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, β2 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.

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Key words: multiple myeloma, refractory, thalidomide

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 C13H10N2O4, 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
Thalidomide treatment in resistant or relapsed MM patients

Table 1. Patients characteristics before thalidomide treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>53</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>16</td>
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</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Age in Years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63.28</td>
<td>63.79</td>
<td>62.36</td>
</tr>
<tr>
<td>Range</td>
<td>32.0-79.0</td>
<td>47.5-79.0</td>
<td>32.0-79.0</td>
</tr>
<tr>
<td>Disease duration (month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>49.1</td>
<td>105.5</td>
<td>36.5</td>
</tr>
<tr>
<td>Range</td>
<td>13.0-104.0</td>
<td>15.0-104.0</td>
<td>13.0-88.0</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.66</td>
<td>4.66</td>
<td>4.42</td>
</tr>
<tr>
<td>Range</td>
<td>1.80-10.60</td>
<td>2.77-3.80</td>
<td>1.80-9.10</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>10.40</td>
<td>10.65</td>
<td>9.95</td>
</tr>
<tr>
<td>Range</td>
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<td>5.50-14.90</td>
<td>7.40-14.10</td>
</tr>
<tr>
<td>PLT (10^9/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>140.80</td>
<td>147.70</td>
<td>148.50</td>
</tr>
<tr>
<td>Range</td>
<td>1.00-249.00</td>
<td>1.00-269.00</td>
<td>18.00-245.00</td>
</tr>
<tr>
<td>β2-M (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.30</td>
<td>6.57</td>
<td>5.82</td>
</tr>
<tr>
<td>Range</td>
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<td>1.30-49.60</td>
<td>1.96-15.00</td>
</tr>
</tbody>
</table>

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.

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 β2-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,
expressed by a decline in the monoclonal protein level by over 75% of the baseline value (Figure 1). In 7 patients (50%) 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 hypoplastic 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.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.12 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.14 treated 17 patients with MM refracto-
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 who had less than 1.5 x 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
Conflict 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. Jesús 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-cytotoxic therapeutic option for resistant and relapsed myeloma.

References