

ANTITUMOR ACTIVITY OF THALIDOMIDE IN REFRACTORY MULTIPLE MYELOMA

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ABSTRACT

Background Patients with myeloma who relapse after high-dose chemotherapy have few therapeutic options. Since increased bone marrow vascularity imparts a poor prognosis in myeloma, we evaluated the efficacy of thalidomide, which has antiangiogenic properties, in patients with refractory disease.

Methods Eighty-four previously treated patients with refractory myeloma (76 with a relapse after high-dose chemotherapy) received oral thalidomide as a single agent for a median of 80 days (range, 2 to 465). The starting dose was 200 mg daily, and the dose was increased by 200 mg every two weeks until it reached 800 mg per day. Response was assessed on the basis of a reduction of the myeloma protein in serum or Bence Jones protein in urine that lasted for at least six weeks.

Results The serum or urine levels of paraprotein were reduced by at least 90 percent in eight patients (two had a complete remission), at least 75 percent in six patients, at least 50 percent in seven patients, and at least 25 percent in six patients, for a total rate of response of 32 percent. Reductions in the paraprotein levels were apparent within two months in 78 percent of the patients with a response and were associated with decreased numbers of plasma cells in bone marrow and increased hemoglobin levels. The microvascular density of bone marrow did not change significantly in patients with a response. At least one third of the patients had mild or moderate constipation, weakness or fatigue, or somnolence. More severe adverse effects were infrequent (occurring in less than 10 percent of patients), and hematologic effects were rare. As of the most recent follow-up, 36 patients had died (30 with no response and 6 with a response). After 12 months of follow-up, Kaplan-Meier estimates of the mean (\pm SE) rates of event-free survival and overall survival for all patients were 22 ± 5 percent and 58 ± 5 percent, respectively.

Conclusions Thalidomide is active against advanced myeloma. It can induce marked and durable responses in some patients with multiple myeloma, including those who relapse after high-dose chemotherapy. (N Engl J Med 1999;341:1565-71.)

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MULTIPLE myeloma accounts for approximately 1 percent of all cancers and 10 percent of hematologic cancers. It is incurable with conventional chemotherapy.¹ Melphalan-based high-dose chemotherapy with hematopoietic stem-cell support increases the rate of complete remission and extends event-free and overall survival.²⁻⁴ However, many patients still relapse, and options for salvage therapy are limited.^{5,6}

Angiogenesis is important in embryogenesis, wound healing, diabetic retinopathy, and tumor progression.^{7,8} The immunomodulatory drug thalidomide can inhibit angiogenesis and induce apoptosis of established neovasculature in experimental models.^{9,10} For these reasons, angiogenesis-inhibiting drugs such as thalidomide may be useful for treating cancers that depend on neovascularization.

Prominent bone marrow vascularization occurs in multiple myeloma. It correlates positively with a high plasma-cell-labeling index (a poor prognostic sign) and disease activity and independently confers a poor prognosis.¹¹⁻¹⁶ Plasma levels of various angiogenic cytokines, such as basic fibroblast growth factor and vascular endothelial growth factor, are elevated in patients with active myeloma.^{11-13,16} In 1965, Olson et al. reported slowing of disease progression in one patient who was treated with thalidomide.¹⁷ These considerations led us to administer thalidomide to five patients with end-stage myeloma through a compassionate-use protocol. One patient with a large tumor burden (as indicated by an IgA level of 8.4 g per deciliter, the presence of more than 95 percent plasma cells in bone marrow, and the need for transfusion), who had had no response to two cycles of high-dose chemotherapy followed by multiple salvage therapies, had a nearly complete remission within three months after the initiation of thalidomide therapy. This observation prompted a phase 2 investigation of tha-

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lidomide in patients with advanced and refractory myeloma.

METHODS

Patients and Treatments

Between December 1997 and June 1998, 84 consecutive, eligible patients with previously treated and progressive myeloma began treatment with oral thalidomide as a single agent after providing written informed consent. No patients were excluded on the basis of renal or cardiopulmonary function, whereas patients could be excluded if the results of liver-function tests were more than twice the upper limit of normal levels. All patients were treated at a single center according to a phase 2 protocol approved by the institutional review board and the Food and Drug Administration (FDA).

Thalidomide was supplied in 50-mg capsules by Celgene (Warren, N.J.) and was administered nightly at a dose of 200 mg. The dose was increased by 200 mg every two weeks for six weeks, so that the final dose was 800 mg per day. Data were analyzed as of June 17, 1999, when the duration of treatment ranged from 2 to 465 days (median, 80) and the median follow-up of surviving patients was 13 months.

Table 1 summarizes the characteristics of the patients and details of prior therapy. Seventy-six patients (90 percent) had received at least one cycle of high-dose chemotherapy with autologous hematopoietic stem-cell support, and 58 (69 percent) had received two or more cycles of intensive chemotherapy. The median time from the last course of high-dose chemotherapy to the beginning of treatment with thalidomide was 14 months. A high-risk cytogenetic abnormality (deletion of chromosome 13) was present in 35 patients (42 percent).²⁰ One patient had received an allograft as a second intervention, with evidence of full donor-type chimerism in normal lymphohematopoietic cells. At the time of enrollment, all patients had progressive disease, with an increase in paraprotein levels of at least 25 percent or at least 50 percent plasma cells in bone marrow. Approximately half the patients had been retreated with dexamethasone or other regimens, but the disease had progressed before thalidomide treatment was begun.

Evaluation

The pretreatment evaluation included complete blood counts, tests of renal and liver function, serum and urine protein electrophoresis, and measurements of serum levels of immunoglobulins, beta₂-microglobulin, and C-reactive protein. Bone marrow aspirates were obtained and biopsies were performed to determine the percentage of plasma cells in bone marrow, to identify karyotypic abnormalities (Giemsa-banded cells in metaphase), and to assess the proliferative activity in plasma cells according to the bromodeoxyuridine method to derive the plasma-cell-labeling index.¹⁸ Follow-up studies included a weekly estimation of paraprotein levels — the myeloma protein in serum and Bence Jones protein in urine — for the first two months, followed thereafter by monthly measurements. Whenever possible, bone marrow was examined at the time of the maximal response or when patients with no response left the study.

The microvasculature of bone marrow was studied in a semi-quantitative fashion in biopsy samples that were obtained with a trephine and stained with an anti-CD34 monoclonal antibody (prediluted Clone QBEnd/10, Cell Marque, Austin, Tex.). The results were expressed as the number of vessels per high-power field (400×).

Assessment of Response

The primary end point of the study was the finding of a decline in the level of paraprotein in serum or urine of at least 25 percent, 50 percent, 75 percent, or 90 percent on two occasions at least six weeks apart. Among patients with detectable levels of both urine and serum paraprotein, the response was judged on the basis of the component showing the smaller decline. Patients with

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	No. OF PATIENTS (%)
Male sex	61 (73)
Durie-Salmon stage III multiple myeloma	51 (61)
IgG paraprotein	51 (61)
Duration of prior therapy >60 mo	18 (21)
Prior high-dose chemotherapy	76 (90)
Receipt of >1 cycle of high-dose chemotherapy	58 (69)
Interval between last cycle of high-dose chemotherapy and initiation of thalidomide >12 mo	43 (57)
Age >60 yr	32 (38)
Hemoglobin <9 g/dl	19 (23)
Platelet count <50 × 10 ³ /mm ³	17 (20)
Serum albumin <3.5 g/dl	22 (26)
Serum creatinine >1.5 mg/dl (133 μmol/liter)	22 (26)
Serum beta ₂ -microglobulin >6 mg/liter	24 (29)
Serum C-reactive protein >3 mg/liter	20 (24)
Serum monoclonal immunoglobulin >1 g/dl	51 (61)
Urine Bence Jones protein >1 g/day	44 (52)
>50% Plasma cells in bone marrow on biopsy	18 (21)
Plasma-cell-labeling index >1%*	13 (15)
Bartl grade II†	19 (23)
Deletion of chromosome 13	35 (42)
Outcome	
Completion of study	19 (23)
Withdrawal from study	
Progression	54 (64)
Intolerance of thalidomide	9 (11)
Death of patient with a response‡	1 (1)
Personal reasons	1 (1)
Final dose of thalidomide	
400 mg/day	72 (86)
600 mg/day	57 (68)
800 mg/day	46 (55)

*The plasma-cell-labeling index represents the percentage of light-chain-restricted plasma cells incorporating bromodeoxyuridine.¹⁸

†The Bartl grading system distinguishes myeloma cells according to their morphologic maturation.¹⁹ Grade II refers to immature plasma cells of cleaved, asynchronous, or polymorphous appearance.

‡This patient had a response to treatment but died on day 37 of treatment.

a reduction of less than 25 percent and those who discontinued treatment before a response could be assessed were considered to have had no response to thalidomide. Thus, the results were evaluated on an intention-to-treat basis. In patients with a response, an increase in serum or urine paraprotein levels by more than 25 percent above the nadir value was considered evidence of relapse. In patients who had a complete remission, evidence of reemergence of the monoclonal protein (determined by immunofixation) on at least two occasions was considered to indicate a relapse. In patients who had a complete remission or a nearly complete remission (≥90 percent reduction in serum or urine paraprotein levels), a bone marrow response was defined as the finding of less than 5 percent plasma cells in the biopsy specimen or aspirate. For the remaining patients with a paraprotein response, the percentage of plasma cells had to decrease by at least 50 percent to qualify as a bone marrow response.

Assessment of Adverse Effects

All patients, irrespective of the duration of therapy, were included in the evaluation of adverse effects. All patients received diaries after providing informed consent, and 83 patients (99 per-

cent) reported having adverse effects. A comprehensive checklist of the adverse effects associated with thalidomide therapy was provided by Celgene; it was based on previous experience in treating patients with leprosy and had been reviewed by the FDA. The data were verified by the patients by direct or telephone interviews. Hematologic values and other laboratory-based measures of adverse effects were assessed at least monthly by the data-management office.

Statistical Analysis

The primary end point for this phase 2 study was a diminution in the plasma level of the myeloma protein or the urine level of Bence Jones protein. Other end points included the time to a response, the time to disease progression, event-free survival, overall survival, the microvasculature of bone marrow, and improvements in other laboratory values. Response was treated as a categorical variable. Comparisons of the response according to other categorical variables were assessed with use of the chi-square test or Fisher's exact test, as appropriate. The times to response and disease progression were calculated with the use of the competing-risk methods.²¹ The time to response was defined as the interval between the start of therapy and a given response (i.e., a decline in the serum or urine level of paraprotein of at least 25 percent, 50 percent, 75 percent, or 90 percent or a complete remission). Competing risks with respect to the time to response included discontinuation of treatment because of progression or a lack of response, an inability to tolerate thalidomide, or death or personal reasons. The time to progression was calculated only for patients with a paraprotein response and was defined as the time from the start of therapy to disease progression. Competing risks with respect to the time to progression included discontinuation of treatment because of adverse effects or death or for personal reasons. Event-free survival and overall survival were estimated according to the method of Kaplan and Meier.²² Event-free survival was calculated from the start of therapy to disease progression, removal from the study for any reason, death from any cause, or the last follow-up visit, whichever occurred first. Overall survival was calculated from the start of therapy to death from any cause or the last follow-up visit. Data on patients who had not had an event by the time of the last follow-up were censored at that time with respect to times to response and progression, event-free survival, and overall survival. Survival was compared with use of the log-rank test.²³ Univariate and multivariate (stepwise) logistic-regression methods were used to evaluate the prognostic importance of various characteristics with respect to the likelihood of achieving at least a 25 percent or 50 percent reduction in serum or urine paraprotein levels. Univariate and multivariate (stepwise) proportional-hazards regression analyses were used to evaluate the prognostic importance of various characteristics with respect to event-free survival and overall survival.

Since the microvascular density of bone marrow was used as a measure of the antiangiogenic action of thalidomide, this variable was extensively modeled. To account for the need for multiple measurements of each patient over time and missing data, we used mixed-models repeated-measures analysis of variance to evaluate the microvascular density of bone marrow.²⁴ The use of compound symmetry and first-order autoregressive covariance structures was compared, and the results were found to be similar according to Akaike's criterion. Therefore, the values obtained with the compound-symmetry models are reported. Measurements of the microvascular density of bone marrow were grouped according to the length of treatment, and values were measured every 50 days for a total of seven times, including the pretreatment value. The natural logarithm of the values for the microvascular density of bone marrow was used in the analysis. Estimates for patients with no response and patients with a complete or nearly complete response (≥ 90 percent reduction in serum or urine paraprotein levels) were used to predict the response in terms of the microvascular density of bone marrow over time.

Improvements in important clinical measures were evaluated on the basis of the percent change from base line to the time of the

maximal response or, for those without a response, the time at which treatment was discontinued. Spearman correlations were used to assess whether the changes within response groups were significant. For variables with no significant correlations, the signed-rank test was used to test the hypothesis within response groups that the change was significantly different from zero. All statistical tests were two-sided.

RESULTS

Decline in Paraprotein Levels

Timely escalations in the daily dose of thalidomide to 400 mg, 600 mg, and 800 mg were possible in 83 percent, 62 percent, and 47 percent of the patients, respectively; the proportions of patients who eventually reached these levels were 86 percent, 68 percent, and 55 percent, respectively (Table 1). In 27 patients (32 percent), the serum or urine paraprotein level declined by at least 25 percent, including 7 (8 percent) with a decline of at least 50 percent, 6 (7 percent) with a decline of at least 75 percent, and 6 (7 percent) with a decline of at least 90 percent; 2 patients had a complete remission (Table 2). The median interval between the start of treatment and a decrease in the paraprotein level of at least 25 percent was 29 days (range, 4 days to 6 months) (Fig. 1). Seventy-eight percent of the responses of this magnitude were apparent within two months; they were observed within four months in all but two patients with a response. More marked reductions in paraprotein, by at least 50 percent and 75 percent, occurred after a median of two and three months of therapy, respectively.

A low plasma-cell-labeling index (assessed as a continuous variable) was the only statistically significant variable associated with a response among both the group with at least a 25 percent decrease in paraprotein levels ($P=0.01$) and the group with at least a 50 percent decrease ($P=0.01$). Using the median plasma-cell-labeling index of 0.2 percent as a cutoff value, we found that 46 percent of patients with values below the median had a reduction in paraprotein levels of at least 25 percent, as compared with 9 percent of patients with higher values ($P<0.05$). On univariate analysis, deletion of chromosome 13 was predictive of an unfavorable response, but not on multivariate analysis.

Bone Marrow Response

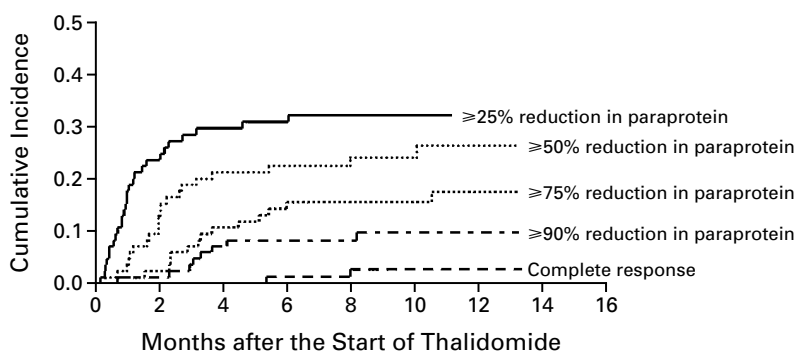
Bone marrow samples were obtained after one to nine months of therapy (median, three) in 48 patients. A paraprotein response was associated with a bone marrow response in 81 percent of the patients who could be evaluated (Table 2). In seven of the eight patients with at least a 90 percent reduction in paraprotein levels, the concurrently examined bone marrow specimens contained less than 5 percent plasma cells. A decline in the percentage of plasma cells in bone marrow by at least 50 percent occurred in only 4 of 27 patients with no paraprotein response (15 percent) who had follow-up bone marrow examinations.

TABLE 2. PARAPROTEIN RESPONSE AND BONE MARROW RESPONSE.

PARAPROTEIN RESPONSE	No. OF PATIENTS (% OF TOTAL)	ASSESSMENT OF BONE MARROW RESPONSE		CURRENT STATUS	
		TOTAL NO.*	NO. WITH RESPONSE (%)†	NO. WITH RELAPSE (%)	NO. WHO DIED (%)
Complete remission	2 (2)	2	2 (100)	0	0
≥90% decrease in paraprotein	6 (7)	6	5 (83)	2	2
≥75% decrease in paraprotein	6 (7)	5	3 (60)	3	1
≥50% decrease in paraprotein	7 (8)	4	4 (100)	3	0
≥25% decrease in paraprotein	6 (7)	4	3 (75)	4	3
Total	27 (32)	21	17 (81)	12 (44)	6 (22)
No response	57 (68)	27	4 (15)	—	30 (53)

*The response could not be evaluated in 6 of the patients with a paraprotein response and in 30 of the patients with no paraprotein response.

†A bone marrow response was defined as the presence of less than 5 percent plasma cells in bone marrow in patients who had a complete paraprotein response or at least a 90 percent reduction in paraprotein levels and as a reduction in plasma cells of at least 50 percent in patients with all other types of paraprotein responses.

**Figure 1.** Times to Various Paraprotein Responses.

Among patients with a response, the median times to a reduction in the serum or urine paraprotein level of at least 25 percent, 50 percent, 75 percent, and 90 percent were one, two, four, and four months, respectively. Seventy-eight percent of the responses at the lowest level (≥25 percent reduction) were apparent within two months after the initiation of treatment.

Microvascular Density of Bone Marrow

The microvascular density of bone marrow was scheduled to be assessed every 50 days for a total of seven measurements, including the pretreatment value. At least one measurement of the microvascular density of bone marrow was made in 74 patients (88 percent); two or more measurements were made in 37 patients (44 percent). In all, measurements were made in 69 patients before treatment and (in 50-day increments) in 17 at time 2, in 22 at time 3, in 11 at time 4, in 12 at time 5, in 4 at time 6, and in 3 at time 7. The microvascular density of bone marrow and the percentage of plasma cells in bone marrow correlated significantly at all times except the last ($r > 0.5$, $P \leq 0.01$). Although the microvascular density of bone marrow decreased markedly in some pa-

tients with a complete or nearly complete remission, estimates of the slope were not significantly different from zero among those with a response ($P = 0.39$) and those without a response ($P = 0.22$).

Other Changes

The percent changes from base line to the time of the maximal response among patients with a response and the time of the last follow-up visit among those without a response were assessed for beta₂-microglobulin, C-reactive protein, lactic dehydrogenase, creatinine, albumin, and hemoglobin levels and the platelet count. Hemoglobin levels increased only in patients with a response (median increase, 11 percent; $P < 0.001$ for the comparison with base-line values). Serum levels of beta₂-microglobulin rose (median in-

crease, 43 percent; $P<0.001$) and serum albumin levels fell (median decrease, 4 percent; $P<0.001$) significantly in patients with no response. Serum creatinine levels did not change significantly in patients with a response, and they increased by a median of 13 percent in those without a response ($P<0.001$).

Adverse Effects

Side effects reported by at least 10 percent of patients at most dose levels are listed in Table 3. Most adverse effects were mild or moderate (grade 1 or 2 according to the system of classification of the World Health Organization). Constipation, weakness or fatigue, and somnolence occurred in one third or more of the patients. Reports of grade 3 or 4 adverse effects were infrequent (less than 10 percent in all cases). One quarter of the patients had no appreciable side effects at the 200-mg dose, whereas virtually all patients had adverse effects of grade 1 or 2 at higher doses. Fewer than 5 percent of patients had grade 1 or 2 leukopenia at any dose, and grade 3 or 4 thrombocytopenia or anemia occurred in only three patients. In most of the patients who had no response, pre-treatment anemia or thrombocytopenia did not worsen, whereas significant increases in the hemoglobin levels occurred in patients with a response. Nine patients could not tolerate thalidomide (four with a response and five with no response) and discontinued treatment after a median of 36 days (range, 10 to 241). In eight patients, an increase in serum creatinine levels of more than 50 percent was related to progressive disease, with increasing Bence Jones proteinuria. One of the patients with a response died suddenly on day 37 of treatment. The death was thought to be related to sepsis, although a possible contribution of thalidomide could not be ruled out.

Time to Progression, Event-free Survival, and Overall Survival

Of the 27 patients with a decrease in paraprotein levels of at least 25 percent, 12 had a recurrence of the disease. After a median follow-up of 14.5 months (range, 12 to 16), the median time to progression had not been reached. The disease in a mean (\pm SE) of 44 ± 10 percent of patients was judged to have progressed at 12 months. The median event-free survival for all 84 patients was three months (Fig. 2). After 12 months of follow-up, 22 ± 5 percent of the 84 patients remained event-free and 58 ± 5 percent were alive. Nineteen patients were still receiving thalidomide 4 to 15 months after starting the treatment (median, 13), including 15 patients with a response and 4 with no response who had had some improvement in various disease indicators but who had not had a decrease in paraprotein levels of at least 25 percent. Multivariate analysis indicated that increases in lactic dehydrogenase levels ($P=0.001$), the plasma-cell-labeling index ($P=0.006$), and C-reactive protein levels ($P=0.007$)

TABLE 3. INCIDENCE OF GRADE 1 OR 2 ADVERSE EFFECTS.*

ADVERSE EFFECT	DOSE OF THALIDOMIDE			
	200 mg/DAY (N=83)	400 mg/DAY (N=72)	600 mg/DAY (N=57)	800 mg/DAY (N=46)
	percentage of patients†			
Constipation	35	44	44	59
Weakness or fatigue	29	31	39	48
Somnolence	34	43	40	43
Tingling or numbness	12	14	19	28
Dizziness	17	25	23	28
Rash	16	18	21	26
Mood changes or depression	16	24	23	22
Incoordination	16	17	14	22
Tremors	10	13	19	22
Edema	6	10	12	22
Nausea	12	15	23	11
Headache	12	10	14	11

*The classification system of the World Health Organization was used. Grade 1 effects are mild, and grade 2 are moderate.

†Values are the percentages of patients at each dose level.

were all predictive of a brief period of event-free survival, whereas low albumin levels ($P<0.001$), the deletion of chromosome 13 ($P=0.004$), and high numbers of plasma cells in bone marrow ($P=0.05$) were associated with a relatively short overall survival.

Thalidomide was discontinued after a median of 52 days (range, 2 to 286) because of a lack of response in 53 patients (4 patients continued to receive the drug without a response) and because of relapse in 12 patients who had had a response. One patient who had a decrease in the paraprotein level of at least 25 percent and who had not previously received high-dose therapy subsequently underwent autologous stem-cell transplantation at his own request. As of June 17, 1999, 36 patients had died, including 30 patients without a response who died of progressive disease or complications of subsequent salvage therapy, as well as 6 patients with a response who subsequently relapsed and died of progressive disease (3) or toxicity from salvage therapy (3).

DISCUSSION

We found that thalidomide had substantial antitumor activity in patients with advanced myeloma. Ten percent of patients had complete or nearly complete remission, and 32 percent had a reduction in serum or urine paraprotein levels of at least 25 percent. In most patients, the decline in paraprotein levels was accompanied by a reduction in the percentage of plasma cells in bone marrow and an increase in hemoglobin levels, both of which are consistent with the



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