

ORIGINAL ARTICLE

Thalidomide and Hematopoietic-Cell Transplantation for Multiple Myeloma

Bart Barlogie, M.D., Ph.D., Guido Tricot, M.D., Ph.D., Elias Anaissie, M.D., John Shaughnessy, Ph.D., Erik Rasmussen, M.S., Frits van Rhee, M.D., Ph.D., Athanasios Fassas, M.D., Maurizio Zangari, M.D., Klaus Hollmig, M.D., Mauricio Pineda-Roman, M.D., Choon Lee, M.D., Giampaolo Talamo, M.D., Raymond Thertulien, M.D., Ph.D., Elias Kiwan, M.D., Somashekar Krishna, M.D., Michele Fox, M.D., and John Crowley, Ph.D.

ABSTRACT

BACKGROUND

High-dose therapy with melphalan can prolong survival among patients with multiple myeloma. We assessed whether the addition of thalidomide, which has activity against advanced and refractory myeloma, would further improve survival.

METHODS

Between October 1998 and February 2004, 668 patients with newly diagnosed multiple myeloma received two cycles of intensive melphalan-based chemotherapy, each supported by autologous hematopoietic stem-cell transplantation. A total of 323 were randomly assigned to receive thalidomide from the outset until disease progression or undue adverse effects, and 345 did not receive thalidomide. The primary end point was the five-year event-free survival rate. Secondary end points were complete response and overall survival.

RESULTS

After a median follow-up of 42 months among survivors, the thalidomide and control groups had rates of complete response of 62 percent and 43 percent, respectively ($P < 0.001$), and five-year event-free survival rates of 56 percent and 44 percent ($P = 0.01$). The five-year rate of overall survival was approximately 65 percent in both groups ($P = 0.90$). Median survival after relapse was 1.1 years in the thalidomide group and 2.7 years in the control group ($P = 0.001$). Severe peripheral neuropathy and deep-vein thrombosis occurred more frequently in the thalidomide group than in the control group.

CONCLUSIONS

When incorporated into high-dose therapy for myeloma, thalidomide increased the frequency of complete responses and extended event-free survival at the expense of added adverse effects without improving overall survival. (ClinicalTrials.gov number, NCT00083551.)

From the Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock (B.B., G.T., E.A., J.S., F.R., A.F., M.Z., K.H., M.P.-R., C.L., G.T., R.T., E.K., S.K., M.F.); and Cancer Research and Biostatistics, University of Washington, Seattle (E.R., J.C.). Address reprint requests to Dr. Barlogie at the Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, 4301 W. Markham St., Mail Slot 816, Little Rock, AR 72205, or at barlogiebart@uams.edu.

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THE STEEP DOSE-RESPONSE EFFECT OF melphalan in patients with multiple myeloma can be used to therapeutic advantage when supported with infusions of autologous peripheral-blood stem cells.^{1,2} After a pilot trial of two transplantations in patients with multiple myeloma,³ a larger trial (the InterGroupe Francophone du Myélome) reported seven-year event-free and overall survival rates of 20 and 40 percent, respectively — twice the rates obtained with single transplantations.^{4,5} Our phase 3 randomized trial was prompted by the demonstration of the efficacy of thalidomide (Kevadon) in multiple myeloma that is refractory to post-transplantation salvage therapies.^{6,7} We sought to determine whether the addition of thalidomide to intensive chemotherapy would improve the outcome among patients with multiple myeloma.

METHODS

PATIENTS

Between October 1998 and February 2004, we enrolled 668 patients who had newly diagnosed progressive or symptomatic multiple myeloma, were 75 years old or younger, and had received no more than one cycle of prior therapy. All patients provided written informed consent in keeping with the guidelines of the participating institution and the National Cancer Institute. The protocol was approved by the institutional review board and the Food and Drug Administration and was monitored by a data and safety monitoring board as required by the National Cancer Institute for phase 3 trials. Data on eligibility, dosing, response, and adverse effects were checked by a certified independent auditing team, usually every six months; each audit involved at least 50 patients (a total of 350 were audited).

Prior local radiotherapy for pain control or cord compression was permitted. Patients had to have a Southwest Oncology Group performance status of less than 3, unless the score was based solely on bone pain. Cardiopulmonary function had to be adequate; renal failure, even that requiring hemodialysis, was not an exclusion criterion.

TREATMENT

The study design (Fig. 1) required stratification of patients according to serum beta₂-microglobulin levels (less than 4 mg per liter vs. 4 mg per liter or more). Table 1 lists the four phases of the protocol and the regimens and doses used.⁸⁻¹⁰

At enrollment, patients were randomly assigned either to a control group (no thalidomide) or to the experimental group (thalidomide). The thalidomide doses were 400 mg daily during induction chemotherapy (withheld on day 5 of cycle 3 of chemotherapy for the collection of peripheral-blood stem cells), 100 mg daily between transplantations, 200 mg daily with consolidation therapy, 100 mg daily during the first year of maintenance therapy, and then 50 mg on alternating days; the drug was given until relapse or adverse events occurred. All patients proceeded to the transplantation phase regardless of the level of response or the lack of response to induction chemotherapy.

Filgrastim was administered to support induction and consolidation chemotherapy regimens, such as dexamethasone, cyclophosphamide, etoposide, and cisplatin; cyclophosphamide, doxorubicin, and dexamethasone; and dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (Table 1), along with prophylactic antibiotics, histamine H₂ blockers, and recombinant erythropoietin as needed. Unless required for the management of pain, renal failure, serious infection, or lack of a caregiver, all treatments including transplantations were given in the outpatient setting by experienced members of the nursing staff. Low-molecular-weight heparin was given prophylactically to all patients in the thalidomide group starting in July 2001 to reduce the incidence of deep-vein thrombosis, since the incidence of this complication had not been reduced by treatment with low-dose warfarin.

LABORATORY EVALUATION

Evaluations included serum and urinary protein electrophoresis; quantitation of serum immunoglobulin levels, 24-hour urinary protein excretion, and serum levels of beta₂-microglobulin and C-reactive protein; morphologic interpretation of bone marrow aspirates and biopsy specimens; and flow cytometry to evaluate nuclear DNA content and cytoplasmic immunoglobulin.¹¹ These tests were performed before protocol therapy was begun, monthly until the initiation of consolidation therapy, and every three to six months thereafter.

Other laboratory studies included peripheral-blood counts and chemistry analyses. Multiple gated acquisition scanning or echocardiography was used for cardiac evaluations; pulmonary status was evaluated by determining the forced expiratory volume in one second and carbon monox-

ide diffusion capacity; all test results had to be within the institutional range of normal before enrollment and before each of the two transplantation regimens. Standard skeletal surveys and magnetic resonance imaging (MRI) studies of the skeleton were also performed.

CRITERIA FOR RESPONSE AND RELAPSE

A complete response required the absence of a monoclonal immunoglobulin or light chain on immunofixation analysis of serum and urine, a normal morphologic appearance of bone marrow aspirates and biopsy specimens, and the absence, on flow cytometry, of aneuploid or light-chain-restricted cells.¹¹ A partial response was defined as a reduction in serum monoclonal immunoglobulin levels by at least 75 percent and in urinary light chains by at least 90 percent and a normal morphologic appearance of bone marrow aspirates and biopsy specimens. For each definition, the criteria had to be met on at least two occasions at least two months apart.

Relapse after a complete response was diagnosed on the reappearance of a monoclonal protein in serum or urine. Relapse after a partial response was diagnosed on the basis of an increase in serum monoclonal immunoglobulin levels or in urinary light chains by at least 50 percent or a doubling from the lowest level, whichever occurred first. Disease progression was defined as an increase in serum levels of myeloma protein or in 24-hour urinary excretion of light chains by at least 25 percent.

In patients with nonsecretory or hyposecretory disease, baseline bone marrow plasmacytosis had to exceed 30 percent or multiple bone lesions had to be detected by MRI (fine-needle aspirates from lesions detected in this manner had to contain at least 30 percent monoclonal plasma cells). A response in patients with nonsecretory multiple myeloma required a complete bone marrow response or resolution of MRI-defined bone lesions. Relapse of nonsecretory multiple myeloma was defined by the reemergence of monoclonal marrow plasmacytosis or focal lesions on MRI. The development of new osteolytic lesions and extramedullary multiple myeloma also constituted relapse or progression in patients with secretory and those with nonsecretory multiple myeloma.

STATISTICAL ANALYSIS

The primary objective of the study was to demonstrate an increase in the five-year event-free sur-

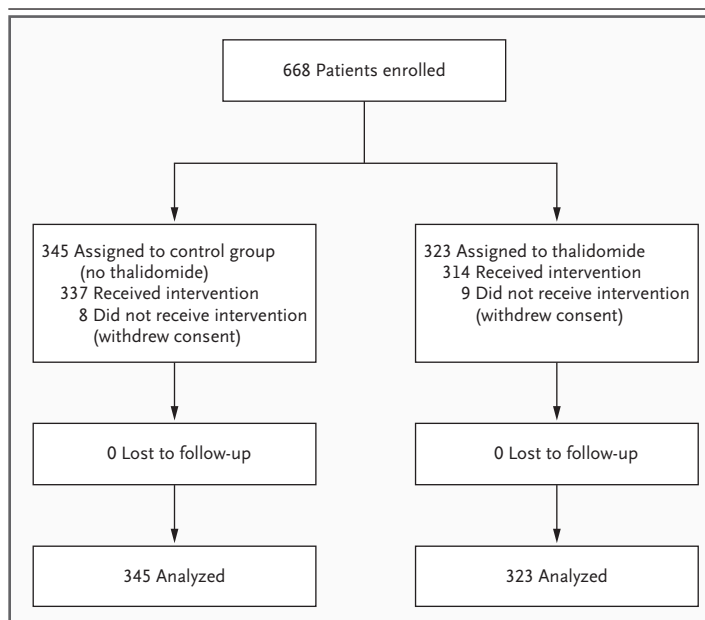


Figure 1. Consolidated Standards of Reporting Trials Chart of the Trial.

vival rate from 40 percent in the control group to 50 percent in the thalidomide group, given a statistical power of 82 percent and a two-sided P value of less than 0.05 by the log-rank test. Interim analyses were performed after the enrollment of 480 patients and once enrollment ended (with the use of tandem one-sided tests for the null and alternative hypotheses and a P value of 0.0025). The data and safety monitoring board approved release of the results in March 2005, one year after study closure. A P value of 0.0225 was considered to indicate statistical significance in the final analysis.¹² In accordance with the policy of the *Journal*, we report only two-sided P values.

The analyses of outcomes in the two groups were conducted according to the intention-to-treat principle. Treatment-related death was defined as a death that was attributable to a treatment given within two months before death. The cumulative incidence of treatment-related mortality was estimated according to the method of Gooley et al.¹³ and compared with the use of the log-rank test. The Kaplan–Meier method¹⁴ was used to estimate event-free survival, overall survival, and survival after relapse. Event-free survival was measured from the date of enrollment until disease progression, relapse, or death from any cause. Data on patients who had no events were censored at the time of last contact. Overall survival was measured from the date of enrollment until death from any cause; data on survi-

Table 1. Treatment Protocol after Randomization.*

Phase	Cycle 1	Cycle 2	Cycle 3 (with PBSC collection)	Cycle 4
Induction (4 cycles of treatment administered 4–5 wk apart)	4-Day continuous infusion of 0.5 mg of vincristine/day, and 10 mg of doxorubicin/m ² of body-surface area/day, plus 40 mg of dexamethasone/day orally on days 1–4, 9–12, 17–20	4-Day continuous infusion of 400 mg of cyclophosphamide/m ² /day, 40 mg of etoposide/m ² /day, and 10 mg of cisplatin/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4	4-Day continuous infusion of 600 mg of cyclophosphamide/m ² /day and 15 mg of doxorubicin/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4 (thalidomide withheld on day 5 for collection of PBSC)	4-Day continuous infusion of 400 mg of cyclophosphamide/m ² /day, 40 mg of etoposide/m ² /day, and 10 mg of cisplatin/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4
Experimental treatment	400 mg of thalidomide daily or no thalidomide	400 mg of thalidomide daily or no thalidomide	400 mg of thalidomide daily or no thalidomide	400 mg of thalidomide daily or no thalidomide
Transplantation (>2 mo apart but not >6 mo apart)	1st Transplantation 200 mg of melphalan/m ² (reduced to 140 mg/m ² for patients >70 yr old or those with a creatinine level >2 mg/dl [177 μmol/liter]) supported by administration of >3×10 ⁶ CD34 cells/kg of body weight	2nd Transplantation 200 mg of melphalan/m ² (reduced to 140 mg/m ² for patients >70 yr old or those with a creatinine level >2 mg/dl) supported by administration of >3×10 ⁶ CD34 cells/kg		
Experimental treatment	100 mg of thalidomide daily (or no thalidomide) resumed after each transplantation once platelet count exceeded 50,000/mm ³			
Consolidation†	Randomly Assigned to Group A (N=66) 4-Day continuous infusion of 300 mg of cyclophosphamide/m ² /day, 30 mg of etoposide/m ² /day, and 7.5 mg of cisplatin/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4, every 3 mo for 4 cycles	Randomly Assigned to Group B (N=55) 4-Day continuous infusion of 300 mg of cyclophosphamide/m ² /day, 30 mg of etoposide/m ² /day, and 7.5 mg of cisplatin/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4 alternating with a 4-day continuous infusion of 600 mg of cyclophosphamide/m ² /day, and 15 mg of doxorubicin/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4, every 6 wk for 8 cycles	All Remaining Patients (N=547)‡ 4-Day continuous infusion of 7.5 mg of cisplatin/m ² /day, 15 mg of doxorubicin/m ² /day, 300 mg of cyclophosphamide/m ² /day, and 30 mg of etoposide/m ² /day, plus 40 mg of dexamethasone/day orally on days 1–4, every 3 mo for 4 cycles	
Experimental treatment	200 mg of thalidomide daily or no thalidomide	200 mg of thalidomide daily or no thalidomide		
Maintenance	1st Yr 3 Million U of interferon/m ² SQ 3 times/wk plus 40 mg of dexamethasone/day on days 1–4, 9–12, 17–20 every 3 months for 4 cycles until disease progression or unacceptable adverse effects	2nd and Subsequent Yr 3 Million U of interferon/m ² SQ 3 times/wk, until disease progression or unacceptable adverse effects		
Experimental treatment	100 mg of thalidomide daily or no thalidomide	50 mg of thalidomide every other day until relapse or the occurrence of adverse events		

* PBSC denotes peripheral-blood stem cells, and SQ subcutaneously.
 † If the level of myeloma protein in serum or urine was not reduced by more than 25 percent during the second cycle of induction therapy with cyclophosphamide, etoposide, cisplatin, and doxorubicin or the platelet count did not recover to exceed 100,000 cells per cubic millimeter after the second transplantation, the patient was given 40 mg of dexamethasone per day on days 1 through 4 every month for 12 months. The doses of cytotoxic agents were adjusted to account for renal function (cisplatin) and myelosuppression (cisplatin, doxorubicin, cyclophosphamide, and etoposide).
 ‡ The protocol was modified after the enrollment of 121 patients, and all subsequent patients received this consolidation therapy.

vors were censored at the time of last contact. Post-relapse survival was measured from the date of progression or relapse to death from any cause, with censoring of data at the time of last contact. The log-rank test was used to compare event-free, overall, and post-relapse survival in the two groups.¹⁵ Cox regression analysis¹⁶ was used to examine multivariate models of prognostic factors. Complete response was examined as a time-dependent covariate. Standard prognostic factors of event-free and overall survival were dichotomized with the use of cutoff points reported as part of the International Staging System for multiple myeloma.¹⁷

All investigators had full access to the data, which were analyzed by Cancer Research and Biostatistics in Seattle.

RESULTS

OUTCOME

The baseline characteristics of the 323 patients who were randomly assigned to thalidomide and the 345 controls were similar (Table 2). As of August 15, 2005, the median follow-up of 478 surviving patients was 42 months (range, 21 to 81), 270 patients had had an event, and 190 had died. There were no significant differences between the two groups in the number who participated in the various phases of treatment or in the reasons for leaving the study (details are given

in Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Overall, 85 percent of patients received one transplant, 67 percent received two transplants, 65 percent started consolidation therapy, and 56 percent began the maintenance phase (Table 1 of the Supplementary Appendix). The time to completion of treatment was also similar in the two groups (Fig. 2A).

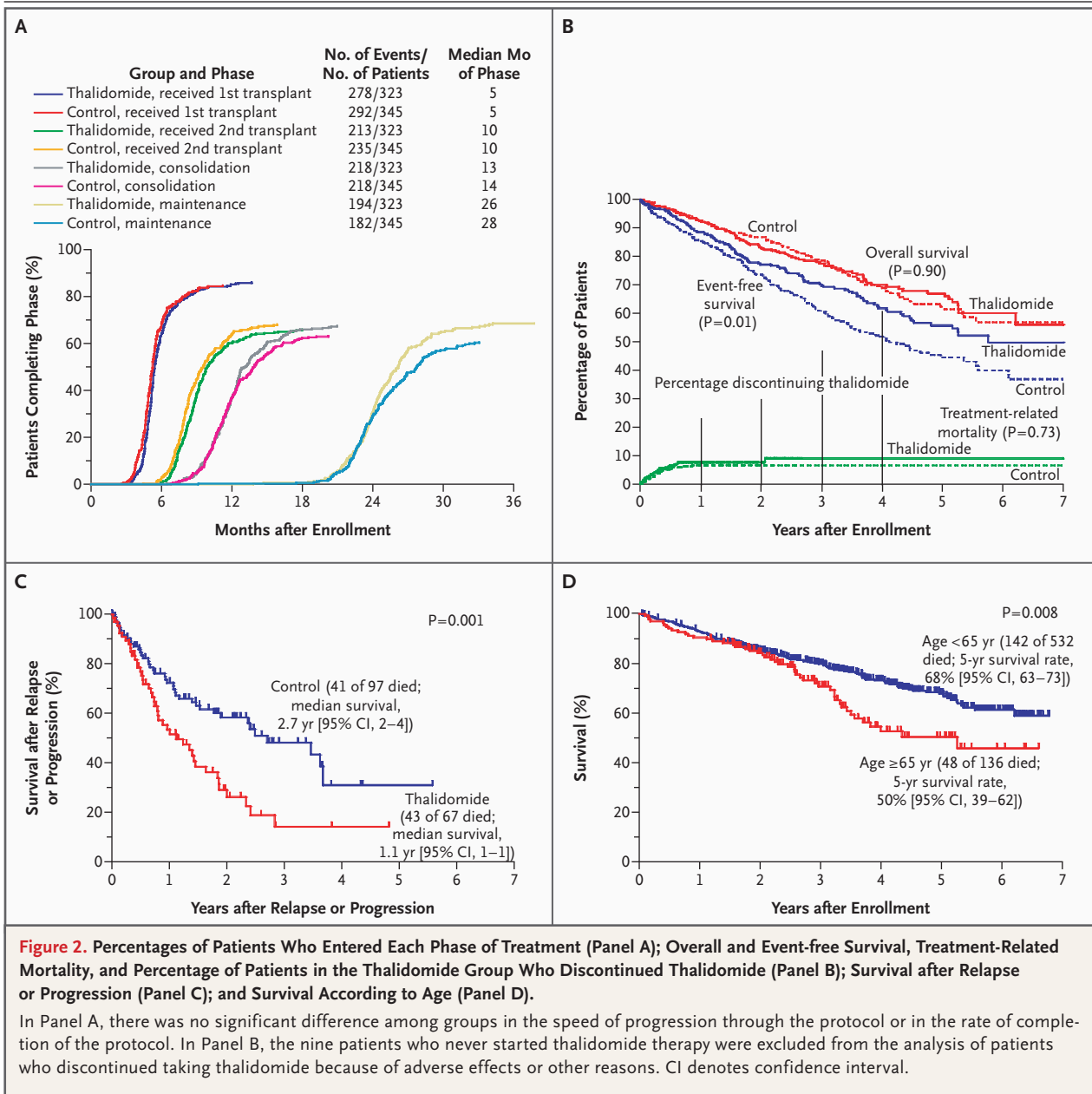
As compared with the control group, the thalidomide group had a higher rate of complete response (62 percent vs. 43 percent, $P<0.001$), a similar rate of complete response at four years (64 percent in both groups), and a higher rate of five-year event-free survival (56 percent vs. 44 percent, $P=0.01$) (Fig. 2B). The cumulative 12-month treatment-related mortality rate was 8 percent in both groups, but it was significantly higher among patients 65 years of age or older than among younger patients (13 percent vs. 6 percent, $P=0.004$), independently of treatment group. Despite a superior event-free survival rate in the thalidomide group, there was no significant difference between the two groups in overall survival, owing in part to significantly shorter survival after relapse in the thalidomide group than in the control group (median, 1.1 years vs. 2.7 years; $P=0.001$) (Fig. 2C). Since the rate of insurance denial for transplantation was higher among patients who were at least 65 years old than among younger patients (24 percent vs. 4 percent, $P<0.001$),

Table 2. Baseline Characteristics of the Patients.*

Characteristic	All Patients	Control Group <i>number/total number (percent)</i>	Thalidomide Group
Age ≥65 yr	136/668 (20)	72/345 (21)	64/323 (20)
Female sex	272/668 (41)	135/345 (39)	137/323 (42)
White race†	599/668 (90)	308/345 (89)	291/323 (90)
IgA isotype	160/668 (24)	76/345 (22)	84/323 (26)
Albumin <3.5 g/dl	119/664 (18)	59/343 (17)	60/321 (19)
Beta ₂ -microglobulin ≥3.5 mg/liter	243/668 (36)	126/345 (37)	117/323 (36)
Creatinine ≥2.0 mg/dl (177 μmol/liter)	62/654 (9)	37/339 (11)	25/315 (8)
C-reactive protein ≥8.0 mg/liter	263/658 (40)	127/339 (37)	136/319 (43)
Lactate dehydrogenase >upper limit of normal (>190 U/liter)	178/666 (27)	86/344 (25)	92/322 (29)
Cytogenetic abnormalities	197/661 (30)	104/339 (31)	93/322 (29)

* There were no significant differences between groups.

† This characteristic was self-assigned.



younger patients had a higher rate of completion of the first transplantation (87 percent vs. 77 percent, $P=0.003$) and second transplantation (72 percent vs. 47 percent, $P<0.001$) and a higher overall survival rate at five years (68 percent vs. 50 percent, $P=0.008$) (Fig. 2D).

PROGNOSTIC FACTORS

The probability of event-free and overall survival was significantly lower among patients with cytogenetic abnormalities, those with a lactate de-

hydrogenase level that exceeded the upper limit of normal, and those with a serum albumin level of less than 3.5 g per deciliter (Table 3). Event-free survival and overall survival were significantly longer among patients who had a complete response than among those who had a partial or no response (evaluated as a time-dependent covariate). Independently of these features, randomization to the thalidomide group was associated with longer event-free survival but not overall survival.

ADVERSE EVENTS

The occurrence of clinically significant adverse events (Table 4) necessitated changes in the dose of thalidomide in a sizable fraction of patients, especially elderly patients. Thalidomide was discontinued within two years after enrollment in 30 percent of patients, and within four years in more than 60 percent (Fig. 2B). Especially during induction chemotherapy, thromboembolic events were almost twice as common among patients assigned to the thalidomide group as among those assigned to the control group. The high incidence of deep-vein thrombosis in the initial phase of the study (34 percent among the first 162 patients randomly assigned to thalidomide, as compared with 18 percent among the first 174 patients enrolled in the control group; $P < 0.001$) (Fig. 1A of the Supplementary Appendix) was not eliminated by prophylactic administration of low-molecular-weight heparin later in the study (24 percent among the last 152 patients enrolled in the thalidomide group, as compared with 15 percent among the last 163 patients enrolled in the control group; $P = 0.064$) (Fig. 1B of the Supplementary Appendix). Syncopal episodes related to sinus bradycardia occurred in 12 percent of patients in the thalidomide group and in only 4 percent of patients in the control group.

Because of concern about drug safety, cardiac pacemakers were implanted in nearly one third of the 38 patients with symptomatic sinus bradycardia. Tremor was encountered twice as frequently in the thalidomide group as in the control group (13 percent vs. 6 percent). Most debilitating was peripheral neuropathy with a grade of more than 2 (i.e., more than moderate) according to the Common Toxicity Criteria of the National Cancer Institute; this adverse event was more common in the thalidomide group than in the control group (27 percent vs. 17 percent, $P < 0.001$) (Table 4) and among patients at least 65 years old than among younger patients (29 percent vs. 20 percent, $P = 0.02$). Forty-one percent of patients who were at least 65 years old and who were receiving thalidomide had peripheral neuropathy, as compared with 17 percent of younger patients in the control group ($P < 0.001$) (Fig. 1C of the Supplementary Appendix). Peripheral neuropathy improved to less than grade 2 within three to four months after a dose reduction or cessation of thalidomide in nearly 90 percent of affected patients. Severe constipation lead-

Table 3. Multivariate Analysis of Features Associated with the Clinical Outcome.*

Variable	Hazard Ratio (95% CI)	P Value
Event-free Survival†		
Randomization to thalidomide (vs. no thalidomide)	0.74 (0.58–0.94)	0.01
Prestudy cytogenetic abnormalities (vs. none)	1.52 (1.18–1.96)	0.001
Lactate dehydrogenase >upper limit of normal (vs. within normal range)	1.60 (1.22–2.08)	<0.001
Albumin <3.5 g/dl (vs. ≥3.5 g/dl)	1.63 (1.21–2.19)	0.001
Beta ₂ -microglobulin >3.5 mg/liter (vs. ≤3.5 mg/liter)	1.50 (1.16–1.95)	0.002
IgA isotype (vs. other isotype)	1.49 (1.13–1.96)	0.005
Complete response (time-dependent)	0.59 (0.44–0.79)	<0.001
Time to 2nd transplantation	0.77 (0.57–1.03)	0.08
Overall survival†		
Prestudy cytogenetic abnormalities (vs. none)	1.88 (1.40–2.52)	<0.001
Lactate dehydrogenase >upper limit of normal (vs. within normal range)	1.63 (1.20–2.23)	0.002
Albumin <3.5 g/dl (vs. ≥3.5 g/dl)	2.01 (1.44–2.79)	<0.001
Complete response (time-dependent)	0.53 (0.37–0.75)	<0.001
Time to 2nd transplantation	0.55 (0.40–0.77)	<0.001

* CI denotes confidence interval.
 † The analysis included 655 patients.

ing to bowel obstruction was noted in 14 percent of patients receiving thalidomide and in 8 percent of patients in the control group ($P = 0.02$) (Table 4). Neutropenia of more than grade 2 was recorded in 46 percent of patients in the thalidomide group during the consolidation and maintenance phases but in only 28 percent of patients in the control group ($P < 0.001$) (Table 4). Despite the higher incidence of various adverse events in the thalidomide group, the treatment-related mortality rate was similar in the two groups (Fig. 2B).

MANAGEMENT AFTER RELAPSE IN RELATION TO PRIOR THALIDOMIDE THERAPY

Of 164 events (deaths excluded), multiple myeloma progressed after transplantation in 136 patients; 107 of these patients received salvage therapies. The proportions of patients receiving specific salvage regimens did not differ significantly in the two groups (44 in the thalidomide group and 63 in the

Table 4. Incidence of Severe Adverse Events of More Than Grade 2, According to Treatment Group and Phase of Therapy.*

Severe Adverse Event	Overall		Induction Therapy		Consolidation and Maintenance Therapy	
	Thalidomide Group (N=314)†	Control Group (N=337)†	Thalidomide Group (N=314)	Control Group (N=337)	Thalidomide Group (N=314)	Control Group (N=337)
	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	P Value
Thrombosis or embolism	95 (30)	58 (17)	75 (24)	42 (12)	20 (6)	<0.001
Syncope	38 (12)	13 (4)	29 (9)	8 (2)	6 (2)	<0.001
Bowel obstruction	44 (14)	28 (8)	28 (9)	20 (6)	10 (4)	0.15
Tremor	40 (13)	20 (6)	32 (10)	15 (4)	9 (3)	0.005
Peripheral neuropathy	86 (27)	56 (17)	61 (19)	41 (12)	37 (15)	0.01
Neutropenia	296 (94)	306 (91)	284 (90)	289 (86)	114 (46)	0.07

* There were no significant differences between study groups during the transplantation phase. The Common Toxicity Criteria of the National Cancer Institute were used to define the severity of adverse events. On this scale, a grade of 0 indicates no adverse events and a grade of 4 life-threatening adverse events.
 † The analysis included only patients receiving at least one cycle of protocol therapy.

control group). These salvage treatments included further thalidomide or thalidomide (75 percent of the thalidomide group and 83 percent of the control group), bortezomib¹⁸ (45 percent and 37 percent, respectively), thalidomide or bortezomib (84 percent and 92 percent, respectively), lenalidomide¹⁹ (9 percent and 11 percent, respectively), and dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide chemotherapy (Table 1) (23 percent and 22 percent, respectively), and further high-dose therapy (7 percent and 2 percent, respectively). Even though the two groups had similar features at baseline and relapse, the incidence of partial responses was higher (71 percent vs. 55 percent, P=0.029) and survival after relapse was longer (2.7 vs. 1.1 years, P=0.001) among patients initially assigned to receive no thalidomide than among those assigned to receive thalidomide (Fig. 2C). Neither the cumulative dose of thalidomide nor the duration of treatment interruption because of adverse events before relapse influenced survival after relapse.

DISCUSSION

The addition of thalidomide to intensive melphalan-based chemotherapy supported with two peripheral-blood hematopoietic stem-cell transplantations improved the rate of complete response and event-free survival among patients with newly diagnosed multiple myeloma. The drug failed, however, to prolong overall survival and was associated with considerable adverse effects. Attal et al. also reported longer event-free survival but not overall survival when thalidomide was given after two transplantations as maintenance therapy in lower doses than the ones we used.²⁰

Relapses in the thalidomide group appeared to be more drug-resistant than relapses in the control group. A higher failure rate with salvage therapy and shorter survival after relapse can partially explain the similar overall survival times in the two groups. Our results indicate that a complete response is not a valid surrogate for survival in myeloma clinical trials. The definition of a complete response in patients with multiple myeloma relies in part on the presence of immunoglobulin-producing plasma cells, although the presence of nonsecretory or hyposecretory plasma cells often accounts for relapses among patients with high lactate dehydrogenase levels²¹;

such cells may be present at diagnosis and preferentially expand during disease progression. Furthermore, as compared with the relatively rapid reduction in levels of the myeloma protein, MRI-defined focal lesions (which harbor myeloma cells) take one or two years to regress and are often the first sites of relapse.²² When multiple myeloma evolves from a documented monoclonal gammopathy of uncertain significance (MGUS), or a smoldering phase, a complete response is infrequent, but when one does occur, it has no effect on the likelihood of survival.²³ This phenomenon presumably reflects the reestablishment of a stable MGUS-like condition.

Superior response rates have been reported for thalidomide plus dexamethasone as compared with dexamethasone alone for induction therapy in patients with multiple myeloma.^{24,25} Since many patients in these trials received high-dose therapy after induction therapy with thalidomide and dexamethasone, the long-term benefit of this combination cannot be ascertained. Reserving thalidomide for maintenance therapy after transplantation, as was done in the pilot and larger trials conducted by the InterGroupe Francophone du Myélome,^{4,5} has several advantages: resistance may be avoided; the risk of thromboembolic complications can be reduced, since this risk is highest during induction therapy, when the burden of tumor is high²⁶; and the incidence of neurotoxic

effects should be reduced with the later introduction of thalidomide at lower doses (50 to 100 mg) during maintenance therapy. High rates of complete response approaching the rates observed with high-intensity treatment plus stem-cell transplantation have recently been found in trials of thalidomide combined with standard treatment with melphalan and prednisone.^{27,28} Similarly, combinations of bortezomib and dexamethasone,^{29,30} plus pegylated doxorubicin³¹ or thalidomide,^{32,33} have shown promise. Little is known, however, about the durability of the responses induced by these treatments, especially after the discontinuation of the drugs. Although standard high-dose melphalan therapy with stem-cell transplantation has considerable acute adverse effects, its low mortality and infrequent chronic adverse effects have to be balanced against the potential of the newer agents for irreversible and incapacitating chronic adverse effects. Acute complications (thromboembolism with thalidomide and lenalidomide) and chronic sequelae (polyneuropathy with thalidomide and bortezomib) may be minimized by combining “old” and “new” therapies, especially since the genomic heterogeneity of multiple myeloma may require a multifaceted approach to treatment to achieve lasting control.³⁴

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No potential conflict of interest relevant to this article was reported.

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