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Original article

Thalidomide and dexamethasone combination for refractory multiple myeloma

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Summary

Background: Thalidomide is effective in approximately 30% of patients with refractory multiple myeloma. Dexamethasone is active in 25% of patients with disease resistant to alkylating agents. We investigated the combination of thalidomide with dexamethasone as salvage treatment for heavily pretreated patients with multiple myeloma, in order to assess its efficacy and toxicity.

Patients and methods: Forty-four patients with refractory myeloma were treated with thalidomide, 200 mg p.o. daily at bedtime, with dose escalation to 400 mg after 14 days, and dexamethasone, which was administered intermittently at a dose of 20 mg/m^2 p.o. daily for four days on day 1–4, 9–12, 17–20, followed by monthly dexamethasone for four days. Patients' median age was 67 years. All patients were resistant to standard chemotherapy, 77% were resistant to dexamethasone-based regimens and 32% had previously received high-dose therapy.

Results: On an intention-to-treat basis twenty-four patients (55%) achieved a partial response with a median time to response of 1.3 months. The thalidomide and dexamethasone combination was equally effective in patients with or without prior resistance to dexamethasone-based regimens and in patients with or without prior high-dose therapy. Toxicities were mild or moderate and consisted primarily of constipation, morning somnolence, tremor, xerostomia and peripheral neuropathy. The median time to progression for responding patients is expected to exceed 10 months and the median survival for all patients is 12.6 months.

Conclusion: The combination of thalidomide with dexamethasone appears active in patients with refractory multiple myeloma. If this activity is confirmed, further studies of this combination as second-line treatment for patients resistant to conventional chemotherapy, and as primary treatment for patients with active myeloma, should be considered.

Key words: dexamethasone, multiple myeloma, thalidomide

Introduction

Approximately one half of patients with previously untreated multiple myeloma respond to several conventional therapies including melphalan and prednisone, vincristine, doxorubicin and pulse dexamethasone (VAD), or pulse dexamethasone alone, with a subsequent median survival for all patients of approximately three years [1]. Over the last decade it has been demonstrated that melphalan-based high-dose chemotherapy with stem cell support increases the response rate and prolongs the overall survival. This modality can be applied to less than 50% of patients with multiple myeloma because of restrictions of age, performance status and other organ functions. Furthermore, most of the transplanted patients still relapse. For these patients, as well as for those who are not eligible for high dose therapy, options for salvage therapy are limited.

Recently, thalidomide, an oral agent with immunomodulatory and antiangiogenetic properties, has shown activity in approximately 30% of patients with refractory multiple myeloma [2]. This agent is usually not associated with myelosuppression but can cause side effects such as constipation, somnolence, fatigue, mood changes, skin rash and peripheral neuropathy. The incidence and severity of these adverse effects are usually dose-related and drug intolerance may be more pronounced in older patients. In order to enhance the therapeutic index of thalidomide, ongoing studies combine this agent to other active agents against myeloma. Preliminary evidence from the M.D. Anderson Cancer Center has shown that four of six patients with resistance to dexamethasone-based regimens and without prior thalidomide, responded to a combination of thalidomide and dexamethasone, indicating improved results with the combination of these two agents [3]. In order to clearly define the activity of this combination in the treatment of refractory myeloma we performed a large phase II multicenter study.

Table 1 Patient characteristics.

	Percent of patients (%)
Male sex	73
Age > 70 years	21
Myeloma type	
IgG	57
IgA	26
Light chain only	12
Non secretory	5
Light chain	
k	59
λ	36
None	5
Performance status ≥ 2	30
Hemoglobin < 8.5 g/dl	23
Platelets < 100 × 10^9/dl	23
Serum calcium > 11.5 g/dl	12
Serum creatinine > 1.5 mg/dl	14
Serum LDH > 220 IU/l	28
Serum β2-microglobulin > 6 mg/l	29
Bone marrow plasma cells > 50%	42

Table 2 Disease status and prior treatment.

	Percent of patients (%)
Disease status	
Primary refractory	34
Resistant relapse	66
Number of prior regimens	
1	11
2	23
3	34
4	25
≥ 5	7
Prior resistance to dexamethasone-based regiment	77
Prior treatment with high dose chemotherapy	32

Patients and methods

Between July 1999 and November 2000, 44 patients were treated with the combination of thalidomide and dexamethasone (TD) after informed consent was obtained from each patient. Patient characteristics are shown in Table 1. The median age was 67 years (range: 38 to 87 years), nine patients were older than 70 years and 32 were male. Features of advanced disease such as severe anemia, thrombocytopenia, extensive bone marrow plasmacytosis, hypercalcemia, markedly elevated serum β2-microglobulin and high levels of serum LDH were often present (Table 1). Thirty-four percent of patients had not responded to any previous regimen (primary refractory) and 66% of patients were relapsing despite chemotherapy (resistant relapse). Three or more treatment regimens were administered to 66% of patients and 77% were resistant to an immediate prior regimen which contained high dose dexamethasone. One-third of patients had also received high-dose therapy (Table 2). The median time from initial treatment to inclusion in this study was 23.3 months (range: 2.7 to 134.4 months).

All patients had baseline evaluations that included physical examination, blood counts, hepatic and renal function tests, bone marrow aspirate and/or biopsy, serum and urine protein electrophoreses, quantitation of serum immunoglobulins, serum LDH and β2-microglobulin. Chest X-ray and a limited bone survey were also performed. For the first two months of treatment patients were followed up with biweekly physical examinations, blood counts, renal and liver function tests and serum and urine electrophoretic studies. Thereafter these tests were repeated on a monthly basis. Bone marrow reassessment was performed when patients' monoclonal protein reached maximum reduction.

The initial dose of thalidomide was 200 mg p.o. daily at bedtime, with dose escalation to 400 mg after 14 days in absence of severe side effects. Dexamethasone was administered intermittently at a dose of 20 mg/m^2 p.o. q.d. for four days on days 1–4, 9–12, 17–20, followed by monthly dexamethasone for four days.

All patients who received the TD combination for at least one day were eligible for assessment of toxicity and response. Toxicity was graded according to the classification system of the Word Health Organization (WHO) [4]. Patients who discontinued treatment before a response could be assessed were considered to have had no response to treatment. Thus, the results were evaluated on an intention-to-treat basis.

Complete response was defined as disappearance of the monoclonal protein by serum and/or urine immunofixation and less than 5% bone marrow plasma cells. Partial response was defined as a greater than 50% reduction of serum myeloma protein and/or greater than 75% reduction of Bence Jones protein, with > 50% reduction of bone marrow plasma cells. For the purpose of this study minor response was defined as at least 25% reduction of serum monoclonal protein, and the disease was considered stable when the serum monoclonal protein changes were < 25% without additional complications of the myeloma. Patients were considered in progression when they did not meet criteria for response or stable disease. Relapse was defined by at least a 25% increase of monoclonal protein from the lowest value, increasing bone lesions or bone marrow plasmacytosis.

The time to response was defined as the interval between the start of therapy and the first confirmation of partial response. The time to progression was defined as the time from the start of therapy to disease progression. Overall survival was calculated from the start of therapy to death from any cause or the last follow-up visit, whichever occurred first. Several clinical and laboratory variables were assessed for their possible association with response to and with overall survival. Those variables which were found statistically significant in the univariate analysis of overall survival were subsequently included in a Cox regression analysis [5]. In order to assess the impact of response to thalidomide and dexamethasone on patients' survival, a landmark analysis was performed [6].

Table 3 Response to treatment.

	Number of patients (%)	95% CI
Partial response	24 (55)	39–69
> 75% ↓ m-peak	13 (30)	17–45
> 50% ↓ m-peak	11 (25)	13–40
Minor response	1 (2)	0–12
Stable disease	8 (18)	8–33
Progressive disease	11 (25)	13–40

Abbreviation. CI – confidence interval.

Results

Twenty-four of 44 patients (55%) achieved a partial response including 13 patients with at least 75% reduction of serum monoclonal protein (Table 3). Furthermore, one patient achieved minor response to treatment. Complete responses were not noted. The median interval between the start of treatment and a decrease in the paraprotein level of at least 50% was 1.3 months (range 0.75 to 3.6 months). Responding patients demonstrated an improvement of their performance status and of

Table 4. Parameters associated with response to TD.

Parameter percent	Response	*P*-value
Performance status		
0	83	
⩾1	37	0.002
Light chain type		
k	73	
λ	25	0.004

Table 5. Toxicity (WHO scale)

Adverse effect	Percent of patients (%)
Constipation	75
Somnolence and/or fatigue	57
Mood changes	33
Xerostomia	34
Tremor	30
Peripheral neuropathy	23
Skin rash	21
Headache	21
Edema	17
Vein thrombosis	7

Table 6. Parameters associated with survival after TD.

Parameter	Median survival (months)	*P*-value
Gender		
Female	Not reached	
Male	12.6	0.05
Disease status		
Primary refractory	Not reached	
Refractory relapse	9.6	0 06
Hemoglobin		
⩾8.5 g/dl	13.0	
<8.5 g/dl	4.8	0.0004
Performance status		
0	13.0	
⩾1	6.6	0.002
Light chain type		
k	Not reached	
λ	6.6	0.004
Serum LDH		
⩽220 IU/l	13.0	
>220 IU/l	6.6	0.009

anemia, and a decrease of previously elevated serum β2-microglobulin and LDH levels.

Several variables such as gender, age, myeloma heavy and light chain type, hemoglobin, platelet count, serum LDH and β2-microglobulin, performance status, bone marrow plasmacytosis, disease status, prior high dose therapy and resistance to dexamethasone, were evaluated for their possible correlation with response to TD. Our combination induced responses in 40% of patients with thrombocytopenia (platelet count $< 100 \times 10^6$/dl) and in 59% of patients without thrombocytopenia ($P = 0.47$). The TD regimen was active in 56% of patients whose disease was resistant to an immediate prior treatment which contained high dose dexamethasone. Also, our

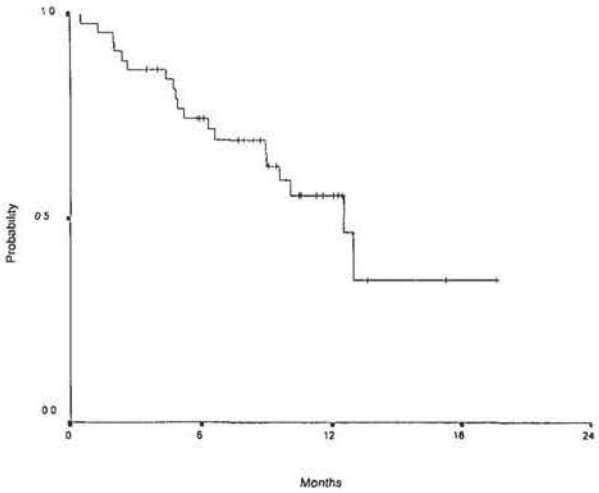

Figure 1. Overall survival after treatment with thalidomide and dexamethasone.

combination induced responses in 57% of patients who had previously received high dose therapy with stem cell support. The TD regimen was equally effective in patients with either primary resistant myeloma or with disease in resistant relapse; partial responses occurred in 60% and 52% of patients respectively. Among all the variables tested for their possible association with response, light chain of lambda type and impaired performance status were associated with a lower probability of response to TD (Table 4).

Furthermore, the TD regimen was administered to eight patients with primary refractory myeloma who were eligible for high-dose therapy with autologous stem cell support, but this procedure could not be performed due to extensive tumor load with heavily infiltrated bone marrow, thrombocytopenia and/or significantly impaired performance status. Four of such patients responded, blood stem cells were collected and subsequently the patients received high dose melphalan with autologous blood stem cells as a consolidation treatment.

Side effects after treatment with TD are shown in Table 5. Most adverse effects were due to thalidomide and were mild or moderate (grade 1 or 2 on the WHO scale). The more common adverse effects were constipation, somnolence and fatigue. Approximately one-third of patients developed mood changes, xerostomia or tremor. Some degree of peripheral neuropathy occurred in 10 patients and this side effect necessitated interruption of thalidomide in three patients. Maculopapular skin rash was not uncommon but it usually subsided with reduction of the dose of thalidomide. Deep vein thrombosis occurred in three patients. Grade 1 or 2 leukopenia occurred in 4 patients. Thrombocytopenia or anemia that could be attributed to the treatment were not seen. The dose of thalidomide was escalated to the scheduled dose of 400 mg p.o. daily in 36 patients (82%). The average daily dose of thalidomide was 400 mg in 32 patients, 300 mg in 3 patients and 200 mg in 9 patients.

The median time to progression for all patients was

4.2 months, whereas the median time to progression for patients achieving a partial response has not been reached as yet and it is projected to exceed 10 months. The median overall survival is 12.6 months (Figure 1). Multiple parameters were assessed for their possible association with survival after treatment with thalidomide and dexamethasone. Variables such as age, serum b2-microglobulin, bone marrow plasmacytosis, prior treatment with high dose therapy and prior resistance to dexamethasone-based regimens were not predictive of survival. However, female gender, primary refractory disease, absence of severe anemia, very good performance status, kappa light chain and normal levels of serum LDH were associated with longer survival after treatment (Table 6). A Cox regression analysis was also performed which indicated that only performance status, gender and disease status retained significance ($P < 0.0001$, $P < 0.002$ and $P = 0.001$, respectively). A landmark analysis at 4 months was performed and showed that the median survival of patients who responded to thalidomide and dexamethesone has not been reached and that of nonresponding patients was 13 months ($P = 0.01$).

Discussion

Singhal et al. first demonstrated that thalidomide has significant activity in one-third of patients with refractory myeloma [2]. This activity was subsequently confirmed by several independent studies (7–9). Thus, besides alkylating agents and corticosteroids, thalidomide now represents the third distinct class of agents with activity in patients with multiple myeloma. The antitumor mechanisms of thalidomide in multiple myeloma are probably complex and not clearly defined. Possible mechanisms of action include inhibition of angiogenesis, modulation of adhesion molecules involved in the interaction of myeloma cells and bone marrow stroma, modulation of several cytokines that may affect the survival of myeloma cells and increased secretion of interferon-γ and interleukin-2 by CD8+ T cells [10]. Furthermore, there is recent evidence that thalidomide and its analogues act directly, by inducing apoptosis or G1 growth arrest, in myeloma cell lines and in patient myeloma cells that are resistant to melphalan, doxorubicin and dexamethasone [11].

Preliminary data have suggested that some patients with resistance to dexamethasone-based regimens achieved a response after treatment with a combination of thalidomide and dexamethasone [3]. Based on this encouraging result we performed a multicenter phase II study in order to evaluate the efficacy and toxicity of TD combination in patients with refractory multiple myeloma. We found that this combination was active in 55% of patients with multiple myeloma, including 30% patients who achieved > 75% reduction of myeloma protein. Responses were associated with an improvement of performance status, an increase in hemoglobin levels and decrease of elevated β2-microglobulin levels. All responding patients showed evidence of antitumor effect within two months, so that trials longer than three months may not be necessary to assess whether this regimen is active in patients with resistant multiple myeloma.

The activity of our TD regimen appeared higher than that observed with single agent thalidomide [7–9]). Our regimen was equally effective in patients with or without prior resistance to dexamethasone-based regimens. Weber et al. recently reported that the combination of thalidomide and dexamethasone was active in 46% of patients who were resistant to prior treatment with high dose dexamethasone and subsequent thalidomide alone [12]. Furthermore, Hideshima et al. recently showed that thalidomide enhances the antimyeloma activity of dexamethasone *in vitro* [11]. All these observations indicate that there is a synergistic effect between thalidomide and dexamethasone. However, a prospective randomized comparison of thalidomide vs. thalidomide and dexamethasone is needed in order to define whether the combination is more active than thalidomide alone in patients with refractory multiple myeloma. Our combination was equally active in patients with either primary refractory disease or with disease in resistant relapse. The TD regimen was also effective in patients with high tumor burden, as indicated by markedly elevated serum levels of β2-microglobulin, and in patients with aggressive myeloma as indicated by high serum LDH. Patients with very good performance status, and with monoclonal kappa light chain had a higher probality of response to TD.

The median time to progression for responding patients is expected to exceed 10 months and the median survival of this group of patients with advanced myeloma was 12.6 months. A Cox regression analysis indicated that female gender, good performance status and primary refractory disease, were independent factors associated with an improved survival after treatment with thalidomide and dexamethasone. Thus, treatment with TD provided an opportunity for symptomatic improvement and prolonged survival in patients with myeloma who had failed not only conventional chemotherapy but also had developed resistance after high dose chemotherapy. Furthermore, the administration of TD provided the opportunity for high dose therapy in 4 of 8 patients who could not previously undergo the procedure because of poor performance status, thrombocytopenia and/or heavily infiltrated bone marrow.

The side effects of the combination were primarily attributed to thalidomide and were generally manageable and reversible with appropriate dose reduction. They consisted primarily of constipation, morning somnolence, mood changes, xerostomia, tremor and peripheral neuropathy. The latter adverse effect may be dose-limiting and its appearance necessitated dose reduction or even interruption of thalidomide. The lack of myelosuppression makes the TD combination a pertinent treatment for patients with heavily infiltrated bone marrow or with hypoplastic marrow due to prior high-dose therapy.

We conclude that the combination of thalidomide and dexamethasone represents an active salvage regimen for patients with refractory myeloma. If its activity is confirmed from randomized studies, it should be used as soon as resistance to high-dose dexamethasone-based regimens is observed. This combination may also be used for the *in vivo* 'purging' of patients with primary refractory myeloma who are otherwise eligible for high dose therapy. The TD regimen is also being evaluated as primary treatment for patients with active myeloma and the preliminary results are very promising [13].

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