$) were significantly improved in arm C as compared with arm B. Thalidomide (arm C/arms A + B) was found to significantly improve the event-free survival ($P = .002$) (Figure 1), relapse-free survival ($P = .003$), and overall survival ($P = .04$) (Figure 2).

**Table 2. Response rate**

| | Arm A; n = 200 | Arm B; n = 196 | Arm C; n = 201 | *P* |
|---|---|---|---|---|
| **After VAD regimen, n (%)** | | | | NS |
| CR or VGPR | 30 (15) | 30 (15) | 32 (16) | |
| **At randomization, n (%)** | | | | NS |
| CR or VGPR | 94 (47) | 92 (47) | 100 (50) | |
| PR | 84 (42) | 84 (43) | 78 (39) | |
| MR | 20 (10) | 16 (8) | 20 (10) | |
| PD | 2 (1) | 4 (2) | 3 (1) | |
| **Best response after randomization, n (%)** | | | | .001 |
| CR or VGPR | 110 (55) | 112 (57) | 135 (67) | |
| PR | 74 (37) | 72 (37) | 60 (30) | |
| MR | 15 (7.5) | 11 (5.5) | 6 (3) | |
| PD | 1 (0.5) | 1 (0.5) | 0 | |

VAD indicates vincristine, doxorubicin, and dexamethasone; CR indicates a complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; PD, progressive disease; and NS, not significant.

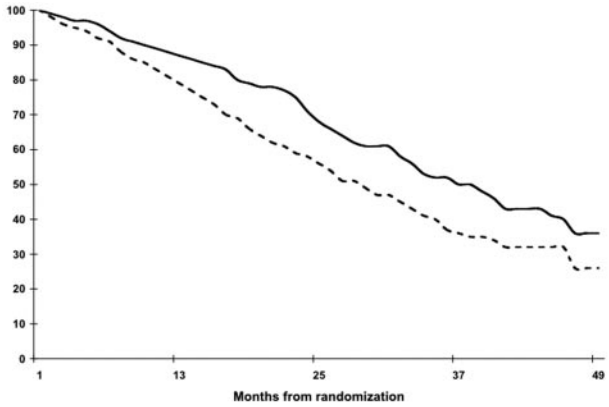


**Figure 1. Event-free survival according to treatment arm.** The probabilities of event-free survival (95% confidence interval) are shown below each time point. Without thalidomide (dotted line); with thalidomide (solid line). The probability of event-free survival (95% CI) after randomization at 2 years, 3 years, and 4 years with thalidomide is 71 (63-78), 52 (43-62), and 36 (22-55), respectively, and without thalidomide is 58 (53-64), 37 (31-44), and 26 (14-41), respectively.

### Salvage therapy

In arm A, 96 patients had a relapse: 6 patients received no salvage therapy, 10 received conventional chemotherapy, 2 received stem-cell transplantation, 61 received thalidomide, and 17 received bortezomib or lenalidomide. With a median follow-up of 13 months from the time of relapse, the probability for 1-year survival after relapse was 78%.

In arm B, 92 patients had a relapse: 8 patients received no salvage therapy, 11 received conventional chemotherapy, 61 received thalidomide, and 12 received bortezomib or lenalidomide. With a median follow-up of 12 months from the time of relapse, the probability for 1-year survival after relapse was 73%.

In arm C, 72 patients had a relapse: 5 patients received no salvage therapy, 19 received conventional chemotherapy, 1 received stem-cell transplantation, 20 received thalidomide plus

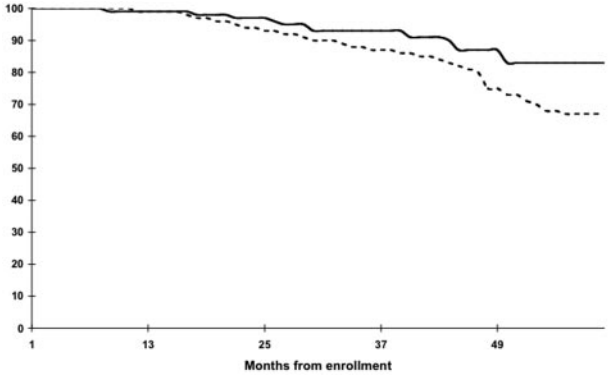


**Figure 2. Overall survival according to treatment arm.** The probabilities of overall survival (95% confidence interval) are shown below each time point. Without thalidomide (dotted line); with thalidomide (solid line). The probability of overall survival (95% CI) after enrollment at 2 years, 3 years, and 4 years with thalidomide is 97 (93-98), 93 (87-96), and 87 (80-93), respectively, and without thalidomide is 94 (91-96), 87 (83-90), and 75 (69-82), respectively.

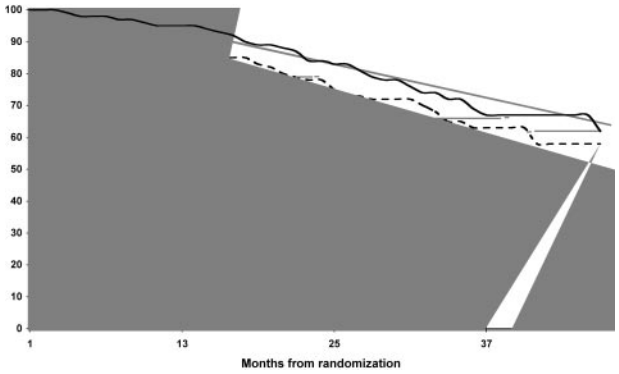


**Figure 3. Survival without skeletal event according to treatment arm.** The probabilities of survival without skeletal event (95% confidence interval) are shown below each time point. Arm A received no maintenance (dotted line); arm B received maintenance with pamidronate (gray line); arm C received maintenance with pamidronate and thalidomide (solid line). The probability of survival without skeletal event (95% CI) after randomization at 1 year, 2 years, and 3 years in arm A is 89 (83-93), 78 (70-83), and 63 (52-74), respectively; in arm B is 91 (87-95), 79 (71-86), and 66 (55-76), respectively; and in arm C is 95 (91-98), 84 (78-90), and 69 (59-79), respectively.

dexamethasone, and 27 received bortezomib or lenalidomide. With a median follow-up of 11 months from the time of relapse, the probability for 1-year survival after relapse was 75%. The survival rates after relapse were similar in the 3 treatment groups ($P = .7$).

### Prognostic factors for event-free survival

In a multivariate analysis of all 597 patients randomly assigned, event-free survival was significantly related to deletion of chromosome 13 ($P < .05$), β-2 microglobulin ($P < .009$), response at time of randomization ($P < .009$), and treatment assignment (with or without thalidomide) ($P < .001$).

We compared the event-free survival according to the treatment group (with or without thalidomide) in different subsets of patients. Thalidomide prolonged the event-free survival in each of the following subsets: patients with β-2 microglobulin level of 3 mg/L or less, with β-2 microglobulin level of greater than 3 mg/L, with LDH level of 330 IU or less, with LDH level greater than 330 IU, with stage I or II DS, with stage III DS, patients aged 50 years or younger, and patients aged 50 years or older. The effect of thalidomide on event-free survival differed according to the deletion of chromosome 13. Patients who did not have a deletion of chromosome 13 had a significant benefit from thalidomide ($P < .006$). Patients who had a deletion of chromosome 13 did not benefit from thalidomide ($P = .2$). The effect of thalidomide on event-free survival differed according to the response achieved at time of randomization. Patients who had at least a very good partial response did not benefit from thalidomide ($P = .4$). Patients who did not have at least a very good partial response had a significant benefit from thalidomide ($P < .004$). The lack of benefit in the patients with deletion 13 was independent from the response.

### Risk of skeletal events

The proportion of patients who had skeletal events was 24% in arm A, 21% in arm B, and 18% in arm C ($P = .4$). The survival without skeletal event was not significantly different between the treatment groups ($P = .2$) (Figure 3).

### Treatment-related toxicity

Patients received thalidomide for a median of 15 months (range, 0.1-50 range). Drug-related adverse events led to discontinuation of thalidomide in 78 patients (39%). The median time elapsed between randomization and the onset of the adverse event that led to the discontinuation of thalidomide was 8 months. Peripheral neuropathy was the main reason for discontinuation. The mean dose of thalidomide received by the patients (calculated from initiation to definite discontinuation) was 200 mg/day (range, 50-400 mg/day), and 30 patients tolerated the maximum thalidomide dose for 12.6 months. Patients received pamidronate for a median of 21 months (range, 0.2-51 months). A total of 16 patients (4%) had drug-related adverse effects necessitating discontinuation of pamidronate.

The adverse events (as defined by the National Cancer Institute Common Toxicity Criteria, version 2) in each treatment group are shown in Table 3. Certain toxicities were more prominent in the thalidomide group, including neuropathy (68%), fatigue (34%), constipation (20%), neutropenia (7%), and cardiac (4%). The incidence of venous symptomatic thrombotic events was not significantly different between the 3 treatment groups.

## Discussion

We found that maintenance treatment with thalidomide after high-dose chemotherapy improves the response rate, the event-free survival, and the overall survival in patients with myeloma. Barlogie et al[27] recently reported that high-dose thalidomide improved the complete response rate and prolonged the event-free survival when added to each phase of an intensive combined therapy (including induction, tandem transplantation, consolidation, and maintenance). However, in this study, thalidomide failed to improve survival because of considerable adverse effects and to the occurrence of drug resistance at time of relapse. Our results strongly suggest that reserving the use of low-dose thalidomide for maintenance after transplantation is an effective strategy: toxicity is acceptable, drug resistance at time of relapse is not observed, and survival is improved. We also found that maintenance treatment with pamidronate, a second-generation biphosphonate, does not decrease or delay the risk of skeletal events. Whether newer third-generation biphosphonates, which are more potent than pamidronate in preclinical models, will achieve this goal remains to be answered.

**Table 3. Adverse events according to treatment arm**

| | Percentage of adverse events (% grade 3-4) | | | |
|---|---|---|---|---|
| | Arm A | Arm B | Arm C | *P* |
| Peripheral neuropathy | 8 (1) | 15 (2) | 68 (7) | < .001 |
| Fatigue | 3 (1) | 7 (2) | 34 (6) | < .001 |
| Constipation | 0 | 2 (0) | 20 (1) | < .001 |
| Neutropenia | 0 | 2 (1) | 7 (6) | .001 |
| Cardiac | 0 | 1 (0) | 4 (1) | .04 |
| Thrombosis | 2 (1) | 1 (1) | 4 (2) | NS |
| Thrombocytopenia | 2 (2) | 2 (2) | 3 (3) | NS |
| Anemia | 2 (1) | 2 (1) | 2 (2) | NS |
| Infection | 17 (4) | 24 (7) | 24 (6) | NS |
| Mood change | 2 (0) | 4 (0) | 5 (1) | NS |
| Renal | 2 (1) | 1 (1) | 3 (2) | NS |
| Osteonecrosis of the jaw | 0 | 1 | 1 | NS |
| Nausea | 2 (0) | 3 (1) | 2 (0) | NS |

NS indicates not significant.

An important objective of our trial was to evaluate the feasibility and tolerance of maintenance treatment with thalidomide. Peripheral neuropathy (68%), fatigue (34%), and constipation (20%) were frequently encountered adverse events. However, the incidence of severe neuropathy (grade 3-4) was acceptable (7%). In our trial, maintenance therapy with thalidomide was not found to increase the risk of thromboembolic complications. We thus confirm that this risk is mainly observed if thalidomide is given during induction therapy when the tumor burden is high.[4,27] Thirty-nine percent of patients had to discontinue thalidomide because of drug-related adverse events, and peripheral neuropathy was the main reason for discontinuation. Thus, lenalidomide,[3,7-8] an analog of thalidomide without neurologic toxicities, might be an attractive candidate for use in maintenance situations. The planned starting dose of thalidomide was 400 mg/day. Because of drug-related toxicities, patients received a mean dosage of 200 mg/day for a median of 15 months. Stewart et al[28] reported that the adverse effects of thalidomide, when used as maintenance therapy after transplantation, were dose related. Because responses may occur with doses of 50 to 100 mg/day,[23] maintenance therapy with these low doses should be proposed.

Our trial shows that thalidomide improves the quality of response after randomization. We have previously reported that the attainment of a very good partial response was an important prognostic factor for survival after high-dose therapy in patients with myeloma.[9] The best quality of response, observed in the thalidomide group, could explain the difference in event-free and overall survival. This hypothesis is supported by the observation that thalidomide could benefit patients who do not have a very good partial response at time of randomization but has a limited effect among patients already in very good partial response at time of randomization. Thus, thalidomide may improve the survival by reducing the tumor mass after high-dose therapy rather than by a pure maintenance effect. This result also suggests that stopping thalidomide as soon as a very good partial response has been reached could be an effective strategy to reduce the side effects and to avoid thalidomide resistance at time of relapse. The combination of thalidomide and corticosteroids was reported to be synergistic in term of response rate.[29,30] A phase 2 trial showed that this combination was tolerable when used after high-dose therapy.[28] Whether this association of thalidomide and corticosteroids would further improve the response rate and the overall survival of patients failing to achieve a very good partial response after high-dose therapy will be clarified in ongoing trials.

The toxicity and costs of thalidomide justify the use of an approach in which patients who could benefit the most from this treatment are selected. Our results indicate that thalidomide could benefit patients who do not have a very good partial response at time of randomization. Our results also indicate that thalidomide could benefit patients who do not have a deletion of chromosome 13. Deletion of chromosome 13 is observed in 50% of multiple myeloma tumors and is associated with a poor prognosis.[31] Singhal et al[1] have also reported a poor response rate to thalidomide in patients with this deletion. Another strategy for patients with the chromosome 13 deletion could be maintenance therapy with bortezomib[2] or lenalidomide,[3] because responsiveness to these agents did not correlate with the deletion.

Finally, our trial shows that maintenance treatment with thalidomide after transplantation significantly improves the overall survival in patients with multiple myeloma. However, the absence of plateau in the curve for event-free survival justifies the evaluation of novel agents to decrease the tumor mass before and after transplantation. Analogs of thalidomide, proteasome inhibitors, agents targeting cell-signaling cascades, or surface receptors are being investigated.

## Acknowledgment

We thank Mr Ian Eustace for his critical reading of the manuscript.

## Appendix

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