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Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma

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Background and Objectives. The immunomodulatory drug thalidomide can inhibit angiogenesis and induce apoptosis in experimental models. It can also induce marked and durable response in advanced myeloma patients. Thalidomide has been used at doses ranging from 200 to 800 mg with significant toxicity. No data are available on the impact of low-dose thalidomide plus dexamethasone as salvage therapy for relapsed patients.

Design and Methods. To address this issue, myeloma patients were treated with 100 mg/day thalidomide continuously and dexamethasone 40 mg, days 1-4, every month. Between June 1999 and August 2000, 77 patients (median age 65 years) who had relapsed or were refractory to chemotherapy were treated with thalidomide plus dexamethasone.

Results. After a minimum of 3 months of treatment, 14 patients (18%) showed a myeloma protein reduction of 75%-100%, 18 patients (23%) showed a response of 50-75%, 19 patients (25%) a response of 25-50% and 26 patients (34%) a response of <25% or disease progression. After a median follow-up of 8 months, median progression-free survival was 12 months. Thalidomide was well tolerated. Constipation (12%) and sedation (6%) were mild. Tingling or numbness were present in 17% of patients, discontinuation of treatment was required in 10% of patients.

Interpretation and Conclusions. The association of low-dose thalidomide plus dexamethasone is active against advanced myeloma. A significant proportion of patients benefit from this treatment as a salvage therapy postponing the delivery of chemotherapy.

Key words: myeloma, thalidomide, dexamethasone, salvage therapy

Angiogenesis is increased in multiple myeloma and has a prognostic value in the disease.[1,2] The antiangiogenic properties of thalidomide[3] provide the rationale for studying the effect of this drug in myeloma. Thalidomide may directly inhibit the growth and survival of myeloma cells;[4] its efficacy may also be linked to modulation of growth-related genes, such as c-myc.[5] The interleukin-6 (IL-6) receptor gene is also dramatically downregulated.[5]

For more than 30 years the initial therapy of multiple myeloma has consisted of melphalan and prednisone.[6-8] A therapeutic strategy to improve clinical outcome is high-dose chemotherapy followed by autologous stem cell transplantation.[9,10] Relapses, however, constantly occur and cure is rarely achieved.[11]

To improve treatment outcome and introduce the possibility of curative therapy, it is necessary to search for new drugs or new uses of old drugs. One such compound is thalidomide. This drug was found to be effective in refractory and recurrent myelomas producing an overall response rate of 32%.[12] The study design called for a gradual increase in the dose, but only 55% of the patients received the intended maximal daily dose of 800 mg. Most patients received 400 mg of thalidomide daily. Glucocorticoids are effective and extensively used in the management of patients with advanced myeloma.[13-15] *In vitro*, thalidomide enhanced the anti-myeloma activity of dexamethasone which, conversely, was inhibited by IL-6.[16]

Based on these pieces of evidence, we evaluated the toxicity and clinical efficacy of low-dose thalidomide combined with corticosteroids on the assumption that lower thalidomide doses are better tolerated and the association with corticosteroids may exert a synergistic effect. Refractory/relapsed myeloma patients were treated with this schedule. Low-dose thalidomide plus dexamethasone was shown to be extremely well tolerated and highly effective.

Design and Methods

Patients

Between June 1999 and August 2000, 77 consecutive patients with refractory or relapsed myeloma entered the protocol. The SWOG[17,18] and Durie and Salmon staging systems were used. At diagnosis, 37 patients were treated with high-dose chemotherapy (two or three courses of melphalan at 100 mg/m^2 as previously described),[19] and 40 were treated with conventional chemotherapy (32 received oral melphalan and prednisone, 8 dexamethasone-doxorubicin-vincristine). These regimens were also used as salvage therapy. Thalidomide plus dexamethasone was administered a median of 46 months after diagnosis. Four patients had primary resistance to induction treatment, 21 were in resistant relapse and 52 were in untested relapse. Twenty-six patients received thalidomide after one line of therapy, 21 after two and 30 after three. Among those receiving high-dose chemotherapy, 17 were in first untested relapse, 18 in second untested relapse and 2 were in resistant relapse. Of those treated with conventional chemotherapy, 4 had primary resistance, 19 were in resistant relapse and 17 in untested relapse. No patients were excluded on the basis of cardiac, renal, pulmonary or liver function. All patients were treated in two hematologic centers. Written informed consent was obtained from all patients.

Treatment

Thalidomide was supplied in 100 mg capsules by Grunenthal GmbH, 52222 Stolberg, Germany. Thalidomide was administered at the dose of 100 mg at bedtime and associated with dexamethasone administered orally at the dose of 40 mg on days 1, 2, 3, and 4 every month. Data were analyzed when the duration of thalidomide treatment ranged from 3 to 16 months (median 6.9). At the time of treatment, all patients had progressive disease with a >50% increase in myeloma protein or reappearance of Bence Jones proteinuria >0.5 g/24h. Pre-treatment evaluation included complete blood count, renal and liver function tests, serum and urine myeloma protein and serum β_2-microglobulin evaluation. Patients were evaluated for neurological abnormalities and electromyography was performed if clinical signs of neuropathy were detected. Patients were evaluated monthly and physical examination and blood test were routinely performed. The patient's characteristics are listed in Table 1.

Response criteria and statistics

Complete remission required disappearance of serum or urine myeloma protein analyzed by standard electrophoresis and marrow plasmacytosis <1% for at least 2 months. Clinical responses were defined according to the reduction of serum myeloma protein: 75%-100%, 50%-75%, 25%-50%, and <25%, respectively. In Bence Jones myeloma, disappearance of urine myeloma protein was recorded as a clinical response of 75%-100%. Clinical responses 50%-75%, and 25%-50% were defined when the reduction of urine myeloma protein was >90%, and >50%, respectively. All other results were recorded as failures. Progression was defined by increases in serum or urine myeloma protein >25%. The curve was plotted according to the method of Kaplan and Meier from the beginning of the treatment with thalidomide.[20]

Table 1. Patients' characteristics.

No. of patients	77
Median age (y)	65
Stage at diagnosis	
IIA	30
IIB	4
IIIA	40
IIIB	3
β2-microglobulin < 3 mg/mL	34
β2-microglobulin > 3 mg/mL	43
	% of patients
M-protein class	
IgG	60
IgA	27
IgM	1
Bence Jones protein	12
Bone marrow plasma cells > 30%	64
WHO performance status >3	13

Table 2. Response.

M-protein reduction	*No. of patients*	*% of total*	
75%-100%	14	18	41
50%-75%	18	23	
25%-50%	19	25	
No response*	26	34	

**Disease progression or stable disease or <25% M-protein reduction.*

Results

Response rate

The daily dose of thalidomide was reduced from 100 mg to 50 mg in 4% of patients and in 10% the administration of thalidomide was suspended after a median of 3 months (range 1-11). The monthly dose of dexamethasone was stopped in 1% of patients. All patients were considered in the evaluation: 41% showed a myeloma protein decline >50%: in 18% the decline was 75-100%, in 23% it was 50-75%, and in 25% it was 25-50% (Table 2). Three percent showed complete remission.

The median time required to obtain the maximum response to thalidomide plus dexamethasone was 4.2 months (range 0.6-10.2): 33% of maximum responses were apparent after 2 months, 15% after 3 months and 17% after 4 months; however, 35% became apparent

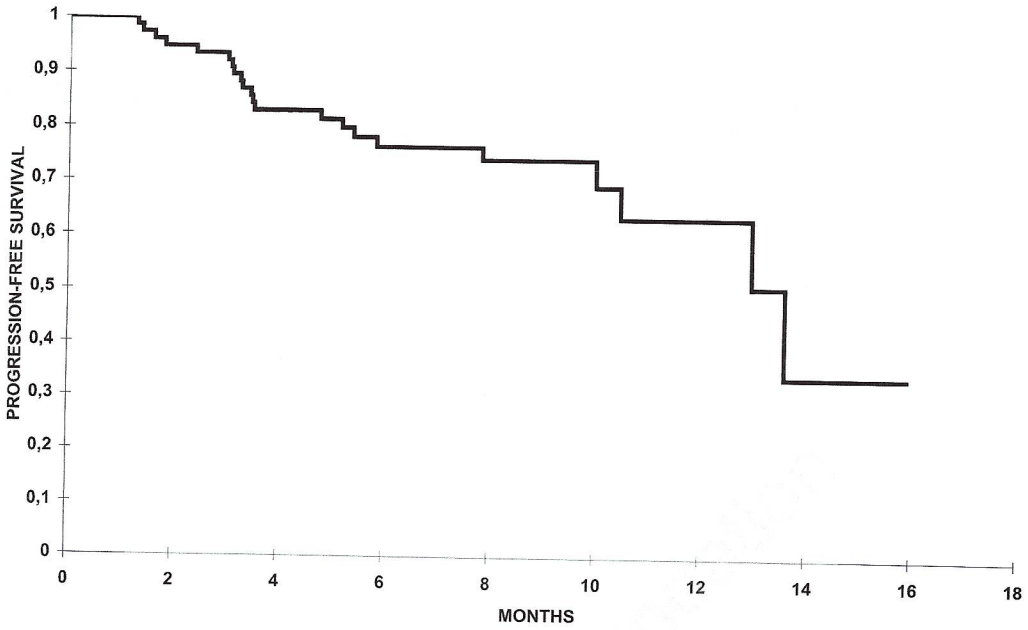

Figure 1. Progression-free survival of myeloma patients treated with thalidomide plus dexamethasone.

between 4 and 6 months. Improvement of performance status, skeletal pain, blood count, anemia and transfusion requirements were slower and related to the degree of response. After a response of 50-100%, the median levels of hemoglobin increased from 11 g/dL to 13 g/dL.

Clinical outcome

Among the 51 patients with a >25% decline in the myeloma protein, 10 showed disease recurrence. After a median follow-up of 8 months (range 3 to 16), the median time to progression was 12 months (Figure 1). The median overall survival was not reached and 91% of patients were alive.

Toxicity

Most adverse effects were recorded as grade I according to the World Health Organization toxicity classification. Thalidomide had to be discontinued because of toxicity in only 8 patients. Constipation was relatively frequent but well controlled with appropriate medication. Sedation was recorded in 6% of patients, changes in full-time or part-time working habits were required in 4% only. Weakness and fatigue were experienced in 8% of patients. These symptoms were drastically reduced when patients took thalidomide at dinnertime. Mood changes or depression were present in 4% of patients, but mainly in elderly subjects. Tingling and numbness were observed in an unexpected 14% of patients as grade I, in 3% as grade II. These symptoms developed after a median time of 3 months. Tingling required thalidomide discontinuation in 5% of patients, but 3% then experienced an improvement. Tremors and inco-ordination were present in 3% of patients and were generally mild. Dizziness was a late adverse effect (3%), and was mainly a clinical progression of foot numbness. One patient developed a severe skin rash on her face followed by vesicles and bullae: erysipelas was diagnosed and successfully treated with oral antibiotics. In another patient, a severe necrotic ulcer of the skull was observed. Two patients had evidence of hypothyroidism. Blood counts generally improved when disease response was achieved. Two patients showed an increase in creatinine levels. In one patient disease progression occurred with a slight increase in Bence Jones proteinuria accompanied by acute renal failure requiring dialysis. No concomitant nephrotoxic therapy was delivered in these subjects. Previously reported episodes of deep vein thrombosis were not observed (Table 3).[21]

Discussion

The association of low-dose thalidomide plus dexamethasone was highly effective in patients with relapsed or refractory myeloma: 41% showed a >50% decrease in myeloma protein. In most patients, the serological response was accompanied by a significant improvement of asthenia and bone pain, and a marked increase in hemoglobin levels. Oral melphalan and prednisone induced a tumor mass reduction >50% in only 20% of resistant/relapsing patients.[22] Our data clearly show that

Table 3. Toxicity.

	No. of patients	% of total
Tingling and numbness	13	17
Constipation	9	12
Weakness and fatigue	6	8
Sedation	5	6
Changes in work habit	3	4
Mood changes and depression	3	4
Tremor	2	3
Dizziness	2	3
Erysipela	2	3
Hypothyroidism	2	3
Renal toxicity	2	3
Toxicity that required discontinuation of treatment	8	10

low-dose thalidomide and dexamethasone have a true anti-tumor effect and that this is superior to that achieved by oral melphalan and prednisone.

Recent data suggest that thalidomide alone is active in 30-60% of patients with refractory/relapsed myeloma.[12,16,21,23,24] With doses ranging from 200 mg to 800 mg/day, side-effects were encountered in 10-50%.[12] In our study, adverse effects were recorded in 5-15%. In the escalating dose studies already performed, no relation between dose and response has been demonstrated.[12,21] In preliminary reports, a dose as low as 50 mg/day was claimed to be effective in myeloma patients.[25,26] In our series, median time to response was 4.2 months. This was longer than previously reported times, perhaps due to the lower dose of thalidomide.

The importance of glucocorticoids has been demonstrated by evaluating melphalan and prednisone administration in the primary management of myeloma. Survival time was found to correlate with the dose of prednisone and not with that of melphalan.[27] In refractory patients high doses of prednisone or dexamethasone may induce remission in a significant proportion of cases.[13,14]

Thalidomide and dexamethasone are a logical combination since they may differ in their action against myeloma. Thalidomide acts via adhesion molecule alteration, anti-angiogenesis and modulation of T-lymphocytes, whereas dexamethasone exerts its effect by inhibiting IL-6 production. *In vitro*, the addition of dexamethasone increased the inhibition of proliferation induced by thalidomide on myeloma cell lines by about 35%. Thalidomide induced apoptosis in cells resistant to dexamethasone, suggesting the potential utility of the combination of these two drugs.[16]

Here, we demonstrate that the combination of thalidomide at 100 mg/day plus dexamethasone at only 40 mg, 4 days each month, is an effective treatment against myeloma. At this dose dexamethasone alone cannot induce partial response in 40% of refractory patients. For these patients, 30% partial responses were recorded when dexamethasone was delivered at 40 mg but 12 days each month.[13] When thalidomide was administered alone at doses ranging from 200 mg to 800 mg partial responses were achieved in 25% of cases in one report[12] and 40% in another.[23]

In conclusion this study confirms previous findings showing that thalidomide is a new compound for the management of myeloma and is the first demonstration that low-dose thalidomide plus dexamethasone is an effective treatment for myeloma patients. The low-dose thalidomide schedule is very well tolerated and highly effective. Whether this efficacy is due to an additive or synergistic effect with dexamethasone is not clear.

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AnP conception, design, interpretation of data, drafting the article; LG, AB, PP SB, CR, ST analysis, interpretation of data, critical revision; EG, AP critical revision, important intellectual suggestions, final approval of the version to be submitted. MB conception, design, drafting the article, final approval of the version to be submitted.

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Disclosures

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Manuscript processing

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Potential implications for clinical practice

Low-dose thalidomide is well tolerated and highly effective on refractory myeloma. A significant proportion these patients benefit from this treatment as a salvage therapy postponing the delivery of chemotherapy.

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