Thalidomide treatment of resistant or relapsed multiple myeloma patients

MAREK HUS,* ANNA DMOSZYNSKA,*
MARIA SOROKA-WOJTASZKO,* DARIUS JAWNIAK,*
WOJCIECH LEGIEC,* HANNA CIEPNUCH,° ANDRZEJ HELLMANN,°
TERESA WOLSKA-SMOLEN,# ALEKSANDER SKOTNICKI,# JOANNA
MANKO,* FOR THE POLISH MULTIPLE MYELOMA STUDY GROUP
*Department of Hematology University Medical School, Lublin, Poland; °Department of Hematology University Medical School, Gdansk; #Department of Hematology Collegium Medicum Jagiellonian University, Krakow

Background and Objectives. Thalidomide is currently used as a very promising drug in patients with recurrent multiple myeloma or those refractory to chemotherapy. Literature data show prolonged survival in patients with advanced multiple myeloma treated with thalidomide but the optimal time and dose of thalidomide treatment remain to be established.

Design and Methods. We have treated 53 refractory or relapsed myeloma patients with thalidomide (Grunenthal, Aachen). The patients received thalidomide orally as monotherapy at a starting dose of 200 mg daily, with a dose increase of 100 mg every week to a maximum well-tolerated dose of 400 mg. All the patients qualified for the therapy underwent clinical and laboratory assessments every 4 weeks. Laboratory tests included complete blood count, electrophoresis, immunoglobulin level, lactate dehydrogenase (LDH), C-reactive protein, β_2 microglobulin concentration, liver and renal function tests and there was also a monthly neurological examination. Bone marrow aspiration was performed every 3 months during the 12-month treatment.

Results. Among 53 evaluable patients, a clinical response was observed in 27 (51%): there was a major response in 7 patients, a partial response in 12 and a minor response in 8.

Interpretation and Conclusions. In responding patients the earliest response was observed after 4 weeks of treatment and the latest after 12 weeks of treatment. Our results, obtained during a long observation period, show that thalidomide is an effective drug, with an acceptable degree of toxicity, in patients with refractory multiple myeloma.

Key words: multiple myeloma, refractory, thalidomide

original paper

haematologica 2001; 86:404-408
http://www.haematologica.it/2001_04/0404.htm

Correspondence: Prof. Anna Dmoszynska M.D., or Marek Hus, M.D., Department of Hematology, University Medical School of Lublin, Jaczewskiego 8, 20-090 Lublin, Poland. Phone: international +488-17425403 - Fax: international +488-17425102 - E-mail: dmoszann@free.med.pl, markhus@go2.pl

Multiple myeloma (MM) is an incurable neoplastic disease of the hematopoietic system and constitutes approximately 10% of all blood neoplasms. The introduction of high-dose chemotherapy followed by peripheral autologous stem cells transplantation has improved the effects of treatment, although only a few patients achieve long-term remission or are cured. It is now known that the process of angiogenesis in the stroma of bone marrow plays a significant role in the biology of MM and this phenomenon correlates with the activity and clinical stage of the disease.[1] It has been demonstrated that plasma concentration of cytokines stimulating angiogenesis is significantly higher in patients with myeloma.[2] These cytokines primarily include vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF).[3,4]

Thalidomide, a derivative of α-N-phthalimidoglutarimide acid $C_{13}H_{10}N_2O_4$, is a drug which has recently been applied in therapy for MM. Thalidomide, known as a sedative drug, was withdrawn because of its teratogenic effect on the fetus. It was experimentally shown that thalidomide inhibits angiogenesis and causes apoptosis of newly created vessels.[5,6] Thalidomide also shows immunomodulatory properties which regulate the secretion of many cytokines,[7-9] such as interleukin (IL)-2, tumor necrosis factor (TNF) and IL-6, but its mechanism of action is still unclear. IL-2, TNF and IL-6 play key roles in the pathogenesis of MM and elevated levels of these cytokines correlate with disease activity.[10,11]

We report the first study with thalidomide conducted by the Polish Myeloma Study Group in patients with relapsed MM or resistant to chemotherapy.

Design and Methods

Between March 1999 and October 2000 fifty-three patients (26 women and 27 men) with relapsed MM (44 patients) or MM refractory to chemotherapy (9 patients), disqualified from further chemotherapy from 3 Polish centers because of hypocellular bone marrow with severe pancytopenia, were treated with thalidomide, which was kindly supplied by Grunenthal GmbH (Aachen-Germany). The study was conducted according

to the principles of the Declaration of Helsinki, having acquired the permission of the Local Ethics Committee and in agreement with the S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety) program.[12] Class IgG myeloma was diagnosed in 40 patients, IgA in 11 patients and in 2 cases light chain disease was recognized. Forty-one patients were in clinical stage III and 12 in stage II according to the classification of Durie and Salmon. The mean age of the treated patients was 63.2 years (range 32-79), the mean number of previously applied chemotherapy lines was 4 (range 2-6), with the mean number of cycles being 18 (range 6-45); 2 patients had previously undergone tandem autologous peripheral blood stem cell transplantation (PBSCT). In the treated group the mean β_2-microglobulin concentration was 6.3 mg/L (range 1.3-49.6), the mean creatinine concentration 1.1 mg/dL (range 0.7-2.4), and the mean percentage of plasmacytes in bone marrow was 26% (range 10-57). The average time from diagnosis to the commencement of the thalidomide therapy was 38 months (6-144). Basic clinical data are presented in Table 1.

The criteria of complete remission were: total disappearance of the serum monoclonal protein and/or a 90% decrease in the baseline value of the 24-hour urinary excretion of light chain protein as well as <5% plasma cells in the bone marrow biopsy, normalization of hemoglobin, albumin and calcium levels. Partial response was defined as a 50% or greater reduction in the pre-treatment value of the M-protein in serum and urine and normalization of serum calcium. Minor response was defined as a between 25 and 50% reduction of the pre-treatment M-protein value. The monoclonal protein concentration was assessed by electrophoresis. An increase in the M-protein concentration by 25% in relation to the lowest value found during the treatment, an increase in 24 hour urinary Bence Jones protein excretion to more than 2.0 g/day and reappearance of the M-component in serum or urine were described as progression during the thalidomide therapy. The time from the commencement of the therapy to the moment of progression, the patient's withdrawal from the treatment for any reason, the patient's death or the date of his/her last visit to the hospital were assumed as the end of the period free from the symptoms of the disease.

The thalidomide therapy started from a dose of 200 mg daily, administered orally in two separate doses. The dose was then increased by 100 mg every seven days of therapy, reaching 400 mg per day in two separate doses (200 mg + 200 mg) in the third week of the treatment. Thalidomide was administered as long as possible until the symptoms of disease progression appeared. All the patients who qualified for the therapy underwent clinical and laboratory assessments every 4 weeks. Laboratory tests included complete blood count, electrophoresis, immunoglobulin level, LDH, CRP, β_2-microglobulin concentration, liver and renal function tests and there was also a monthly neurological examination. Bone marrow aspiration was performed every 3 months during the 12-month treatment. The curves of survival were calculated using the Kaplan and Meier method. Statistical analysis of morphologic and biochemical parameters in the treatment group was performed using the Wilcoxon's pair test.

Table 1. Patients characteristics before thalidomide treatment.

	All patients	*Responders*	*Non-responders*
Total	53	27	26
Sex			
Male	27	16	11
Female	26	11	15
Age in Years			
Mean	63.28	63.79	62.36
Range	32.0-79.0	47.0-79.0	32.0-79.0
Durie-Salmon	II-13	II – 9	II – 4
Staging	III-40	III – 18	III – 22
Refractory	9	7	2
Relapsed	44	20	24
Number of chemotherapy cycles			
Median	18	15.5	20.5
Range	6.0-45.0	6.0-45.0	11.0-36.0
Disease duration (month)			
Median	49.1	105.5	36.5
Range	13.0-104.0	15.0 – 104.0	13.0-88.0
WBC ($\times 10^9$/L)			
Median	4.66	4.66	4.42
Range	1.80-10.60	2.77-3.80	1.80-9.10
Hb (g/dL)			
Median	10.40	10.65	9.95
Range	5.50-14.90	5.50-14.90	7.40-14.10
PLT ($\times 10^9$/L)			
Median	140.80	144.70	148.50
Range	1.00-229.00	1.00-299.00	18.00-245.00
β_2-M (mg/dL)			
Median	6.30	6.57	5.82
Range	1.30-49.60	1.30-49.60	1.96-15.00

Results

The results of the thalidomide treatment are presented in Table 2.

Responder group

The first signs of improvement in clinical parameters, correlating with the improvement in disease activity parameters, were observed as early as 4 weeks after starting the therapy. Twenty-seven treated patients (51%) from the whole group responded to the treatment. Nineteen of them (35.8%) achieved a clinical response expressed by a 50% decline in the total monoclonal protein level in comparison with the value before the thalidomide therapy, and also by a decline in the level of β_2 microglobulin, LDH and plasmacytes in bone marrow, and by more than 50%. In this group, 8 patients (13.2%) had a major response to the treatment,

Table 2. Types of clinical response to thalidomide treatment.

Therapy time	N	% response	Decline of protein M level			
			25-50%	>50-75%	> 75%	NCR
To 6 months	19	5 (26.3%)	3	2	–	–
6–9 months	9	4 (44.4%)	–	2	2	1
9–12 months	13	12 (92.3%)	5	6	1	–
> 12 months	12	6 (50%)	–	2	4	3
Total	53	27 (51%)	8 (15%)	12 (22.6%)	7 (13.2%)	(7.5%)

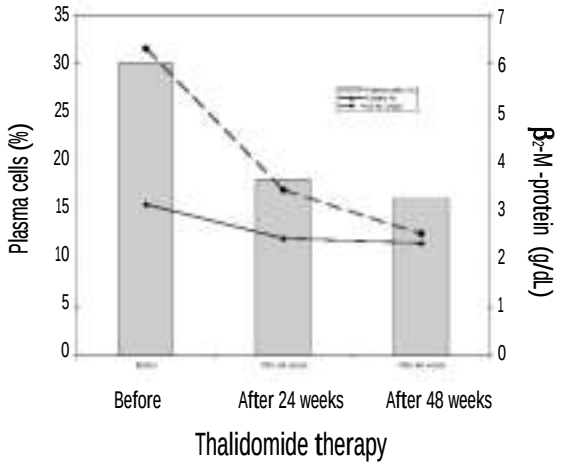

Figure 1. Percentage of plasma cells in bone marrow, serum level of β_2-microglobulin and M-protein before, after 24 and 48 weeks of thalidomide therapy ($p<0.05$ in the responders group).

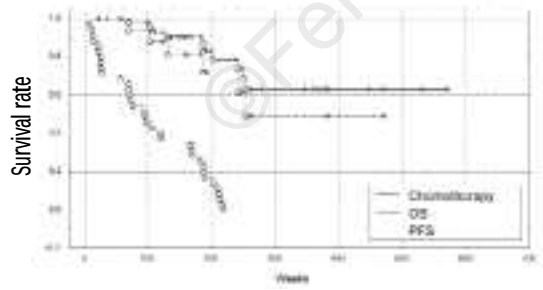

Figure 2. Overall survival (OS) and progression-free survival (PFS) of the 53 relapsed myeloma patients with thalidomide therapy vs. OS of the 35 myeloma patients with chemotherapy ($p<0.001$).

expressed by a decline in the monoclonal protein level by over 75% of the baseline value (Figure 1). In 4 of these patients (7.5%) complete hematologic remission (CR), defined as a complete disappearance of the monoclonal protein in blood and/or urine, was achieved.

Non-responder group and non-evaluated patients

Out of the group of 53 patients included in the thalidomide treatment, 17 patients did not respond to the therapy, 5 patients were excluded from the therapy because of side effects of thalidomide, and 4 patients died during the first 7 days of the therapy. In total, this group consisted of 26 patients (49%). Seventeen patients in the non-responder group with minimal response (less than 25% reduction in the M-protein) were treated with thalidomide up to 6 months because of the lack of any alternative treatment. These patients were resistant to 4-5 lines of chemotherapy (including high dose corticosteroids) and showed hypocellular bone marrow. Five patients with minimal response discontinued the treatment in the 3rd month of the therapy because of daily fever and apathy leading to depression.

Analyzing the Kaplan-Meier curve estimates of overall survival (OS) in the group treated with thalidomide and a comparison historical group of 35 relapsed or resistant MM patients treated in 3 centers participating in this study in the years 1990-94, it was found that there was a statistically significant difference in the thalidomide therapy group from the 12th month of observation and that there was a clear tendency towards a longer OS in this group. Statistical analysis showed that mean survival time in the whole group of thalidomide-treated patients was about 250 weeks vs. 210 weeks (for MM patients with chemotherapy) and progression-free survival in the responder group was 240 weeks (Figure 2).

Side effects of the therapy

Drowsiness and deterioration of psychomotor functions were observed in all the treated patients in the first week of the therapy. In the prevailing majority of cases these symptoms gradually subsided along with duration of the therapy; in 5 cases (9.4%) the symptoms were accompanied by persistent vertigo. In 31 patients (54%) we observed constipation requiring either additional pharmacologic agents or new dietary habits (e.g. a glass of juice on an empty stomach). In 5 cases the thalidomide therapy was accompanied by circadian high fever with generalized malaise and influenza-like symptoms. In 2 patients we observed progressive apathy accompanied by depression. Two patients also developed allergic symptoms manifested as a desquamating micropapular rash on the skin of the whole body, which required additional therapy. Leukopenia was found in 14 treated patients (26.4%). Twelve patients (22.6%) developed peripheral sensory polyneuropathy during the therapy. Sinus bradycardia was observed in 3 patients. In the twelfth month of the therapy deep vein thrombosis of the lower limbs requiring antithrombotic treatment was observed in 2 patients. After completion of the low molecular heparin treatment, the thalidomide therapy was restarted with a smaller dose reduced to half of the dose administered before the occurrence of the thrombotic episode (200 mg/day).

Table 3 shows the side effects of the thalidomide treatment according to the WHO staging.

Discussion

Multiple myeloma still remains an incurable disease, despite indubitable advances in the treatment and prolongation of survival time of patients treated with high-dose chemotherapy supported by peripheral blood stem cell grafting (PBSCT). Survival has improved from a median of 7 months in the 1950s to over 30 months in recent years.[13] The most important treatment improving factors are: progress in chemotherapy, improved treatment of renal failure, infections and hypercalcemia, earlier diagnosis and high dose chemotherapy supported by peripheral blood stem cell grafting. Transplantation of stem cells from peripheral blood or bone marrow cannot be performed in all patients, often because of a patient's advanced age and concomitant illnesses, especially cardiac diseases. In some patients primary resistance to cytostatic treatment is observed, and in the others resistance usually increases with duration of the therapy. It is for this group of patients that new methods of treatment are being searched for. Such an opportunity has recently been created by thalidomide therapy.[2,14]

Data obtained from our study on 53 MM patients with relapsed disease or resistant to chemotherapy showed responses in 51%, a major response being recorded in 7 patients. In this group we observed one patient with a dramatic effect who was primary resistant to 3 lines of therapy which was confirmed by overexpression of mdr 1 gene and glycoprotein 170 on plasma cells at diagnosis. He obtained a complete hematologic remission and at present is undergoing a PBSCT procedure. Another 6 patients with very spectacular responses were heavily pretreated and transfusion-dependent because of anemia and thrombocytopenia. After 4-8 weeks of thalidomide therapy they all became transfusion-independent and have started to work again. Data obtained from our study indicated that the CR+PR rate after thalidomide treatment was significantly higher than after other chemotherapy used for refractory MM such as VAD or high dose melphalan without PBSCT (51% vs 21%).

The most relevant observations available so far in the literature have been published by Americans from the Center for Treatment of Multiple Myeloma in Arkansas. Singhal *et al.*[2] report that in a group of 84 patients undergoing thalidomide therapy an improvement in clinical condition together with a reduction in disease activity parameters was achieved in 32% of patients. Good response to treatment, defined as a 50% or greater decrease in the M protein level in blood serum and/or urine was achieved in 22% of treated patients, two of whom achieved complete hematologic remission. The American observations have already extended beyond 24 months, and these authors now suggest that thalidomide may successfully be applied in the therapy inducing remission in combination with chemotherapy before autologous grafting of peripheral stem cells in MM patients.[15]

Kneller *et al.*[16] treated 17 patients with MM refractory to chemotherapy with thalidomide in doses of 200 to 800 mg per day and observed a very good response to the treatment. In 11 patients the decline in the M protein was over 75%, and in 5 patients it was greater than 50%. Durie *et al.*[17] used thalidomide in doses from 50 mg to 400 mg per day in a group of 36 patients with relapsed MM or in the phase of rapid progression of the disease and they achieved improvement in 40% of the treated patients and a very good response in 16% of the patients. Juliusson *et al.*[18] achieved partial remission in 43% of 23 patients with relapsed MM treated with thalidomide in doses from 200 to 800 mg, strongly emphasizing that for 30% of the patients this response showed that the treatment was much more effective than previous methods of treatment. In most of our patients (responders and non-responders to the thalidomide therapy) a significant increase in the hemoglobin concentration, red blood cell and platelets counts was observed. One could speculate that this stimulating effect of thalidomide, also observed in the non-responder group, depends on the influence of thalidomide on pro-angiogenic and pro-inflammatory cytokines. It is known for instance, that TNF-α blocks erythropoietin and granulocyte colony-stimulating factor.[19] TNF-α level is elevated in MM patients, so by decreasing TNF-α level thalidomide could improve morphologic blood parameters.

Schiller *et al.*[20] analyzed a group of 8 MM patients treated with thalidomide. Two of the 8 patients had progressive pancytopenia and renal insufficiency. The authors described evident improvement in the disease activity parameters, as well as normalization of blood morphologic parameters and renal function, which is in agreement with our earlier observations.[21]

After 12 months of treatment, 6 of our responder patients developed progressive disease: 3 of these patients were then successfully treated with VAD. It should be stressed that these patients were refractory to VAD before the thalidomide treatment. So, it seems that thalidomide could, in some way restore sensitivity to chemotherapy but this finding needs to be confirmed on a larger group of patients.

Table 3. Side effects of thalidomide treatment.

Symptoms	*Total number of patients*	*WHO I°*	*WHO II°*	*WHO III°*
Somnolence	42	42	–	–
Weakness or fatigue	38	35	3	–
Constipation	31	–	–	–
Tingling or numbness	12	10	2	–
Peripheral neuropathy	12	10	2	–
Leukopenia	14	9	2	3
Fever	5	4	1	–
Skin rash	4	3	1	–
Mood changes or depression	3	1	2	–
Bradycardia	3	2	1	–

Our results, obtained during a long observation period, showed that thalidomide has an acceptable degree of toxicity. Most adverse effects were mild (grade 1 or 2 according to WHO grading) Somnolence, constipation, weakness or fatigue occurred in 60% of the patients. One quarter of the patients had polyneuropathy during the therapy. Apart from this, increasing leukopenia was found in 14 treated patients: this required periodic administration of G-CSF in 4 patients who had less than 1.5×10^9 cells/L. However, we did not observe any increase in the frequency of infections in comparison to in patients with normal white blood cell counts. Comparing our own observations and data from literature, it seems that thalidomide, by affecting newly discovered key pathways of proliferative signals in MM, offers extremely promising possibilities in the treatment of different proliferative blood diseases including multiple myeloma. Nevertheless, it also seems that there is a need to conduct large multicenter studies to assess complex mechanisms of angiogenesis and immunomodulation and confirm the efficacy of therapy with thalidomide or its new analogs, so that this drug can find its proper place in the treatment of multiple myeloma.

Contributions and Acknowledgments

MH: co-ordination of the multicenter study, analysis and interpretation of data; AD: conception and final approval of paper, revising it critically for important intellectual content; MSW: collection of clinical data; DJ: collection of clinical data and statistical analyses. WL, HC, TWS, AS, JM: collection of clinical data .

Disclosures

Confict of interest: none.

Redundant publications; no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Prof. Jésús F. San Miguel, who acted as an Associate Editor. The final decision to accept this paper was taken jointly by Prof. San Miguel and the Editors. Manuscript received January 9, 2001; accepted March 21, 2001.

Potential implications for clinical practice

Thalidomide therapy is the most promising, non-cytostatic therapeutic option for resistant and relapsed myeloma.

References

1. Munshi N, Wilson CS, Penn J, et al. Angiogenesis in newly diagnosed multiple myeloma: poor prognosis with increased microvessel density in bone marrow biopsies. Blood 1998; 92(Suppl 1):98a.
2. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999; 341:1565-71.
3. Bellamy WT, Richter L, Frutiger Y, Grogan TM. Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. Cancer Res 1999; 59:728-33.
4. Gasparini G. The rationale and future potential of angiogenesis inhibitors in neoplasia. Drugs 1999; 58:17-38.
5. Vacca A, Di Loreto M, Ribatti D, et al. Bone marrow of patients with active multiple myeloma: angiogenesis and plasma cell adhesion molecules LFA-1, VLA-4, LAM-1 and CD44. Am J Hematol 1995; 50:9-14.
6. Vacca A, Ribatti D, Presta M, et al. Bone morrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. Blood 1999; 93:3064-73.
7. Dmoszynska A, Rolinski J, Bojarska-Junak A, Domanski D, Hus M. Immunophenotype changes in multiple myeloma patients during thalidomide treatment. The Haematology Journal 2000; 1(Suppl 1):167.
8. Hus M, Dmoszynska A. Thalidomide once again. Novel clinical application. Ann UMCS 1999; 54:119-26.
9. Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor α production by stimulated human monocytes. J Exp Med 1991; 173:699-703.
10. Berenson JR, Bergsagel PL, Munshi N. Initiation and maintenance of multiple myeloma. Semin Hematol 1999; 36:9-13.
11. Rowland TL, McHugh SM, Deighton J, Dearman RJ, Ewan PW, Kimber I. Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells. Immunopharmacology 1998; 400:11-20.
12. Zeldis JB, Williams BA, Thomas D, Elsayed ME. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. Clin Ther 1999; 21:319-30
13. Attal M, Harousseau JL, Stoppa A, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996; 335:91-7.
14. Barlogie B, Desikan R, Munshi N, et al. Single course DT PACE antiangiochemotherapy effects CR in plasma cell and fulminate multiple myeloma. Blood 1998; 92(Suppl 1):273b.
15. Barlogie B, Jagannath S, Desikan KR, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999; 93:55-65.
16. Kneller A, Raanani P, Hardan I, et al. Therapy with thalidomide in refractory multiple myeloma patients: the revival of an old drug. Br J Haematol 2000; 108:391-3.
17. Durie BGM, Stepan DE. Efficacy of low dose thalidomide in multiple myeloma. Blood 1999; 94 (Suppl 1):316a.
18. Juliusson G, Celsing F, Turesson I, et al. Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 2000; 109:88-96.
19. Backx B, Broeder L, Bot FJ, Lowenberg B. Positive and negative effects of tumor necrosis factor on colony growth from highly purified normal human progenitors. Leukemia 1991; 5:66-70.
20. Schiller G, Vescio R, Berennson J. Thalidomide for the treatment of multiple myeloma relapsing after autologous peripheral blood progenitor cell transplant. Blood 1999; 94(Suppl 1):317a.
21. Hus M, Dmoszynska A, Wojtaszko M, Szerej A. Effective thalidomide therapy of a patient primarily resistent to chemotherapy for multiple myeloma. Acta Haematol Pol 2000; 31:187-92.