

Thalidomide Alone or With Dexamethasone for Previously Untreated Multiple Myeloma

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Purpose: To evaluate the activity of thalidomide in patients with asymptomatic multiple myeloma and of thalidomide-dexamethasone in patients with previously untreated symptomatic myeloma.

Patients and Methods: Twenty-eight patients with previously untreated asymptomatic myeloma were treated with thalidomide 100 to 200 mg orally (PO) at bedtime (qhs) with serial increments of 50 to 100 mg at weekly intervals, as tolerated to a maximum of 600 mg PO qhs. Forty consecutive previously untreated patients with symptomatic myeloma were also treated as above (maximum dose 400 mg) and received dexamethasone 20 mg/m² for 4 days beginning on days 1, 9, and 17; the second and third cycles of repeated dexamethasone were begun on day 30. Both groups of patients were treated for at least 3 months.

Results: The response rate was 36% for patients treated with thalidomide alone and 72% for patients treated with thalidomide-dexamethasone, the latter including complete

remission in 16% of patients. The median time to remission was 4.2 months with thalidomide alone and 0.7 months with thalidomide-dexamethasone. Grade 3 toxicity included infections (nine patients) and thrombotic/embolic events (seven patients). Five deaths have occurred as a result of multiple myeloma (two patients), infection (one patient), unknown cause (one patient), and a possible thromboembolic event (one patient).

Conclusion: Thalidomide alone was effective in patients with newly diagnosed myeloma. The combination with dexamethasone induced a high frequency of response, rapid onset of remission, and low incidence of serious irreversible toxicity. These observations support further studies of this promising combination for patients with newly diagnosed multiple myeloma.

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ALTHOUGH MANY treatments have been useful for patients with multiple myeloma, the disease eventually relapses and becomes resistant to treatment. Combinations of multiple alkylating agents with glucocorticoids or of vincristine-doxorubicin-dexamethasone (VAD) have not improved survival in comparison with melphalan-prednisone.¹ Whereas treatments such as myeloablative therapy with autologous stem cell support have improved survival for many patients, other patients achieve limited or no gain because of early death, short remission, or persistent resistant disease.

Recently, Singhal et al² described a 26% response rate for patients with resistant myeloma treated with thalidomide, as determined by $\geq 50\%$ reduction of myeloma protein, which has been reported and confirmed by others.³⁻⁶ After confirming a response rate of approximately 25% with thalidomide alone among patients with resistant disease, we then assessed a combination of thalidomide and dexamethasone in patients with disease who were resistant to a sequence of dexamethasone-containing regimens and single-agent thalidomide (not necessarily consecutive treatments).^{3,4} The observed 46% response rate in patients with resistant disease despite multiple therapies was

superior, perhaps by a synergistic effect of both drugs. This response rate was also confirmed by others.⁷

Although the mechanism of action of thalidomide remains unclear and may be related to antiangiogenic or direct antitumor effects against myeloma, the drug is effective despite resistance to multiple standard therapies including alkylating agents, anthracycline, glucocorticoid combinations, and intensive therapy with stem cell support. Consequently, thalidomide may also be effective at diagnosis, possibly leading to improved response rate, particularly complete response (CR), and eventually impacting survival. We therefore initiated trials for previously untreated disease with thalidomide alone for asymptomatic patients, and in combination with repeated dexamethasone for symptomatic disease. Based on our prior experience in patients with resistant disease, we postulated that the combination of thalidomide-dexamethasone would induce rapid reduction of tumor mass, allowing prompt collection of autologous blood stem cells with granulocyte-colony-stimulating factor alone. Therefore, in eligible patients, treatment with thalidomide-dexamethasone was followed by intensive therapy with autologous stem cell support in an attempt to achieve maximum reduction of tumor burden.

PATIENTS AND METHODS

Patients and Drug Regimens

Between May 1999 and September 2001 we defined the role of thalidomide alone (provided by Celgene Corporation, Warren, NJ) in 28 consecutive patients with asymptomatic multiple myeloma. Only those patients at high risk for progression were eligible based on previously described combinations of risk factors (lytic bone lesion, IgA type, monoclonal protein ≥ 3.0 g/dL, Bence Jones protein [BJP] > 50 mg/d, or abnormal magnetic resonance imaging).⁸ High-risk disease was defined by lytic bone lesions or ≥ 2 risk factors, where the median time to progression was approximately 18 months. The initial dose of thalidomide was planned at 200 mg PO qhs, with serial increments of 50 to 200 mg at 1- to 2-week intervals

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in absence of serious toxicity, to a maximum of 600 mg PO qhs: two patients were started at 100 mg, two patients at 150 mg, and 24 patients at 200 mg. With moderate side effects, the thalidomide dose was reduced by 50- to 100-mg decrements until an acceptable level was reached and maintained. For severe toxicity, thalidomide was held and restarted using the aforementioned decrements after the side effect had improved. The median maximum dose achieved was 400 mg (one patient received a maximum dose of 150 mg, nine patients 200 mg, three patients 300 mg, 10 patients 400 mg, two patients 500 mg, and three patients 600 mg).

Between July 2000 and July 2001, we also treated 40 consecutive, previously untreated patients with symptomatic multiple myeloma with thalidomide in a similar schedule, but with a maximum dose of 400 mg and combined with dexamethasone 20 mg/m² for 4 days beginning on days 1, 9, and 17. Whereas the initial thalidomide dose was planned to be 100 mg, escalated weekly by 100 mg increments to 400 mg, 28 patients started at 100 mg, seven patients at 150 mg, and five patients at 200 mg. Only patients with low or intermediate tumor mass were eligible. Second cycles of repeated dexamethasone began on day 30, as did third cycles in 10 patients whose myeloma had improved but was not in remission. The median maximum dose of thalidomide received was 200 mg (three patients received a maximum dose of 150 mg, 18 patients received 200 mg, one patient 250 mg, 10 patients 300 mg, and eight patients 400 mg). Treatment with the combination was continued for at least 3 months (unless there was disease progression) until the earliest occurrence of maximum plateau of myeloma protein reduction, autologous transplant-supported intensification, other treatments (VAD, PS-341) for resistant disease, or unacceptable toxicities (thrombotic events in two patients occurred prior to more effective prophylaxis with therapeutic doses of coumadin). For responding patients not in CR, and for those not proceeding to myeloablative therapy, thalidomide alone was continued in a maximum dose with tolerable side effects alone or with dexamethasone for 4 days each month. Patients in CR received at least 4 months of thalidomide-dexamethasone and then were observed without maintenance therapy. For both trials, more than 80% of patients received thalidomide in an average daily dose of 100 to 200 mg each evening during the initial 2 months of therapy.

The first 24 patients who received the combination were given coumadin 1 mg PO daily (qd) for prophylaxis of deep venous thrombosis (DVT). After it was clear that this was not preventive, therapeutic doses of prophylactic anticoagulation with coumadin or low-molecular weight heparin were given to the remaining 16 patients. These treatments were conducted after approval by our institutional review board and in accordance with an assurance filed with and approved by the Department of Health and Human Services. All patients provided written informed consent and were observed on the Celgene system for thalidomide education and prescribing safety (STEPS) program. Table 1 lists patient characteristics before therapy.

Staging and Clinical Response

The diagnosis of multiple myeloma was based on standard criteria: all showed bone marrow plasmacytosis of more than 15% except for 16 patients who had biopsy-proven plasmacytomas and multiple lytic bone lesions, all patients showed a monoclonal globulin on serum or urine electrophoresis, and 28% of asymptomatic patients and 80% of symptomatic patients had lytic bone lesions. Plasma cell tumor mass was defined in each patient as high, intermediate, or low.^{9,10} High tumor mass was defined by either corrected serum calcium more than 11.5 mg/dL or hemoglobin less than 8.5 g/dL, and patients with such advanced disease were excluded. Low tumor mass required normal serum calcium, hemoglobin more than 10.5 g/dL, and serum myeloma protein less than 4.5 g/dL. All other patients were classified as intermediate tumor mass. Thus, as summarized in Table 1, asymptomatic patients treated with thalidomide alone had less advanced disease than symptomatic patients given thalidomide-dexamethasone.

Partial response (PR) was defined as reductions by ≥ 75% of serum and/or urine myeloma protein synthesis on two measurements taken at least 1 month apart; CR required disappearance of serum and urine myeloma protein by immunofixation and less than 5% plasma cells in bone marrow.¹¹ Patients with complete disappearance of BJP in the absence of a serum myeloma protein were not included in the determination of CR. Relapse was defined by earliest of a 20% increase of myeloma protein from nadir value, new lytic bone lesions, or hypercalcemia.

Using the same criteria, we evaluated our previous trials for similar groups of previously untreated patients for frequency and speed of myeloma

Table 1. Patient Characteristics (median and range)

	Thalidomide (n = 28)	Thalidomide-Dexamethasone (n = 40)
Tumor mass (no. of patients)		
Low	24	20
Intermediate	4	20
Hemoglobin (g/dL)	11.9 (9.2-14.4)	11.6 (8.6-14.8)
Monoclonal serum paraprotein (g/dL)	3.2 (0.9-6.1)	3.0 (0.2-9.6)
Marrow plasmacytosis (%)	22 (5-52)	35 (0-85)
β ₂ microglobulin (mg/L)	3.2 (1.4-12.9)	3.9 (1.6-15.7)
Bence Jones only (no.)	1	9

response. This included 140 patients treated between June 1997 and May 2000 with dexamethasone alone (20 mg/m² PO qd on days 1 to 4, 9 to 12, and 17 to 20 and repeated at 4 to 5 weeks with subsequent maintenance days 1 to 4, every 4 weeks), 170 patients treated between January 1992 and August 1997 with melphalan-dexamethasone (melphalan 8 mg/m²/d PO for 4 days and same regimen of dexamethasone every 5 weeks), and 128 patients treated between December 1984 and October 1993 with VAD (vincristine 0.4 mg/d and doxorubicin 9 mg/m²/d by continuous infusion IV over 24 hours for 4 days with dexamethasone as above repeated every 4 to 5 weeks).^{12,13,14}

RESULTS

Frequency of Remission

Disease remission was noted in 10 patients (36%) treated with thalidomide alone and in 29 patients (72%) treated with thalidomide-dexamethasone. Five patients treated with the combination achieved CR (16%) based on disappearance of serum myeloma protein and, if present, urine paraprotein by immunofixation; two of nine additional patients with only Bence Jones protein had complete disappearance by urine immunofixation. Two patients achieved CR by immunofixation, but follow-up marrow was not available at the time of this report. Five patients included as PRs had reductions of serum paraprotein by 75% (median pretreatment serum level of 3.6 g/dL, median posttreatment value of 0.8 g/dL) but did not achieve 75% reduction of minimal BJP (< 200 mg/d; median pretreatment BJP 0.021 g/d, median posttreatment BJP 0.012 g/d). All responding patients showed relief of bone pain, correction of anemia when present, and in 25 patients with posttreatment marrow available, reduction of marrow plasmacytosis to less than 10%. Two responding patients required vertebroplasty for relief of persistent back pain.

The median time to remission for patients responsive to thalidomide alone was 4.2 months, in contrast to 0.7 months for those who received thalidomide-dexamethasone. For patients responsive to combination therapy, 86% of patients were in remission within 2 months; the median time to complete remission was 2.3 months (range, 1.6 to 2.9 months). No clinical or laboratory features, including β₂-microglobulin and paraprotein level, correlated with response. At a median follow-up of 25 and 9 months, respectively, relapse had occurred in three patients on thalidomide alone after 4, 12, and 21 months, and in one patient on the combination, so it is premature to assess remission duration and survival.

Autologous Blood Stem Cells

Eligibility for high-dose melphalan supported by autologous stem cells required being less than 70 years of age, having good

health and performance, having adequate insurance support, and having the capacity to live near our center for 2 months. Twenty-one patients treated with thalidomide-dexamethasone proceeded to stem cell collection after 1.5 to 9.8 months (median, 5.5 months). Collection was rapid (median, 2 days) and efficient (median, 7.7×10^6 CD 34 cells/kg) with neupogen alone in all but two patients who received chemotherapy priming.

Toxicity

Although side effects with thalidomide were frequent, they were nearly always mild, short term, and reversible. One patient on the combination died unexpectedly of possible pulmonary embolus less than 1 week after thalidomide-dexamethasone was discontinued. Side effects noted most frequently are summarized in Table 2. Virtually all side effects were of grade 1 or 2 degrees; grade 3 toxicities included infections (nine patients), thrombotic/embolic events (six patients) despite low-dose coumadin prophylaxis and in one asymptomatic patient, constipation (one patient), and fatigue (one patient). No patient experienced grade 2 neutropenia or thrombocytopenia. Most patients treated with dexamethasone developed mild, reversible cushingoid features. Hospitalization for infection was required for three patients on thalidomide alone and for five patients on thalidomide-dexamethasone because of pneumonia in seven patients and cellulitis in one patient. Five deaths have occurred, two patients who received thalidomide alone (both of progressive myeloma) and three patients after combination therapy (one of infection, one of unknown cause after discontinuation of thalidomide, and one of postoperative complications after spinal surgery who showed a preoperative cardiac thrombus 1 week after stopping thalidomide).

DISCUSSION

Thalidomide produced remissions in 36% of patients with previously untreated asymptomatic multiple myeloma, similar to the frequency observed in patients with resistant disease.^{2,3} This effect was similar to that of other single agents, such as melphalan and high-dose dexamethasone, supporting the potential for more frequent control with combinations of these drugs that act by different mechanisms. Furthermore, our results with thalidomide as a single agent were nearly identical to those reported by Rajkumar et al,¹⁵ who observed six responses in 16 similar patients (38%) using doses ranging from 200 to 800 mg/d.

Among previously untreated patients with more advanced and symptomatic disease, the combination of thalidomide-dexamethasone doubled the response rate and induced remissions more rapidly, indicating that the combination of both drugs was superior to either alone. This experience conforms well with the superiority of the same combination among patients with resistant disease, even those who had been resistant to sequential trials of dexamethasone and thalidomide separately.^{4,5} Our results with this combination were also similar to the response rate of 64% observed by Rajkumar et al¹⁶ in 50 comparable, newly diagnosed patients.

Given the 25% incidence of thrombotic/embolic events in the first 24 patients treated with thalidomide-dexamethasone and warfarin 1 mg PO qd, and the absence of thrombotic events in the subsequent 16 patients given therapeutic doses of warfarin,

Table 2. Number and Percentage of Patients With Side Effects

Side Effect	Thalidomide (%)		Thalidomide-Dexamethasone	
	No. of Patients	%	No. of Patients	%
Total no. of patients	28		40	
Constipation	19	68	22	55
Neurologic				
Numbness/tingling	19	68	20	50
Unsteadiness	12	43	5	13
Tremors	10	36	12	30
Fatigue	11	39	22	55
Rash/dry skin	17	61	22	55
Edema	7	25	14	35
Infections	4	14	5	13
Thrombotic/embolic events	1	4	6	15

further characterization of coagulation factors at baseline and during treatment and the preventive role of therapeutic anticoagulation in high-risk patients should be addressed. Whereas most other side effects were mild and reversible with dose reduction or temporary cessation of thalidomide, neuropathy was rarely irreversible. These uncommon side effects should not detract from the higher response rate of thalidomide-dexamethasone with little or no serious toxicity in the majority of patients. The newer immunomodulatory derivatives (IMiDs) of thalidomide, which seem more potent *in vitro*, may avoid or reduce serious side effects such as neuropathy while retaining significant antitumor effects.^{17,18}

The potential value of thalidomide alone as prophylactic therapy for asymptomatic myeloma remains unclear. While the time to disease progression may be prolonged for those with responsive disease, premature and long-term therapy in asymptomatic patients may contribute to later drug resistance when the more effective thalidomide-dexamethasone combination may be necessary for disease progression. In some asymptomatic patients who experience neuropathy, prolonged therapy with thalidomide may also prevent future use of this and other potentially neuropathic drugs (thalidomide, vincristine, PS-341) when the disease becomes symptomatic. Randomized controlled studies that include data on later sensitivity to induction therapy for symptomatic disease, remission time, and late side effects are required to clarify these questions.

The mechanism of myeloma control with thalidomide remains unclear. Thalidomide inhibits angiogenesis *in vitro*, induces apoptosis, and reduces the high levels of certain angiogenesis factors, such as VEGF and bFGF, that are present in patients with multiple myeloma and other hematologic malignancies.¹⁹⁻²¹ However, no correlation between marrow vascularization and clinical response of myeloma has been noted.² Recently, a direct effect inducing G1 growth arrest and subsequent apoptosis, perhaps through interleukin-6 downregulation, has been demonstrated *in vitro*.²¹

Regardless of the mechanism, thalidomide-dexamethasone provided a simple, relatively safe, and remarkably effective primary treatment for nearly three-fourths of patients with previously untreated symptomatic multiple myeloma. Results seemed superior to previous experiences in comparable patients with dexamethasone alone, or in combination with melphalan, and similar to those with VAD, but with fewer complications (Table 3). A current randomized comparison of dexamethasone

Table 3. Response Rates in Previously Untreated Patients With Low or Intermediate Tumor Mass

	No. of Patients	Early Death <2 months	Response Rate (%)	CR (%)*	Myeloma Halving (median months)†
Melphalan-dexamethasone ¹³	170	2	51	8	0.3
Dexamethasone ¹⁴	140	1	47	7	0.4
Vincristine- doxorubicin-dexamethasone ¹²	128	3	66	13	0.5
Thalidomide	28	2	36	0	1.5
Thalidomide-dexamethasone	40	3	72	16	0.3

*Complete remission (CR) defined by disappearance of serum myeloma protein by immunofixation. For patients with only Bence Jones protein, urine disappearance for historical data was assessed primarily by electrophoresis and did not usually include immunofixation studies. Therefore, patients with only Bence Jones protein were excluded for assessment of CR in both historical and current data.

†Among responding patients with serum myeloma protein.

versus thalidomide-dexamethasone by the Eastern Cooperative Oncology Group should clarify this question. We also showed a major effect against myeloma with low and acceptably tolerated doses of thalidomide, especially when combined with dexamethasone, so that the frequent and severe side effects observed with higher doses were usually avoided.^{2,3,15,16} With therapeutic doses of coumadin to maintain international normalized ratio between 2.0 to 3.0, we have observed only rare occurrences of deep venous thrombosis in recently treated patients. Because the combined effect with dexamethasone poses a risk of gastrointestinal bleeding (or bleeding from other causes), future study of risk factors for hypercoagulability may identify more clearly those patients who should receive therapeutic anticoagulation.

Since the complete remission rate remained low, this program of induction therapy should be followed by intensive consolidation

therapy in most eligible patients to achieve complete remission that translates into longer survival.²² Because serious irreversible toxicity was rare and myelosuppression virtually nonexistent, patients with responsive disease proceeded early to stem cell collection with granulocyte colony-stimulating factor alone, followed by high-dose melphalan therapy with stem cell support. Considering the ease of oral administration, the infrequency of serious irreversible side effects, and the rapidity of response permitting early stem cell collection, the combination of thalidomide-dexamethasone may well represent the treatment of choice for myeloma patients with disease of low or intermediate tumor mass.

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