Acta Poloniae Pharmaceutica – Drug Research, Vol. 65 No. 6 pp. 771–774, 2008 ISSN 0001-6837
Polish Pharmaceutical Society

EFFICACY AND SAFETY OF THALIDOMIDE IN THE TREATMENT OF MULTIPLE MYELOMA

KRZYSZTOF WARZOCHA, MARIA KRAJ*, RYSZARD POGŁÓD, TOMASZ SZPILA, EWA MENDEK-CZAJKOWSKA, MONIKA CHEŁSTOWSKA and RENATA HAGEDORNA TRONINA

Institute of Hematology and Transfusion Medicine, 14 Indira Gandhi St., 02-776 Warsaw, Poland

Keywords: multiple myeloma, thalidomide

The therapeutic efficacy of thalidomide – a derivative of glutamic acid – has been studied in numerous trials on refractory/relapsed multiple myeloma (MM) patients (1, 2). They showed that single-agent thalidomide can induce a partial response in approximately 30% of patients with refractory myeloma. The combination of thalidomide with dexamethasone is active in approximately 50% of patients with refractory myeloma (3). The therapeutic efficacy of thalidomide increases significantly when it is combined with cyclophosphamide (4) or melphalan (5, 6) and used in front-line treatment (7, 8).

Thalidomide exerts its anti-myeloma effect through different mechanisms. It can directly inhibit the growth and survival of myeloma cells; and it also targets marrow stromal cells (9).

The aim of this study was to assess thalidomide tratment efficacy and draw attention to severe, especially cardiac, complications and possibility of extramedullary myeloma development following this therapy (10).

EXPERIMENTAL

Six patients with newly diagnosed and 26 patients with relapsed or refractory MM who have failed at least one prior line of treatment, including 3 patients treated with high dose therapy and autologous stem cell transplantation, were treated with thalidomide at the Department of Hematology of the Institute of Hematology and Transfusion Medicine in Warsaw. Patients characteristics are presented in Table 1.

As monotherapy, thalidomide (Myrin, Talizer or THA Pharmion GmbH, UK) was administered at a dose of 100 mg/day to a maximum dose of 400 mg/day. In 7 patients dexamethasone 40 mg on days 1-4, in a 28-day cycle, was added to the thalidomide (TD). Nine patients has been treated with MPT regimen, repeated every 4 weeks, which consisted of oral administration of melphalan at 4 mg/m^2 on days 1-7, oral prednisone at a dose of 40 mg/m^2 on days 1-7 and thalidomide 100 mg per day, continuously. CTD regimen, which was applied in 6 newly diagnosed MM patients, consisted of i.v. administration of cyclophosphamide at 500 mg/m^2 on day 1, dexamethasone 20 mg on days 1-4; 8-11, in a 28-day cycle, and thalidomide 100 mg/day, continuously.

Responses to treatment were assessed according to IMWG criteria (11). For treatment efficacy evaluation there were taken into account only those patients who received thalidomide alone for at least three months or at least 3 cycles of combination therapy. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, Version 2.0).

All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki; an approval was obtained from the local Institute Bioethics Commission.

RESULTS

Of 10 patients treated with thalidomide alone, partial response was achieved in 3 patients and remission lasted 6 to 10 months (Table 2). In 4 patients the disease progressed, including one in whom in sixth month of thalidomide therapy myeloma evolved into plasma cell leukemia. Time to disease progression since the onset of thalido-

* Corresponding author: Prof. Maria Kraj MD, PhD, e-mail: mkraj@ihit.waw.plmail.com.

Table 1. Baseline patient's characteristics and disease features

Age, years, median (range)	59 (33-78)
Gender, Male/Female (%)	21/11 (66/34)
M-protein isotype (N)	
IgG (κ : λ)	25 (19 : 6)
IgA (κ : λ)	3 (2 : 1)
IgM	1 (0: 1)
Light chain (κ : λ)	3 (1 : 2)
ISS Staging I/II/III, %	52, 34, 14
β_2M mg/L, median	2.9
Albumin g/dL, median	3.7
Bone marrow plasma cells %, median	30
Lytic bone lesions, %	81
Durie Salmon Staging I/II/III, %	3,25, 72
Median time since myeloma diagnosis to onset of thalidomide therapy (months)	23
Prior therapy (N)	
MP	5
CP	5
VMCP	9
VBAP	9
VAD	22
EDAP	3
Autologous stem cell transplantation	3
Radiation therapy	8
Number of prior regimens of treatment	1.6 (0-4)

Abbreviations: MP, melphalan, prednisone; CP, cyclophosphamide, prednisone; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; VBAP, vincristine, carmustine, adriamycin, prednisone; VAD, vincristine, adriamycin, dexamethasone; EDAP, etopozide, dexamethasone, cytosine arabinosid, cisplatin; ISS, International Staging System.

Table 2. Overall response rates to thalidomide alone and thalidomide in combination with dexamethasone, cyclophosphamide or melphalan in multiple myeloma (MM) patients.

Phase of disease and treatment	No of patients (evaluable)	PR (%)	Response		
			MR	S	PD
Relapse Thalidomide	10 (9)	3 (33)	2	2	2
TD	7 (6)	4 (66)	0	0	2
MPT	9 (6)	6 (100)			
Induction therapy CTD	6 (2)	2 (100)			

Abbreviations: PR, partial response; MR, minimal response; S, stabilization; PD, progression of disease; T, thalidomide, D, dexamethasone; C, cyclophosphamide; P, prednisone.

mide therapy ranged from 5 to 10 months. In 3 patients the treatment was discontinued due to adverse events: Morgagni-Adams-Stokes-syndrome, bradyarrhythmia – atrial fibrillation, sudden loss of hearing and enormous debilitation, respectively (Table 3). Of 7 patients, in whom thalidomide was administered together with high-dose dexamethasone, partial remission was achieved in 4 patients. In one of those patients partial remission lasted 10 months but the treatment had to be stopped due to bradycardia, while in 3 remaining patients partial remission lasted 3 months and ended with plasma cell leukemia in one patient, and with plasma cell infiltration of lymph nodes in the other one. In all assessed patients treated according to MPT or CTD regimens a partial response was achieved. The longest time of thalidomide treatment is 24 months. In this group, the treatment was stopped in two patients; in one due to atrial fibrillation recurrences, and in

Table 3. Grade 3-4 adverse events during thalidomide treatment

Event	Number of patients receiving thalidomide (N = 32)
Bradyarrhythmia	1
Atrial fibrillation	2
Bradycardia	4
Morgagni-Adams-Stokes syndrome	1
Hypertension	1
Sudden loss of hearing	1
Enormous fatigue	2
Neuropathy – motor	2
Neuropathy – sensory	1
Muscle weakness	1
Constipation	3
Extensive skin lesions	1
Acute renal failure	1
Pneumonia	2
Neutropenia	1

the other one due to extensive skin lesions. In the latter case, after 3.5 month-treatment with thalidomide 100 mg/day, the patient developed nodular skin lesions of abdomen and underbelly that shortly evolved into diffuse, papular – nodular eruption of whole body skin with strong itching. Thalidomide was stopped. Histopathology of skin nodule was typical for allergic type of lesions – in corium abundant infiltrations composed of small lymphocytes T (CD3+) and sparse B lymphocytes (CD 20+) and numerous eosinophilic granulocytes. One month later, the patient presented with intense itching and disseminated papular exanthema of the thorax and abdomen. Treatment with anti-scabies drugs, and then with steroids, due to transformation of his skin lesions into allergic dermatitis and erythroderma, resulted in almost complete regression of exanthema and itching.

DISCUSSION

In our study 3 of 9 evaluable relapsed MM patients achieved partial response after treatment with thalidomide alone. The median duration of the response was 6 months. Time to progression of disease in all 9 patients receiving thalidomide alone ranged from 5 to 10 months. In the first study of 169 patients with relapsed or refractory MM thalidomide 200-800 mg per day yielded responses (> 50% reduction in M protein) in 30% of patients with a 2% complete response rate; 2-year event free survival and overall survival in this study were 20% and 48%, respectively (1). A review of 42 studies with target doses of single-agent thalidomide ranging from 50 mg/day to 800 mg/day revealed similar results. In the 1629 patients included in the intention-to-treat analysis, the overall response rate (50% or greater M-protein reduction) for single-agent thalidomide was 30%; 2% of patients showed a 90% or greater reduction. Across studies, grade 3/4 adverse events included constipation, somnolence, neutropenia, and neuropathy and toxicities appeared both cumulative and dose dependent. The incidences of somnolence, peripheral neurotoxicity, and thromboembolism were all more frequent at doses higher than 200 mg/day, and worsened with treatment duration (2).

In 4 of our patients the thalidomide treatment was discontinued due to cardiac toxicities; they included sinus bradycardia, which in one case with MAS syndrome required pacemaker implantation, bradyarryhythmia – atrial fibrillation and atrial fibrillation recurrences. Fahdi et al. (12) studied the medical records of 96 patients who received thalidomide and 104 control group patients. They found that 53% of patients (52 patients) receiving thalidomide had a heart rate of < 60 beats/min at some point during follow-up and 19% of thalidomide patients (10 patients) developed symptom-related bradycardia. They showed that thalidomide induces sinus bradycardia through an intrinsic decrease in sinus-node pacemaker activity. Ballanti et al. (13) reported a patient with multiple syncopal episodes and ECG documented complex cardiac event comprising both tachyarrhythmia and bradyarrhythmia during maintenance thalidomide treatment. Reports on effects of thalidomide treatment in heart failure patients are ambiguous (14, 15).

Observed in our study and by others (16) sudden loss of hearing may be an adverse effect of thalidomide treatment. One our patient developed extensive skin lesions. Unusual cutaneous involvement in multiple myeloma patient during plasma cell leukaemia phase after thalidomide therapy, was reported by Alexandrescu et al. (17).

Three of our MM patients receiving thalidomide developed symptoms of extramedullary plasma cell proliferation; one presented with plasma cell infiltration of lymph nodes and two with plasma cell leukemia. Thalidomide targets marrow stromal cells, alters IL-6 and TNF-α production and

decreases adhesion of malignant plasma cells (9). Due to modified cell-to-cell contacts and interactions within bone marrow microenvironment, malignant plasma cells may become resistant to therapy and may develop tendency to disseminate and infiltrate other tissues in the periphery (17). Saba et al. (18) and others (17, 19) have reported that aggressive extramedullary disease may appear after thalidomide treatment despite a good response in the bone marrow. The fact that thalidomide has therapeutic potential in patients with bone marrow plasma cell involvement but does not show activity in soft tissue plasmacytomas (20), further suggests such a mechanism of plasma cell transformation.

In our study, in all assessed patients treated according to MPT or CTD regimens a partial response was achieved. In the IFM trial (6) and GIMEMA trial (5) at least partial response rates for MPT in patients with newly diagnosed MM were each 76%. In the Dimopoulos et al. study (4) in previously treated MM patients CTD resulted in an overall response rates of 60%.

CONCLUSIONS

In relapsed/refractory myeloma the rate of response to thalidomide alone is 33% and to thalidomide in combination with dexamethasone is 66%, with median duration of response of 6 months. Our preliminary results suggest that in myeloma induction therapy the rate of response to thalidomide in combination with dexamethasone and cyclophosphamide or melphalan reaches 100%. These findings suggest that thalidomide is effective in initial reduction of a more mature plasma cell compartment confined to the marrow, and allows relatively immature myeloma cell compartment to escape marrow microenvironment. In one third of the patients the treatment with thalidomide had to be discontinued due to adverse events especially connected with cardiac toxicity as well as peripheral somatic and autonomic neurotoxicity.

REFERENCES

1. Barlogie B., Desikan R., Eddelmon P. et al.: Blood 98, 492 (2001).
2. Glasmacher A., Hahn C., Hoffmann F. et al.: Br. J. Haematol. 132, 584 (2005).
3. Bamias A., Dimopoulos M.A.: Expert Opin. Investig. Drugs 14, 45 (2005).
4. Dimopoulos M.A., Hamilos G., Zomas A. et al.: Hematol. J. 5, 112 (2004).
5. Palumbo A., Bringhen S., Caravita T. et al.: Lancet 367, 825 (2006).
6. Facon T., Mary J.Y., Hulin C. et al.: Lancet 370, 1209 (2007).
7. Cavo M., Zamagni E., Tosi P. et al.: Blood 106, 35 (2005).
8. Rajkumar S.V., Blood E., Vesole D. et al.: J. Clin. Oncol. 24, 431 (2006).
9. Hideshima T., Chauhan D., Podar K. et al.: Semin. Oncol. 28., 607 (2001).
10. Kraj M., Szpila T., Chełstowska M. et al.: Haematologica 92 Suppl. 2, 168 (2007).
11. Durie B.G.M., Harousseau J-L., Miguel J.S. et al.: Leukemia 20, 1467 (2006).
12. Fahdi I.E., Gaddam V., Saucedo J.F. et al.: Am. J. Cardiol. 93, 1052 (2004).
13. Ballanti S., Mastrodicasa E., Bolli N. et al.: Nat. Clin. Pract. Oncol. 4, 722 (2007).
14. Orea-Tejeda A., Arrieta-Rodriguez O., Castillo-Martinez L. et al.: Cardiology 108, 237 (2007).
15. Gullestad L., Semb A.G., Holt E. et al.: Am. Heart J. 144, 847 (2002).
16. Rajkumar S.V., Gertz M.A., Lacy M.Q. et al.: Leukemia 17, 775 (2003).
17. Alexandrescu D.T., Koulova L., Wiernik P.H.: Clin. Exp. Dermatol. 30, 391 (2005).
18. Saba S., Epstein A., Niesvizky R., Coleman M.: Haematologica 90 Suppl. 1, 143 (2005).
19. Avigdor A., Raanani P., Levi I. et al.: Leuk. Lymphoma 42, 683 (2001).
20. Bladé J., Perales M., Rosinol L. et al.: Br. J. Haematol. 113, 422 (2001).