ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LV, 16 SECTIO D 2000

Department of Haematology, University School of Medicine, Lublin
Klinika Hematologii Akademii Medycznej w Lublinie

ANNA DMOSZYŃSKA, MARIA SOROKA-WOJTASZKO,
MAREK HUS, DARIUSZ JAWNIAK

The results of thalidomide treatment of resistant or relapsed multiple myeloma patients — own experiences

Wyniki leczenia talidomidem chorych z oporną bądź nawrotową postacią szpiczaka plazmocytowego — doświadczenia własne

INTRODUCTION

Multiple Myeloma (MM) is an incurable neoplastic disease of the haemopoietic system and it constitutes approximately 10% of all blood neoplasms. The introduction in the recent years of high-dose chemotherapy assisted by grafting of peripheral autologous stem cells has improved the effects of treatment, however, only few patients can achieve long-term remission or be cured.

Thalidomide (THA) (a derivative of α-N-phthalimidoglutarimide acid) C13H10N2O4, is a drug which has recently been applied in the therapy for MM. It is a sedative drug, introduced in the mid-50s and withdrawn from pharmacies all over Europe in the late 60s due to its teratogenic effect on the fetus. The first reports on the use thalidomide in the treatment of multiple myeloma appeared 2 years ago. It was experimentally shown that thalidomide inhibits angiogenesis and causes apoptosis of newly created vessels, hence the interest in the drug for the therapy of neoplasms whose growth depends on creation of new vessels [6, 9, 10]. Multiple myeloma belongs to diseases with significant vascularization and an increase in the concentration of cytokines stimulating angiogenesis such as vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF) [4, 14]. Recently studies have demonstrated that THA has specific immunomodulatory properties affecting the secretion of cytokines released by T lymphocytes (IL-1β, IL-2, IL-6, IL-12 and TNF) whose activity in MM is, according to many authors, the key mechanism accelarating the development of the disease [7, 15, 16].

Therefore undertaking further extensive research on the efficacy of this drug in multiple myeloma seems justified.

MATERIALS AND METHODS

Thirty patients (14 women and 16 men) with relapsed or primarily refractory multiple myeloma, disqualified from further chemotherapy have been treated with thalidomide at the Department of Hematology of the University Medical School in Lublin since March 1999. The study has been conducted according to the principles of the Declaration of Helsinki, having acquired the permission of the Ethics Committee from the University School of Medicine in Lublin No. KE-0254/35/99, and in agreement with S.T.E.P.S. programme (System for Thalidomide Education and Prescribing Safety) [20].

Class IgG myeloma was recognized in 24 patients, IgA in 5 patients and in one case disease of light chains was recognized. The mean age of the treated patients was 62 years (39–77), the number of previously applied chemotherapy lines was 4 (2–6), with the mean number of cycles — 16 (6–45), 2 patients had previously undergone tandem auto PBSCT. In the treated group the mean $\beta 2$ microglobulin concentration was 4.28 mg/l (1.9–8.6), the mean creatinine concentration 1.1 mg/dl (0.7–2.4), the percentage of plasmocytes in bone marrow 26% (10–57). The average time from diagnosis to the starting of the THA therapy was 38 months (6–144). Basic clinical data are presented in Table 1.

The THA therapy started from a dose of 200 mg, administered orally in two separate doses during the day. Then the dose was increased by 100 mg every seven days of the therapy, reaching in the third week of the treatment 400 mg per day in two separate doses (200 mg + 200 mg). All the patients qualified for the therapy were put under clinical observation with a full profile of additional examinations performed every 4 weeks and assessed according to the MTF criteria and with a monthly neurological examination. Moreover, the patients obtained written information about potential risks and benefits of the therapy and gave informed written consent to undergo the treatment.

RESULTS OF THE THERAPY

The results of THA treatment are presented in Table 2.

The first signs of improvement in clinical parameters, correlating with improvement in disease activity parameters were observed as early as 4 weeks after the starting of the therapy. Eighteen treated patients (60%) responded to the treatment. Ten of them (33%) achieved clinical expressed by decline in the level of complete protein together with a fraction of monoclonal protein by 50% in comparison with the value before the THA therapy, and also by decline in the level of $\beta 2$ microglobulin, LDH and plasmocytes in bone marrow, also by over 50%. In this group, 4 patients (13%) had a very good response to the treatment expressed by decline in the monoclonal protein level by over 75% of the baseline value. In 2 of those patients (7%) complete hematological remission (CR) was achieved. Moreover, a very good response to THA was achieved in 1 patient [11], primarily resistant to several-line cytostatic therapy,

Table 1. Clinical date of patients thalidomide treatment

Patient	Age/ sex	Type MM	Clinical stage	Number cycles of chemotherapy before THA	Time from diagnosis to THA therapy (month)	Beta2 micro-globulin	Plazmo-cytes
1	59/M	Ig G	III(3,A,d)	21	44	4,8	25
2	53/M	Ig G	II(3,a,c)	10	19	3,3	24
3	77/K	Ig A	III(2,a,c)	18	31	8,5	26
4	47/M	Ig G	III(2,A,c)	29	81	4,0	13
5	73/K	Ig G	III(3,B,c)	11	36	6,3	20
6	61/K	Ig G	II(2,A,c)	28	68	3,6	29
7	50/K	Ig G	III(3,A,c)	37	69	2,0	10
8	69/K	Ig G	II(2,A,c)	14	28	2,6	16
9	60/M	Ig G	II2,A,c)	24	38	3,2	19
10	68/M	Ig G	III(3,B,c)	19	35	8,5	53
11	64/K	Ig A	III(3,A,c)	18	23	4,2	50
12	62/M	Ig G	II(3,A,c)	18	41	2,5	15
13	70/M	Ig G	III(3,A,c)	45	144	3,8	30
14	75/K	Ig G	III(2,A,c)	16	21	4,7	47
15	62/K	Ig G	III(3,A,c)	15	18	4,3	27
16	63/M	Ig G	III(3,B,c)	6	6	2,9	10
17	59/M	Ig G	II(3,A,c)	19	41	1,9	18
18	69/K	Ig G	II(2,A,c)	14	64	4,3	13
19	73/K	Ig A	III(2,A,c)	14	25	3,7	28
20	63/K	Ig G	II(2,a,c)	12	24	3,9	23
21	71/K	Ig G	II(2,A,c)	13	20	2,5	18
22	49/M	Ig G	II(2,A,c)	15	26	3,4	21
23	71/M	Ig G	III(3,A,c)	12	20	3,6	25
24	63/K	Ig G	III(3,A,c)	20	50	5,3	44
25	42/M	Ig G	II(1,A,c)	13	22	3,0	15
26	52/M	Ig A	III(2,A,d)	14	21	2,9	31
27	70/K	Ig G	II(2,A,c)	15	21	4,2	15
28	39/K	Ig A	III(3,B,d)	10	24	8,6	27
29	64/M	Ig G	III(3,A,d)	22	48	7,5	57
30	69/M	L.ch.d	III(3,A,c)	16	24	3,5	24

L.ch.d. — light chain disease

Table 2. Types of clinical response to thalidomide treatment

Therapy time	N	% of response	25–50%	>50–75%	> 75%	NCR
To 6 months	14	7 (50%)	5	2	-	-
6–9 months	8	4 (50%)	-	2	2	(1)
9–12 months	8	7 (87,5%)	3	2	2	(1)
Total	30	18 (60%)	8 (27%)	6 (20%)	4 (13%)	(7%)

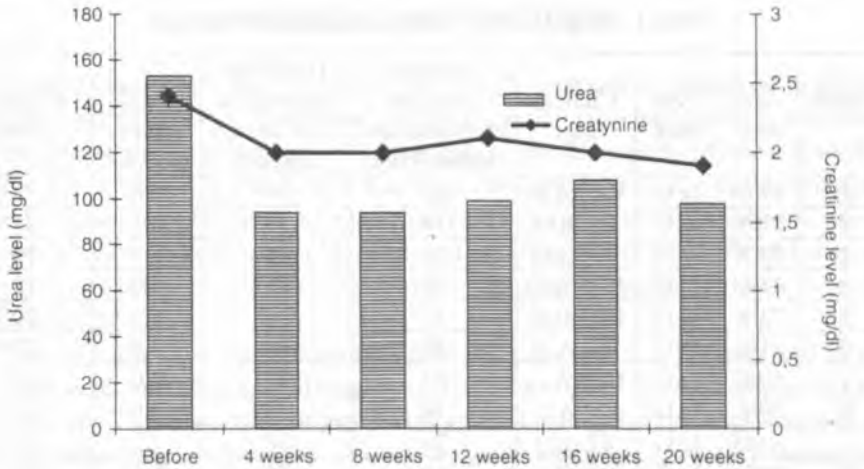

Figure 1. Patient Nr 18. Urea and creatinine level before and during thalidomide therapy

with confirmed overexpression of mdr 1 gene and glycoprotein gp 170 on plasmatic cells at the moment of diagnosis.

In most of the treated patients who responded to the therapy with decline in the monoclonal protein level, a systematic improvement in morphotic and biochemical parameters of blood was observed. In 1 patient with increasing renal insufficiency before the THA therapy we observed normalisation of the kidney function with normal creatinine and urea values (Figure 1) and normalization hypertonia which had previously required intensive combined treatment (Iporel, Tertensif, Isoptin).

Patients not responding to the therapy

Out of the group of thirty patients included in the THA treatment, 12 patients (40%) did not respond to the therapy (NR). Three patients with grade III MM (3, B, d) died in the first week of the therapy. One woman died during the 12th week of the treatment because of cerebral stroke due to thrombocytopenia observed in the patient for many months before the THA therapy. Two patients discontinued the treatment in the 3rd month of the therapy because of daily fever and apathy leading to depression. One patient resistant to all previously applied courses of chemotherapy, after 6 months of the THA treatment and 2 courses of treatment with cyclophosphamide + etoposide + GM-CSF underwent the procedure of autologous grafting of peripheral stem cells.

In 5 remaining patients the THA therapy was discontinued after 3–6 months from its begining due to rapid progression of MM. Those patients are alive until this moment and they are treated in our Department in a very individual way.

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, and in 5 cases

(17%) the symptoms were accompanied by persistent vertigo. In 21 patients (72%) we observed constipation requiring either additional pharmacological agents or forming of new dietary habits (e.g. a glass of juice on an empty stomach). In 2 cases the THA 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 expressed by desquamating micropapular rash on the skin of the whole body, which required additional therapy. Neutropenia was found in 14 treated patients (48%). Three patients developed peripheral sensory polyneuropathy during the therapy, and sinus bradycardia was observed in 1 patient. In the twelfth month of the therapy deep vein thrombosis of the lower limbs requiring antithrombotic treatment was found in 2 patients. After the completion of the micromolecular heparin treatment, the THA therapy was restarted with smaller dose reduced to half the value of that administered before the occurrence of the thrombotic episode (200 mg/day).

DISCUSSION

Despite indubitable advances in the treatment and prolongation of survival time of patients treated with high-dose chemotherapy supported by peripheral stem cells grafting, multiple myeloma still remains an incurable disease. Transplantation of stem cells from peripheral blood or bone marrow can not be performed in all patients often because of patient 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 is created by the thalidomide therapy. For the last 2 years there have been many reports, especially in American literature, on the subject of the efficacy of thalidomide in the treatment for refractory and relapsed MM [2, 5, 18, 19].

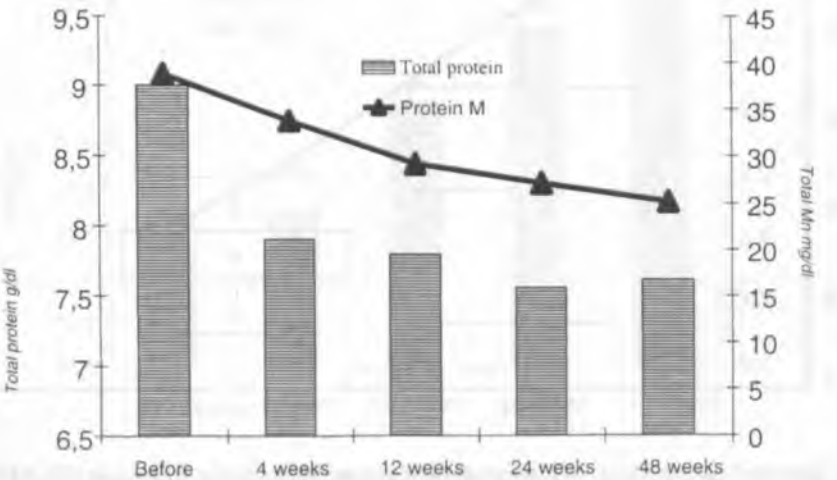

Figure 2. Level of total and monoclonal protein in patients during thalidomide treatment

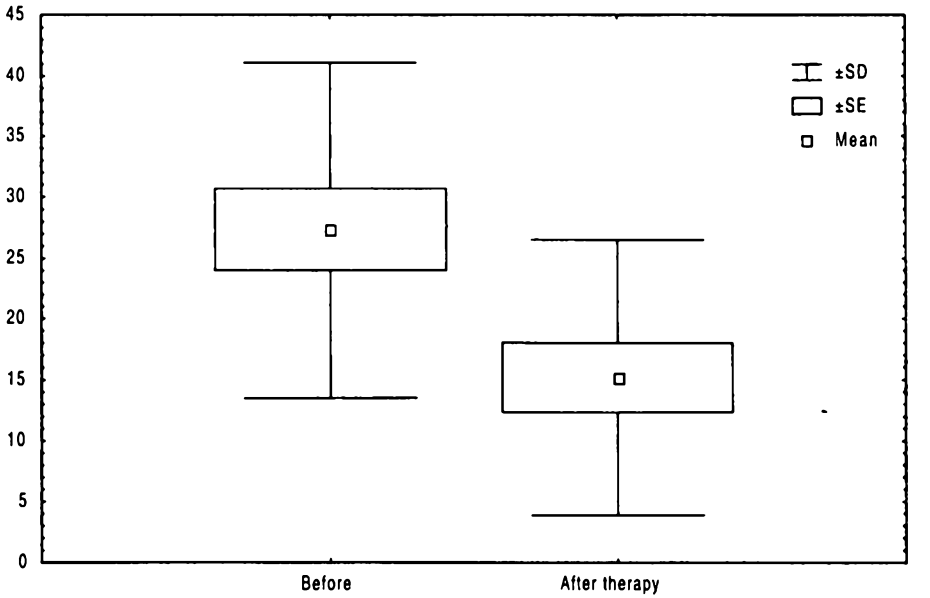

Figure 3. Percentage of plasmocytes in bone marrow during thalidomide treatment (Z=3,516196; p=0,000438)

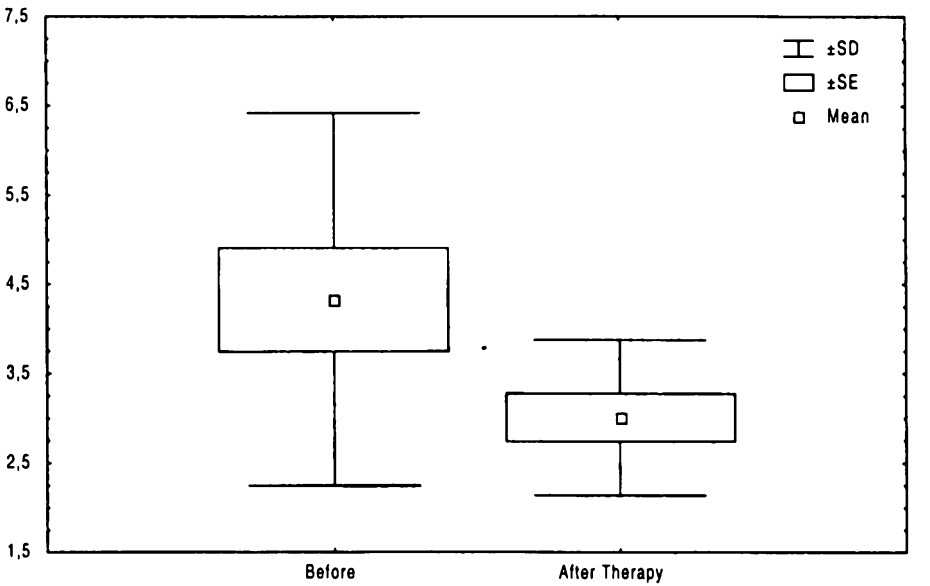

Figure 4. Concentration of β_2-microglobulin during thalidomide treatment (Z=2,191483; p=0.028424)

In the study we have conducted, the good clinical response to treatment during 12 months from the application of thalidomide, in a group of 30 patients with relapsed or primarily refractory multiple myeloma was 60%. In 7% of the patients complete haematological response was stated. In the group of patients responding to THA there was a tendency to quick normalization of complete protein, most frequently as early as 4 weeks after the begining of the therapy and to slow decline in the monoclonal protein level (Figure 2), combined with improvement in the disease activity parameters typical of MM such as bone marrow plasmocytosis, $\beta 2$ microglobulin and LDH (Figure 3, 4). Normalization of blood morphology was observed simultaneously. In the majority patients with anemia and thrombocytopenia before the treatment, a significant improvement in the erythrocyte and platelet number (Figure 5) was achieved, slight leucopenia in nearly all the treated patients, which required periodic administration of small doses of G-CSF was noted (Figure 6). These results are in agreement with the results of other authors. Kneller et al. [13] treating 17 patients with MM refractory to chemotherapy used THA in doses of 200 to 800 mg per day observed a very good response to the treatment (decline in M protein by over 75%) in 11 patients and in 5 patients decline in M protein was over 50%. Brian and Durie [8] used THA 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 (reduction in M protein by over 75% in comparison with the baseline value) in 16% of the patients. Juliusson et al. [12] achieved partial remission in 43% of patients in a group of 23 with relapsed MM treated with THA in doses from 200 to 800 mg, emphasizing strongly that for 30% of

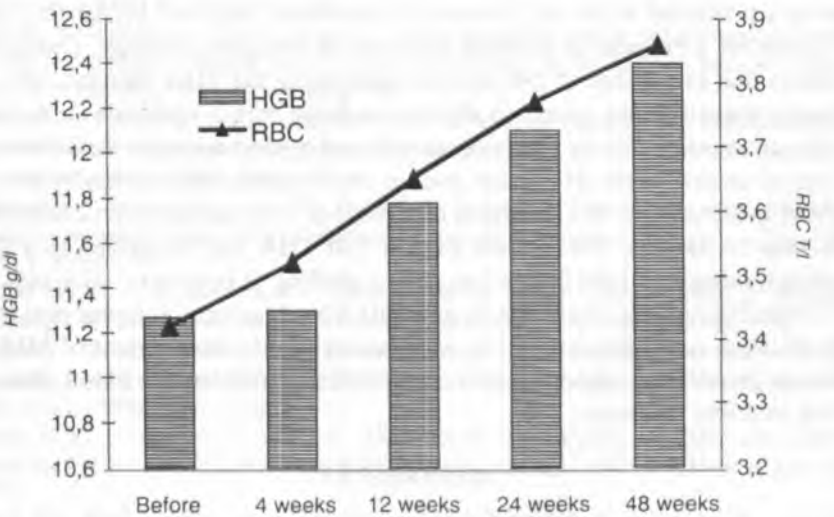

Figure 5. Increase of erythroid parameters in patients during thalidomide treatment

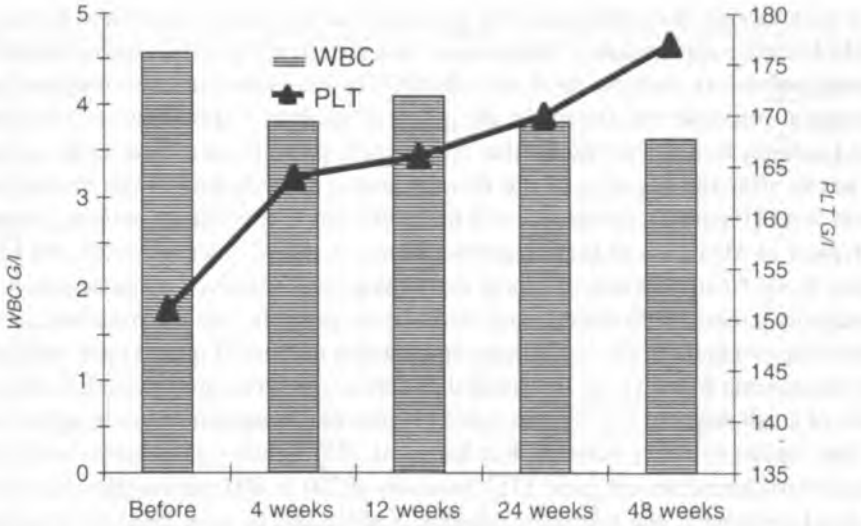

Figure 6. Leukocytes and thrombocytes level in patients during thalidomide treatment

the patients this response was much more effective than previous methods of treatment, such as VAD therapy or high dose of melfalan with autologous grafting of stem cells. Schiller et al. [17] analysed a group of 8 patients treated with THA with progressive MM, deep pancytopenia and renal insufficiency, and they described evident improvement in the disease activity parameters (PR — 50%) as well as normalization of blood morphotic parameters and normalization of renal function. This is in agreement with our earlier observations [11]. The most relevant observations and results of treatment published so far are presented in available literature by Americans from the Center for Treatment of Multiple Myeloma in Arkansas. Barlogie, Desikan et al. [1] report that in a group of 180 patients undergoing the THA therapy, 58% of the patients achieved improvement in clinical condition with a reduction in the disease activity parameters, 26% of the patients achieved a good response to the treatment, defined as decline in the M protein level in blood serum and/or urine by over 50%, and 10% achieved CR. The american observations have already been continuing for more than 24 months. The authors suggest that THA can be applied in a therapy inducing remission in MM before autologous grafting of peripheral stem cells [3].

Comparing our own observations and data from literature, it seems that thalidomide affecting newly discovered key pathways of proliferative signals of MM offers extremely promising possibilities of treating different proliferative blood diseases including multiple myeloma.

REFERENCES

1. *Barlogie B, Desikan R, Eddlemon P, Munshi N, Zangari M., Badros A., Anaissie E.*: Thalidomide is an active agent in multiple myeloma. Abstract book, VII International Multiple Myeloma Workshop, Stockholm, Sweden, September 1–5, 1999, p. 47.

2. *Barlogie B., Desikan R., Munshi N., Siegal D. et al.*: Single course DT PACE antiangiochemotherapy effects CR in plasma cell and fulminate multiple myeloma. 40th ASH Meeting, 4–8 Dec. 1998, Miami, Blood, abstr. p. 4180.
3. *Barlogie B., Jagannath S., Desikan K.R., Mattox S., Vesole D., Siegel D., Tricot G., Munshi N., Fassas A., Singhal S., Mehta J., Anaissie E., Dhodapkar D., Naucke S., Cromer J., Sawyer J., Epstein J., Spoon D., Ayers D., Cheson B., Crowley J.*: Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999; 93: 55–65.
4. *Bellamy W.T., Richter L., Frutiger Y., Grogan T.M.*: Expression of vascular endothelial growth factor and its receptors in hematopoietic malignancies. Cancer Res. 1999;59: 728–33.
5. *Berenson J.R, Bergsagel P.L. Munshi N.*: Initiation and maintenance of multiple myeloma. Semin. Haematol. 1999; 36:9–13.
6. *Dmoszyńska A., Roliński J., Bojarska-Junak A., Domański D., Hus M.*: Expression of activation markers on T lymphocytes during thalidomide therapy in multiple myeloma patients Annales UMCS 1999; 54:156 (abstract).
7. *Dmoszyńska A.*: Talidomid — nowe możliwości leczenia szpiczaka plazmocytowego. Acta Haemat. Pol. 2000; 31:5–9.
8. *Durie B.G.M., Stepan D.E.*: Efficacy of low dose thalidomide in multiple myeloma.
9. *Gasparini G.*: The rationale and future potential of angiogenesis inhibitors in neoplasia. Drugs, 1999; 58: 17–38.
10. *Hus M., Dmoszyńska A., Wojtaszko M., Szerej A.*: Skuteczna terapia talidomidem chorego z pierwotnie opornym na chemioterapię szpiczakiem plazmocytowym Annales UMCS Sectio D 1999; 54:152–153.
11. *Hus M., Dmoszyńska A.*: Talidomid — raz jeszcze .Nowe zastosowanie kliniczne. Annales UMCS 1999; 54:119-26.
12. *Juliusson G., Celsing F., Turesson I., Lenhoff S., et al.*: Frequent good partial remissions from thalidomide including best response ever in patients with anvanced refractory and relapsed myeloma Br J Haemat. 2000; 109:88–96.
13. *Kneller A., Raanani P., Hardan I., Avigador A., Levi I., Berkowicz M., Ben-Bassat I.*: Therapy with thalidomide in refractory multiple myeloma patients — the revival of an old drug. Br J Haematol 2000; 108:391–93.
14. *Munshi N., Wilson C.S., Penn J., Epstein J. et al.*: Angiogennesis in newly diagnosed multiple myeloma: poor prognosis with increased microvessel density in bone marrow biopsics. 40th ASH Meeting. 1998, Blood, abstr. 400.
15. *Rowland T.L., McHugh S.M., Deighton J. et al.*: Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells. Immunopharmacology 1998; 400:11–20.
16. *Sampaio E.P., Sarno E.N., Galilly R., Cohn Z.A., Kaplan G.*: Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. J. Exp. Med. 1991; 173:699–703.
17. *Schiller G., Vescio R., Berennson J.*: Thalidomide for the treatment of Multiple Myeloma relapsing after autologous peripheral blood progenitor cell transplant, Abstr. 1417.
18. *Singhal S., Mehta J., Desikan R.*: Antitumor activyty of thalidomide in refractory multiple myeloma N Eng J Med. 1999;341:1565–71. VII Int.Multiple Myeloma Workshop Stockholm 1–5.IX.1999 Abstr. book. p. 111.
19. *Weber D.M., Gavino M., Delasalle K., Alexanian R.*: Thalidomide for refractory multiple myeloma VII Int. Multiple Myeloma Workshop Stockholm, 1–5.IX.1999, Book of abstracts, p. 77.
20. *Zeldis J.B., Williams B.A, Thomas D., Elsayed M.E*: S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide. Clin. Ther. 1999; 21:319–30.

STRESZCZENIE

Talidomid (TAL) jest nowym lekiem o właściwościach immunomodulacyjnych, którego pełne spektrum działania nie jest w pełni poznane. Wyniki badań *in vitro* wskazują, że immunologczny efekt działania TAL jest częściowo zależny od jego hamującego wpływu na sekrecję wielu cytokin produkowanych przez limfocyty T (IL-6, TNF, INFγ) a także poprzez modulowanie ekspresji molekuł adhezyjnych wpływających na procesy apoptozy. Talidomid jest także inhibitorem angiogenezy. Terapią TAL objęto grupę 30 chorych z nawrotową lub oporną postacią szpiczaka plazmocytowego (MM — *Multiple Myeloma*). Pacjenci otrzymywali TAL doustnie w dawce 200 mg na dobę, zwiększając ją o 100 mg tygodniowo do 400 mg na dobę od 3 tygodnia. W grupie leczonych kliniczną odpowiedź na terapię, zgodnie z kryteriami *Myeloma Task Force* uzyskano u 18 chorych (60%). U 10 z nich (33%) redukcja białka monoklonalnego i odsetka plazmocytów w szpiku była większa niż 50% a u dwóch chorych (7%) uzyskano prawie całkowitą remisję hematologiczną.