Extramedullary multiple myeloma escapes the effect of thalidomide

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A B S T R A C T

Background and Objectives. Thalidomide is an antiangiogenic drug that produces a response rate ranging from 32 to 64% in patients with refractory/relapsed multiple myeloma (MM). However, the efficacy of thalidomide in patients with soft-tissue plasmacytomas is controversial. The aim of this study was to assess the response rate to thalidomide in patients with advanced MM and to correlate the response rate with the presence of extramedullary involvement.

Design and Methods. Thirty-eight patients with refractory/relapsed MM were treated with thalidomide. Eleven patients had extramedullary involvement when therapy was initiated. The response rate was evaluated according to the criteria of the European Group for Blood and Marrow Transplantation.

Results. Sixteen of the 38 patients (42%) responded to thalidomide. The response rate was significantly higher in patients without extramedullary involvement (59% vs 0%, p=0.0006). Although four of the 11 patients with extramedullary involvement had a serological response, a progression of the soft-tissue masses was observed in all of them.

Interpretation and Conclusions. Thalidomide is effective in patients with advanced MM. However, extramedullary disease does not respond to thalidomide, as delivered in this series. The mechanisms to explain different response to therapy depending on tumor homing warrant further investigation.

Key words: multiple myeloma, plasmacytomas, thalidomide.

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Multiple myeloma (MM) accounts for about 10% of hematologic malignancies and 1% of all malignant diseases. This disease is clinically characterized by lytic bone lesions, anemia, hypercalcemia, renal function impairment, recurrent bacterial infections and extramedullary involvement, all this leading to a median survival of about three years. Extramedullary involvement by the disease (i.e., palpable or radiographically visualized masses) has been reported in 15% to 20% of patients at diagnosis and in an additional 15% during the course of the disease.[1,2] Several studies have shown an increased microvessel bone marrow density in patients with MM,[3] the degree of bone marrow angiogenic activity being correlated with disease progression. The anti-angiogenic properties of thalidomide provided the rationale for its use in patients with MM. When given as a single agent, this drug produces a response rate ranging from 32 to 64% in patients with refractory/relapsed disease.[4-11] Although plasmacytomas are tissues with high neovascularization,[12,13] controversial results on the response to thalidomide in these patients have been reported.[12,14] Furthermore, cases of extramedullary or bone marrow progression despite a good serological response have been recognized.[5,15,16] The latter observations would support a bone marrow microenvironment-mediated mechanism the effect of thalidomide in MM. We report the results of treatment with thalidomide in 38 consecutive patients with refractory/relapsed MM, eleven of which had extramedullary involvement.

Table 1. Characteristics of patients with extramedullary plasmacytomas (EMP).

Patient Number	*Age/ Sex*	*Platelet count ($\times 10^9$/L)*	*LDH* (UI/L)*	*Previous HDT*	*Serum M-protein g/L (Start /After)*	*Urine M-protein g/24h (Start/After)*	*M-protein response*	*Evolution EMP* (Start/After)*	*Overall response*
2	59/F	96	392	No	8.7-ND	0.05–0.014	Progression	Yes /New	Progression
9	52/M	97	329	Yes	43.7–61.8	2–2.1	Progression	Yes/New@	Progression
12	80/M	214	–	No	39.2–34.2	ND	No change	Yes/No change	No change
14	65/F	180	405	Yes	7.2-11	1.9–7.4	Progression	Yes /@	Progression
19	61/M	88	359	No	63–45.1	1.5–1.9	MR	Yes /@	Progression
25	64/F	315	246	Yes	10.2–10.5	2.5–4.7	Progression	Yes /@	0Progression
28	57/M	173	521	Yes	7–10.5	0.01–0.01	Progression	Yes / New@	Progression
29	77/M	147	914	No	18.3–16.2	0.02–0.09	No change	Yes / No change	No change
30	41/M	86	–	No	25.4–10.4	9–4.8	MR	Yes /@	Progression
31	66/F	123	305	No	61.4–38.8	0.1–0.05	MR	Yes/New	Progression
38	49/M	251	–	Yes	21.7-12	ND-ND	PR	Yes /New@	Progression
3	48/F	322	–	Yes	34.2–16.1	ND	PR	No/New	Progression
17	51/F	220	379	No	14-18	0.2–0.6	Progression	No/New	Progression

*PR: partial response; MR: minimal response; ND: not done; New: appearance of new soft-tissue plasmacytomas; @:increase in size of soft-tissue plasmacytomas: *normal values < 450 UI/L.*

Design and Methods

Patients

From November 1999 to December 2002, 38 consecutive patients from a single institution (20 males, 18 females, median age 63 years) with previously treated and progressive MM were given thalidomide treatment as a single agent. The M-protein type was IgG in 25 cases, IgA in 7, light chain in 5 and IgM in 1. The type of light chain was κ in 23 patients and λ in 15. The median time from the first chemotherapy to treatment with thalidomide was 41 months (range 6-165). The median number of prior chemotherapy regimens was 2 (range 1 - 4). Fifteen patients (40%) had relapsed after an autologous stem cell transplantation (SCT). Eighteen patients had refractory disease (refractory relapse 14, primary resistance 4) while the remaining 20 patients had untested relapse. Eleven patients had extramedullary plasmacytomas when treatment with thalidomide was initiated (Table 1).

Treatment

Thalidomide was started at a single nightly dose of 200 mg. The dose was escalated by 100 or 200 mg every 2 weeks, depending on the patient´s tolerance, up to a maximum of 800 mg/day. The median dose administered was 400 mg (range, 200 to 800). Eight patients received a dose of 600 mg or higher and six reached the upper dose limit of 800 mg. In three patients, treatment with thalidomide was prematurely discontinued because of severe toxicity. In patients who achieved a response, the dose was gradually reduced to a maintenance daily dose of 100 mg. No prophylactic anticoagulation was given.

Evaluation of response

The response was assessed according to the European Group for Bone and Marrow Transplantation (EBMT)/ International Bone Marrow Transplant Registry (IBMTR)/ Autologous Blood and Marrow Transplant Registry (ABMTR) criteria.[17] The plasmacytomas were evaluated by measuring changes in its size and the appearance of new soft-tissue masses. Given the locations of plasmacytomas in most cases the evaluation of response was made by physical examination. CT scans and/or MRI were only performed when clinically indicated. All patients who started thalidomide treatment were included in this analysis. Thus, the results were analyzed on an intention-to-treat basis.

Statistical methods

Fisher's exact test and Mann-Whitney´s U test were used to assess the statistical significance of comparisons between different patients' characteristics and response to therapy. The duration of response was estimated using the Kaplan and Meier method.[18]

Results

Response to treatment

Sixteen out of the 38 patients (42%) responded to thalidomide (95% CI 26-59%). Eight (21%) achieved a partial response and 8 (21%) a minimal response. Three of the patients categorized as having a minimal response had almost a partial response since the serum M-protein decrease was higher than 40%. The median time to maximal response was 80 days (range 37 – 133). The response rate was significantly higher

Table 2. Location of soft-tissue plasmacytomas before and after thalidomide therapy.

Patient number	*Before thalidomide therapy*	*After thalidomide therapy*
2	*Frontoparietal mass 6×7 cm*	*Frontoparietal, frontal*
9	Pre-esternal 5×4 cm	Pre-sternal 7×8 cm, para-sternal 5×4 cm, frontoparietal 4×4 cm, frontotemporal 2×2 cm
12	Paravertebral D1	No change
14	Parietal mass 6x5 cm	Skull parietal mass 8×8 cm
19	Frontal 6x6 cm	Increased size
25	Frontoparietal 6x4 cm	Frontoparietal 6×8 cm
28	Right thoracic wall mass arising from 5th rib, skin, trunk 14×7×12 cm	Thoracic wall mass 24×12 cm, multiple skin nodules
29	Disseminated skin nodules of variable size	No change
30	Parietal, multiple cutaneous nodules, sphenoids, cavernous sinus	Increased size
31	Parietooccipital mass 3×3 cm	Parieto-occipital (no change), frontal 3×3 cm, infrascapular 6 cm
38	Multiple cutaneous nodules	Cutaneous nodules, paravesical mass, liver masses
3	Absence	Retro-orbital mass 2×3 cm, breast masses, skin nodules
17	Absence	Pre-sternal mass

in patients without extramedullary involvement (59% vs 0%, p= 0.0006).

The characteristics of patients with extramedullary involvement are detailed in Table 1. The location of soft-tissue plasmacytomas before and after thalidomide therapy is shown in Table 2. As can be observed, except one patient (case 12) who had a paravertebral mass only shown by CT scan examination the remaining 10 patients had palpable soft masses. In seven patients the soft-tissue plasmacytomas likely arised from underlying bone lesions (skull, ribs, vertebrae, sternum) while four patients had multiple cutaneous nodules. None of the eleven patients with extramedullary plasmacytomas responded to thalidomide. Although one of these patients showed a decrease in the size of soft-tissue involvement, this response did not last the 6 weeks required by the EBMT criteria.[17] This patient had relapsed after autologous SCT, with an increase in serum M-protein and appearance of soft-tissue plasmacytomas in trunk and left leg. One month after treatment with thalidomide had been started, the trunk plasmacytoma disappeared and a >75% reduction in his left-leg plasmacytoma was noted. However, this response was transient (3 weeks' duration) with reappearance of cutaneous masses as well as a huge paravesical mass and multiple hepatic plasmacytomas. Of interest, this patient had achieved an stable partial serological response despite extramedullary progression. Three of the remaining patients with extramedullary plasmacytoma achieved minimal response according to the serum M-protein decrease but showed progression of their extramedullary disease. On the other hand, two patients without extramedullary involvement when therapy with thalidomide was started, developed soft-tissue plasmacytomas while on thalidomide treatment. One of these patients had achieved a serological partial response with a serum M-protein decrease from 34 g/L to 16 g/L, but developed multiple extramedullary plasmacytomas in her left orbit, left breast and skin, whereas the other patient showed a progressive increase in M-serum protein size along with the appearance of soft-tissue plasmacytomas. Also of interest, one of our long-term responders with very limited skeletal involvement at initiation of thalidomide, in whom the serum M-protein had decreased from 51 g/L to 22 g/L, relapsed with hypercalcemia and extensive skeletal disease leading to several pathological fractures of long bone while her M-protein remained stable at 22 g/L.

Of note, the dose of thalidomide given to patients with extramedullary involvement was significantly higher than that in patients without soft-tissue plasmacytomas (median 550 mg /day vs 400 mg/day,

p=0.048). There were no significant differences regarding age, gender, M-protein type, amount of serum M-protein, proportion of bone marrow plasma cells or presence of lytic bone lesions between patients with or without extramedullary plasmacytomas. Nine out of the 16 patients who had achieved a response have relapsed so far. The median duration of the response was 15.9 months (range 1-43+).

Toxicity

About 75% of patients complained of somnolence, fatigue or constipation. Less frequent side effects were mild distal tremor, dizziness and paresthesia. Five patients developed generalized skin rash and one patient had ampollous lesions in both feet. Thalidomide was discontinued in this patient because of progressive disease with development of new soft tissue plasmacytomas. Thalidomide were prematurely discontinued in another 3 patients because of severe adverse effects: one patient developed severe facial angioedema 6 days after thalidomide initiation and other had a sudden cardiac arrest 15 days after starting therapy due to a ventricular arrhytmia and was successfully resuscitated. Finally, a third patient developed two episodes of syncope due to Mobitz type I atrioventricular block and the treatment was discontinued. No cases of deep venous thrombosis or thromboembolism were observed.

Discussion

A number of studies have shown that increased bone marrow angiogenesis is associated with faster disease progression in patients with multiple myeloma.[19-25] Moreover, solitary bone plasmacytomas have increased angiogenic activity.[13] Of interest, patients with marked neovascularization in solitary plasmacytomas have a significantly higher risk of progression to MM.[13] Both clinical and experimental studies suggest that angiogenesis is crucial in the pathogenesis of MM.[21,26,27] On this background, anti-angiogenic agents, particularly thalidomide, are being used in the treatment of MM. Thalidomide, when administered as a single agent, produces a response rate ranging from 32 to 64% in patients with refractory/relapsed disease.[4-11] Although the rationale for using thalidomide in MM was its antiangiogenic potential, its precise mechanism of action is still not fully understood. The overall response rate of 42% reached in this series falls within the expected rate in relapsed/refractory patients treated with thalidomide9 but the duration of the response was longer than that reported in other studies.[9,11]

There was, however, a clear difference in the response rate of those patients without and with extramedullary plasmacytomas (59% vs 0%, p=0.0006). Interestingly, in this series a serological response (i.e. decrease in the M component) was observed in four patients with soft-tissue masses but in none of them this was accompanied by a decrease in the size of the extramedullary plasmacytomas. One patient with no extramedullary plasmacytomas at initiation of thalidomide developed retro-orbital and multiple subcutaneous masses while in serological response and another patient, in whom no decrease in M-protein level was observed, developed a presternal mass shortly after initiation of thalidomide. Furthermore, one patient with long-lasting response to thalidomide had a relapse with multiple pathologic fractures in long bones due to extensive osteolytic lesions although she had no increase in her serum M-protein level. The results from this study confirm and extend the data on the lack of efficacy of thalidomide in patients with MM and extramedullary involvement reported in a smaller series of patients by our group[14] and adds to other reports pointing out to the same concept.[5,15] Recently it has been recognized that relapses may occur under thalidomide maintenance with an increase in bone marrow plasma cells and no increase in the M-protein size.[16] The reasons for the poor response of extramedullary plasmacytomas to thalidomide are unknown. It should be emphasized that the dose of thalidomide given to patients with extramedullary involvement was significantly higher than that given to those with no extramedullary involvement. However, Biagi *et al.*[12] reported three patients who had a predominantly extramedullary relapse after allogeneic transplantation and all three responded to thalidomide. Although based on a small number of cases, these authors postulated that the efficacy of thalidomide on extramedullary involvement after allogeneic transplantation could be different to that in patients who had received only conventional chemotherapy.[12] In any event, data from other groups with larger series of patients are needed to confirm our observation. In a tumor mouse model, thalidomide was shown to be less potent in suppressing tumor growth that its immunomodulatory analogs -IMiDs-28. Thus, IMiDs more efficiently decreased the development of tumors after malignant cell inoculation and induced greater tumor regression in already established tumors than did thalidomide.[28] Morever, the effect of thalidomide on angiogenesis in tumors induced in mice was lower than that achieved with IMiDs.[28] The above *in vivo* experiments are in line with our clinical observation on the lack of efficacy of thalidomide in extramedullary plasmacytomas, supporting the concept that tumor cell homing in different tissues may influence response therapy. The mechanisms explaining the different responses depending on the tumor

location warrant futher investigation.[29] In fact, the introduction of thalidomide in the treatment of MM has constituted a major first step forward in the investigation of innovative therapies, such as IMiDs[30] or the proteasome inhibitor bortezomib,[31] which target not only the malignant plasma cell but also the microenvironment.[32] Whether or not these new agents, with anti-angiogenic/pro-apoptotic mechanisms of action, will also show different efficacy depending on the myeloma cell homing will need to be carefully investigated in future trials.

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