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The efficacy and safety of the low-thalidomide dose CTD (cyclophosphamide, thalidomide, dexamethasone) regimen in patients with multiple myeloma—A report by the Polish Myeloma Study Group

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ABSTRACT

Multiple myeloma (MM) remains an incurable disease, but response rates to new drugs are promising, offering the majority of patients a significant prolongation of overall survival.

The objective of this study was to evaluate time to progression (TTP), event-free survival (EFS), and overall survival (OS) in MM patients treated with a combination of cyclophosphamide (CY), thalidomide (THAL) and dexamethasone (DEX).

This study included 132 untreated and relapsing/resistant patients treated with the low-thalidomide dose CTD regimen. The patients received CY 500 mg/m^2 *i.v.* or 625 mg/m^2 orally at day 1, THAL 100 mg/day á la longue and DEX 20 mg/day at days 1–4 and 8–11, every 28 days. Patients received 6–9 cycles; ORR by 3 months was 59.1%, by 6 months 65.6% and by 9 months 75.6%. In patients responding to CTD therapy (CR, nCR, PR), the probability of survival for 20 months was 89.3%. The outpatient low-thalidomide dose CTD regimen is well tolerated and produces a significant response rate both in untreated and relapsing/resistant MM patients.

1. Introduction

During the last few years many studies have shown that thalidomide alone, or in combination with other drugs, is a very effective, valuable drug in multiple myeloma (MM) therapy. The first report concerning the application of thalidomide (THAL) in relapsed/refractory myeloma patients was published in 1999 by Singhal et al. [1]. These authors reported that THAL, as a single drug, induced an objective response in about 30% of heavily pretreated patients. Since then, the efficacy of THAL has been confirmed by many other groups [2–4].

The precise mode of action of thalidomide is still unknown. Proposed mechanisms of action include angiogenesis inhibition, possibly by the downregulation of proangiogenic cytokines including vascular endothelial growth factor (VEGF); immune modulation by increasing natural killer cell activity, interleukin-2, and gamma interferon; and increasing the apoptosis. The response rate has been shown to be substantially higher when thalidomide is combined with older drugs such as melphalan or dexamethasone and cyclophosphamide (CTD) [5,6]. Thalidomide plus dexamethasone has been proven to be effective in relapsed/refractory multiple myeloma [7,8], with response rates of 42–72%, while the addition of cyclophosphamide (the CTD regimen) has resulted in response rates of 62.9–89%, with CR/nCR rates of 2–17% (various response criteria) [9–11].

In the multicentre study presented, the objective was to assess the efficacy and toxicity of the CTD regimen used both as induction therapy prior to HDT/ASCT, as well as salvage therapy in relapsed/refractory MM patients.

2. Patients and methods

2.1. Patients

Between February 2006 and April 2008, 132 consecutive patients from 6 collaborating centres were included in this study after signing the written informed consent. The study protocol and written informed consent were approved by the Local Ethics

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Table 1
Patient characteristics before thalidomide treatment.

Characteristics	Number	Percentage
Demographic data		
Males	61	46.2%
Females	71	53.8%
Immunoglobulin isotype		
IgG	83	62.8%
IgA	33	25.0%
IgD	1	0.8%
Light chain disease	15	11.4%
Light chain type		
Kappa	93	73.0%
Lambda	36	27.0%
Laboratory		
Serum albumin <3.5 g/l	34	25.8%
Beta-2-microglobulin >3.5 mg/l	59	44.4%
Serum creatinine ≥2 mg/dl	21	15.9%
Genetic abnormalities		
Isolated del(17p13)	1	3.5%
Complex abnormalities: del(13q14), del(17p13), t(4;14)	7	24.1%
Without abnormalities	21	72.4%
Therapy lines in pretreated patients		
1 line	17	12.9%
2 lines	30	22.7%
≥ 3 lines	21	15.9%
ISS prognostic index		
ISS 1	46	34.8%
ISS 2	43	32.6%
ISS 3	43	32.6%

Committee (KE-0254/1730/2006, KE-0254/174/2006). Sixty-four patients (48.5%) were untreated, and 68 (51.5%) had been previously treated. Median age was 57.5 years (range 23–83) and median serum monoclonal protein concentration was 43.5 g/l (range 11.5–151.9). Fluorescence in situ hybridization (FISH) analysis of bone marrow was performed in 29 of 132 patients as described by Fiserova et al. [12]. The detailed patients' characteristics before the start of CTD therapy are summarised in Table 1.

2.2. Therapeutic protocol

We used the CTD regimen consisting of cyclophosphamide (CY), thalidomide (THAL) and dexamethasone (DEX). Patients received drugs in 28-day cycles: CY was administered intravenously at a dose of 500 mg/m^2, or orally at an equivalent dose of 625 mg/m^2 on day 1; THAL was administered orally at a dose of 100 mg á la longue; and DEX was administered orally at a dose of 20 mg on days 1–4 and 8–11. All patients received aspirin at a dose of 75 mg daily as a deep venous thrombosis (DVT) prophylaxis.

2.3. Assessment of response

The efficacy of the CTD regimen was analyzed within three groups of patients with untreated, chemotherapy resistant, and relapsed multiple myeloma, respectively. The response to the therapy was assessed according to the modified criteria of the European Group for Blood and Marrow Transplantation (EBMT) [13]. The analysis was carried out on patients who had completed at least 3 cycles of the CTD regimen.

2.4. Statistical analysis

The survival analyses were carried out using the Kaplan–Meier method. The influence of independent variables on survival was tested by proportional Cox hazard regression. The differences in clinical parameters between the groups were tested by non-parametric Kruskall–Wallis ANOVA and Mann–Whitney *U*-tests.

3. Results

3.1. Response rates

Patients were given at least 3 and up to 9 cycles of the CTD regimen (a median of 6), and had been assessable for disease activity for 4 weeks after the last cycle. The overall response rate (ORR) after 3 cycles of CTD was 59.1% (78 out of 132 patients). In 96 patients continuing therapy up to 6 cycles, ORR increased to 65.6% (63 patients), and in 45 patients treated with 9 cycles of CTD, ORR was 75.6% (34 patients). Although genetic studies were performed in a minority of patients, it should be noted that among 7 high-risk patients, defined as carrying more than one abnormality, we observed responses lasting 10 and 11 months only in 2 cases and the other 5 patients did not respond to CTD. The analysis of the response rates in each group of patients is shown in Table 2.

3.2. Time to progression (TTP) and event-free survival (EFS)

The Kaplan–Meier estimate of TTP is illustrated in Fig. 1. In patients responding to CTD therapy (CR, nCR, PR) the probability of survival of 22 months without disease progression was 54.8% (median not reached; panel 1A). Patients achieving only disease stabilization as well as progressive patients, had a significantly shorter TTP ($p < 0.05$; $p < 0.00001$, respectively) with a median of 12.0 and 6.0 months.

The median TTP estimated by the Kaplan–Meier method was 21.2 months in previously untreated patients and it was significantly longer as compared to the median TTP of chemotherapy resistant (median 15.2 months; $p < 0.02$) or relapsed patients (median 10.0 months; $p < 0.003$; panel 1B). TTP analyzed by the ISS prognostic index showed a similar pattern for patients with ISS 2 and ISS 3, patients with ISS 1 had a significantly higher probability of survival ($p < 0.05$ vs. ISS 2; panel 1C). The probability of survival without progression for untreated patients did not differ from patients treated by a single line of chemotherapy, but was significantly higher as compared to patients treated with two or more lines ($p < 0.007$; panel 1D).

The Kaplan–Meier estimate of EFS is illustrated in Fig. 2. Patients responding to CTD therapy (CR, nCR, PR) had 54.9% of probability of survival of 22 months (median not reached) without any event (panel 2A). Patients achieving only disease stabilization as well as progressive patients had significantly shorter EFS ($p < 0.05$; $p < 0.00001$, respectively) with a median of 11 months and of 6 months (panel 2A). The probability of event-free survival for untreated patients did not differ from patients treated by single line of chemotherapy, but was significantly higher as compared to patients treated with two or more lines ($p < 0.005$; panel 2B).

Table 2
Response rate analyzed by disease status.

Response	Untreated ($n = 64$)	Resistant ($n = 51$)	Relapsed ($n = 17$)	Total ($n = 132$)
CR + nCR + PR	47 (73.5%)	25 (49.0%)	11 (64.7%)	83 (62.9%)
CR	6 (9.4%)	2 (3.9%)	1 (5.9%)	9 (6.8%)
nCR	17 (26.6%)	7 (13.7%)	5 (29.4%)	29 (22.0%)
PR	24 (37.5%)	16 (31.4%)	5 (29.4%)	45 (34.1%)
SD	5 (7.8%)	16 (31.4%)	1 (5.9%)	22 (16.7%)
PD	12 (18.7%)	10 (19.6%)	5 (29.4%)	27 (20.4%)

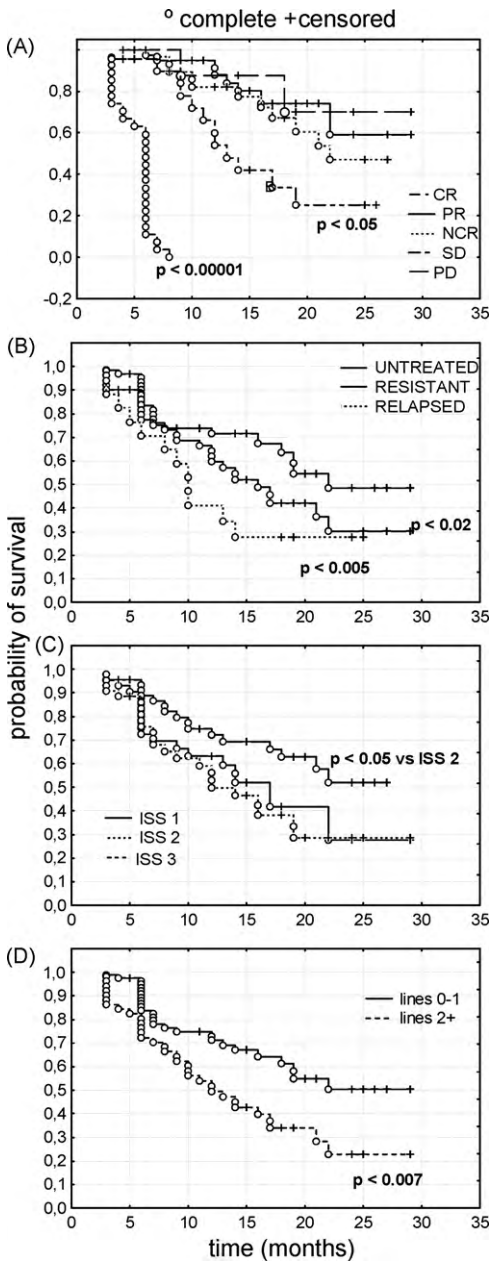

Fig. 1. TTP demonstrated by Kaplan–Meier curves. (Panel A) Patients responding to CTD (CR, nCR, PR) had 54.8% of probability of survive 22 months without MM progression (median not reached); patients achieving only disease stabilization as well as progressive ones had significantly shorter TTP ($p < 0.05$; $p < 0.00001$, respectively) with a median of 12 and 6 months. (Panel B) Median TTP of previously untreated patients was significantly longer as compared to chemotherapy resistant (21.2 months vs. 15.2 months; $p < 0.02$) or relapsed patients (vs. 10.0 months; $p < 0.003$). (Panel C) TTP analyzed by ISS index did not differ for patients with ISS 2 and ISS 3, patients with ISS 1 had significantly higher probability of survival ($p < 0.05$ vs. ISS 2). (Panel D) TTP was significantly longer for patients who got 0–1 lines of chemotherapy as compared to patients treated with ≥2 lines ($p < 0.007$).

3.3. Overall survival (OS)

The Kaplan–Meier estimate of OS is illustrated in Fig. 3. In patients responding to CTD therapy (CR, nCR, PR), the probability of overall survival for 24 months was 81.7% (panel 3A). In 67.1% of patients achieving disease stabilization, the probability of survival was 24 months, and their OS did not differ significantly from CTD responders (median not reached; panel 3A). Only progressive patients had a significantly shorter survival rate, and

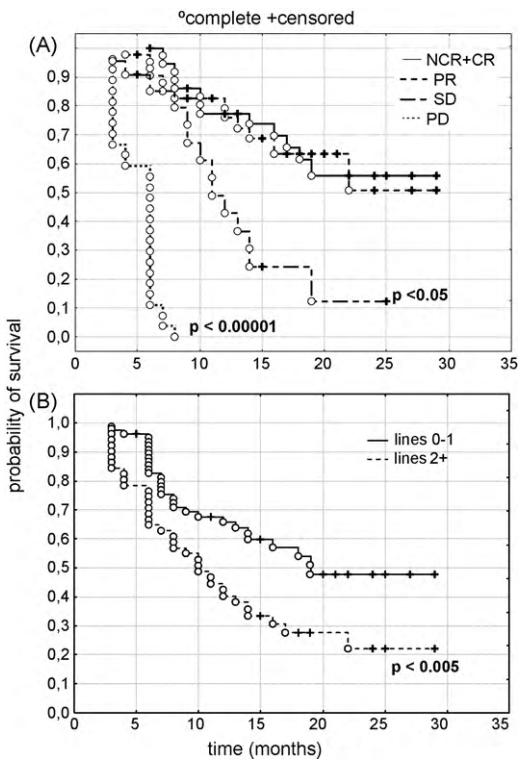

Fig. 2. EFS demonstrated by Kaplan–Meier curves. (Panel A) Patients responding to CTD (CR, nCR, PR) had 54.9% of probability to survive 22 months without any event (median not reached); patients achieving only disease stabilization as well as progressive ones had significantly shorter EFS ($p < 0.05$; $p < 0.00001$, respectively) with a median of 11 months and 6 months. (Panel B) EFS was significantly longer in patients who got 0–1 lines of chemotherapy as compared to patients treated with ≥2 lines ($p < 0.005$).

at 24 months only 20.4% stayed alive, despite introducing salvage therapies ($p < 0.00001$; panel 3A). In previously untreated as well as resistant patients the probability to survival of 20 months was 72.9% as compared to 50.7% of relapsed patients (median not reached; $p < 0.05$; panel 3B). An analysis by the ISS prognostic index showed that only patients with ISS 3 had a significantly lower probability of survival as compared to ISS 1 ($p < 0.01$; panel 3C).

3.4. Follow-up

The follow-up median time was 13 months (4–30 months). Among 83 CTD-responding patients, forty (30.3%) had been consolidated by high-dose chemotherapy supported by stem cell transplantation, between them one by allogeneic BMT, and had a significantly higher probability of survival without progression (median not reached) as compared to patients without high-dose consolidation (median TTP 18 months; $p < 0.0001$; Fig. 4). Forty-three CTD-responders not suitable for HDT/ASCT were maintained: thirty patients received thalidomide in doses of 50–100 mg/day and the next 13 patients other therapies (thalidomide with dexamethason—4, cyclophosphamide with dexamethason—3, bortezomib monotherapy—1). Forty-nine patients, not responding to CTD, were decided to continue other therapy, including PAD (18), VMBCP (10), MPT (7), VAD (7), MP (6), and bortezomib monotherapy (1).

From the start of the study we noted progression in sixty patients (45.5%), among them 25 (18.9%) patients had died due to progressive disease. At the last follow-up, we found 15 (11.4%) of the patients in CR (mainly transplanted), 18 (13.6%) in nearCR, 44 (33.3%) in PR and 18 (13.6%) were in stable disease.

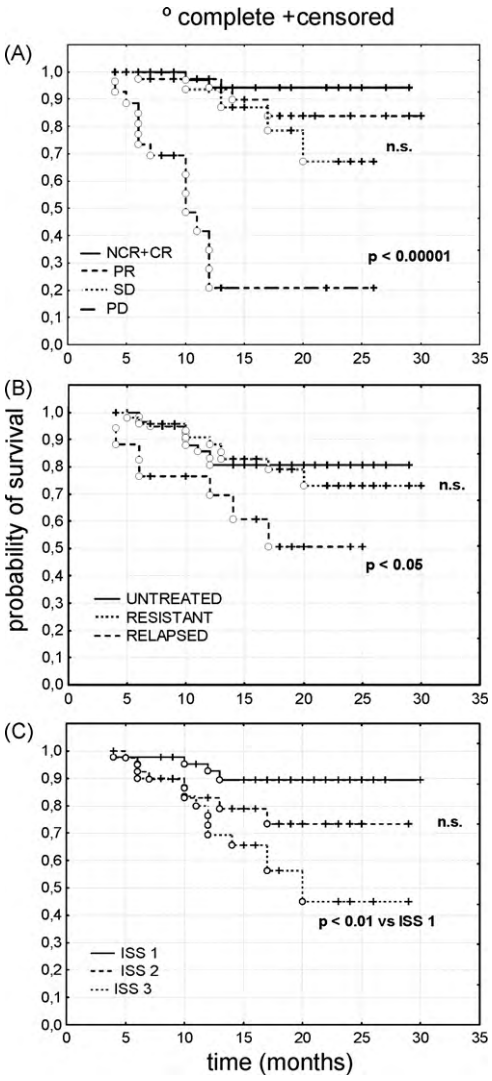

Fig. 3. OS demonstrated by Kaplan–Meier curves. (Panel A) Patients responding to CTD (CR, nCR, PR) had at least 81.7% probability to survive for 24 months (median not reached) vs. 67.1% in patients achieving disease stabilization; only progressive patients had significantly lower OS rate at 20 months (20.4%; $p < 0.00001$). (Panel B) In previously untreated as well as resistant patients the probability to survive 20 months was 72.9% vs. 50.7% in relapsed (median not reached; $p < 0.05$). (Panel C) Patients with ISS 3 had significantly lower probability of survive as compared to ISS 1 ($p < 0.01$; median not reached); OS analyzed by ISS index did not differ significantly for patients with ISS 1 and ISS 2 (median not reached).

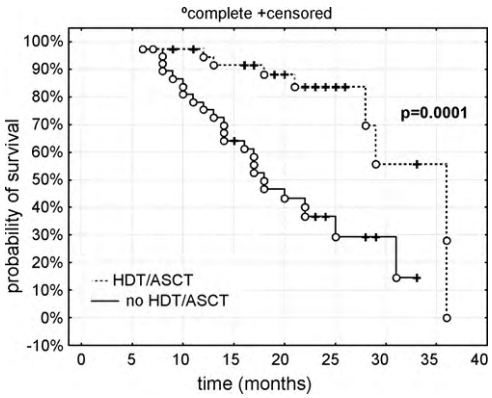

Fig. 4. Influence of high-dose chemotherapy and stem cell support on TTP in therapy responding patients demonstrated by Kaplan–Meier curves. CTD-responding patients consolidated by HDT/ASCT had significantly higher probability of survive without progression (median not reached) as compared to of patients without high-dose consolidation (median TTP 18 months; $p < 0.0001$).

3.5. Toxicity

The CTD regimen was safe and well tolerated. The main toxicity was neuropathy, observed in 34 patients (25.8%), including grade 1 neuropathy in 20 patients (15.2%), grade 2 in 10 patients (7.6%), grade 3 in 3 patients (2.3%) and grade 4 in 1 patient (0.8%). We did not observe toxic death during treatment. The therapy was withdrawn due to toxicity in 10 patients (7.6%): grade 3–4 sensory neuropathy in 4 patients (3.0%), grade 3 DVT in 2 patients (1.5%) grade 4 pulmonary embolism in 1 patient, grade 4 arterial event (stroke) in 1 patient, grade 3 leucopoenia and grade 3 infection in 1 patient, and grade 3 somnolence in 1 patient. Two patients refused therapy continuation due to intolerance.

4. Discussion

The introducing of thalidomide (THAL) and its new analogues substantially improved the prognosis for multiple myeloma patients. To increase the clinical effect of THAL, this drug had been combined first with dexamethasone (DEX), and later with other anti-myeloma agents [14–16]. In order to decrease several adverse effects connected with THAL the dose of THAL was markedly decreased from 800 mg in the first trial to 100 mg or even, recently, 50 mg/day [9,17,18].

A direct comparison between the efficacy of our CTD and the CTD schemes used by other authors is not easy due to the use of a variety of doses as well as dosing schemes. That is why, in order to discuss our results in relation to other groups, we divided CTD regimens into two subgroups: low-dose CTD and high-dose CTD. In the low-dose group we included schemes where THAL was used in doses of 50–200 mg, and in the high CTD group we included regimes where THAL was supplied in doses ranging from 300 to 800 mg/day. Selected examples of the CTD regimens are shown in Table 3. The overall response rate (ORR) in the whole group, as one of the largest patient groups treated so far with CTD, was 62.9%. In previously untreated patients, ORR was higher, reaching 73.4%, including 36% of CR + nCR, in contrast to chemotherapy resistant patients, where ORR was 49% (CR + nCR = 17.6%). Surprisingly, there were no significant differences in the time of survival between untreated patients and patients resistant to first line of therapy, suggesting that resistance to one line therapy does not exclude obtaining a complete response to CTD and prolongation of survival in a high percentage of patients. What is more, patients achieving disease stabilization could also benefit from CTD therapy since a relatively long OS gives them time for the next salvage therapy. The median TTP in previously untreated patients was 21.2 months, compared to 10.0 months in relapsed patients. This means that CTD is less effective treatment in relapsed patients, and this group may need other therapeutical options, e.g. bortezomib. EFS was comparable to TTP as a result of the lack of early toxic deaths. García-Sanz et al. [19], using THAL at escalating doses (up to 800 mg) and a higher dose of DEX (40 mg/day for 4 days) every 3 weeks, obtained ORR of 77% (CR + PR + MR) and CR of 10%, but 12.6% of patients had protocol interruption due to toxicity. In the Medical Research Council (MRC) Myeloma IX study, which has included 900 patients, CTD was compared with C-VAD as induction regimen before PBSCT. The CR rate in the CTD group was 20.3% and 11.7% after C-VAD. This difference was observed at 100 days after HDT/ASCT. A higher rate of response shows the additive value of HDT/ASCT when CTD was used as an induction therapy [20]. The highest response rate to CTD was reported by Wu et al. [11] in newly diagnosed patients. These authors, using a high-dose CTD, obtained ORR of 89%, including 45% CR + VGPR. In 11% of patients, grade 3 and 4 DVT was observed. No DVT prophylaxis was given. Seven percent of patients had infections. Neuropathy and neutrope-

Table 3
Selected examples of CTD (cyclophosphamide/thalidomide/dexamethasone) scheme used in multiple myeloma therapy.

Drug	Daily dose	Administration		ORR	Authors
HD thalidomide					
C	300 mg/m^2 *i.v.* bid	1–3			
T	Up to 400 mg	á la longue	Every 3 weeks	84.0%	Kropff et al. [18]
D	20 mg/m^2	1–4, 9–12, 17–20			
C	50 mg *p.o.*	á la longue			
T	Up to 800 mg	á la longue	Every 3 weeks	77.0%	Garcia-Sanz et al. [19]
D	40 mg	1–4			
C	150 mg/m^2 *p.o.* bid	1–5			
T	400 mg	1–5, 14–18	Every 4 weeks	67.0%	Dimopoulos et al. [5]
D	20 mg/m^2	1–5, 14–18			
C	500 mg *p.o.*	1, 8, 15			
T	Up to 400 mg	á la longue	Every 4 weeks	89.0%	Wu et al. [11]
D	40 mg	1–4, 12–15			
LD talidomide					
C	50 mg *p.o.* bid	21 days			
T	200 mg	á la longue	Every 4 weeks	62.9%	Suvannasankha et al. [9]
P	50 mg	á la longue			
C	500 mg *p.o.*	Every 7 days			
T	100–200 mg	á la longue	Every month	70.0%	Mangles et al. [23]
D	40 mg	1–4, 15–18			
C	150 mg/m^2 *p.o.*	1–4			
T	50 mg	á la longue	Every 4 weeks	72.5%	Kim et al. [10]
D	20 mg/m^2	1–5, 15–19			

Abbreviations: P, prednisone; bid, twice a day; HD, high dose; LD, low dose; ORR, overall response rate.

nia occurred in 4% of patients. In our study, CTD was a well-tolerated regimen, with manageable toxicity. Adverse events, both hematological as well as non-hematological were not significant, mainly grade 1 or 2 according to WHO. The treatment was stopped in only 10 patients (7.6%) due to toxicity including grade 3–4 DVT observed in only 2 patients (1.5%). These results show that using THAL at a low dose in combination with DEX at a dose lowered to 20 mg/day could significantly decrease the incidence of thrombotic complications. The higher risk of DVT observed in multiple myeloma patients receiving thalidomide or lenalidomide, especially in combination with dexamethasone, requires antithrombotic prophylaxis. Various strategies were described using low-molecular-weight heparin (LMWH), aspirin or vitamin K antagonists [21,22]. Based on our experience, it seems that aspirin prophylaxis is sufficient for protocols with a low dose of THAL and DEX. However, further studies are warranted to define the best prophylaxis strategy.

Another method to decrease the incidence of thrombotic and neurological complications was proposed by Dimopoulos et al. [5]. These authors used an intermittent way of THAL administration (in combination with CY and DEX) in 53 previously treated MM patients. Complete response was achieved in 5%, and partial response in 55% of patients. THAL was given in doses of 400 mg on days 1–5 and 14–18 in a 28-day cycle. The authors conclude that a pulsed regimen is associated with a lower incidence of DVT and peripheral neuropathy of 2% and 4%, respectively. We do not know whether continuous administration of THAL is necessary to obtain a full anti-myeloma effect, but a lower ORR in comparison to other studies suggest that the administration of THAL á la longue seems to give better results.

Summing up our results, low-thalidomide dose CTD, as an oral regimen, is well tolerated, showing significant clinical effects both in newly diagnosed and relapsed/refractory MM patients. It is suitable as routine therapy in an outpatient basis.

Conflict of interest

The authors declare that they have no potential conflicts of interest.

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References

[1] Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565–71.
[2] Juliusson G, Celsing F, Turesson I, Lenhoff S, Adriansson M, Malm C. Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 2000;109:89–96.
[3] Hus M, Dmoszynska A, Soroka-Wojtaszko M, et al. Thalidomide treatment of resistant or relapsed multiple myeloma patients. Haematologica 2001;86:404–8.
[4] Leleu X, Magro L, Fawaz A, Bauters F, Facon T, Yakoub-Agha I. Efficacy of a low dose of thalidomide in advanced multiple myeloma. Blood 2002;100:1519–20.
[5] Dimopoulos MA, Hamilos G, Zomas A, et al. Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma. Hematol J 2004;5:112–7.
[6] Palumbo A, Bertola A, Falco P, et al. Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. Hematol J 2004;5:318–24.
[7] Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 2003;121:768–71.
[8] Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood 2008;112:3107–14.
[9] Suvannasankha A, Fausel C, Juliar BE, et al. Final report of toxicity and efficacy of a phase II study of oral cyclophosphamide, thalidomide, and prednisone for patients with relapsed or refractory multiple myeloma: a Hoosier Oncology Group Trial, HEM01-21. Oncologist 2007;12:99–106.
[10] Kim YK, Lee JJ, Lee SR, et al. Clinical efficacy of thalidomide containing regimens as a first line therapy in patients with multiple myeloma. Haematologica 2007;92(Suppl. 2):177 [abstr.].

[11] Wu P, Davies FE, Horton C, et al. The combination of cyclophosphomide, thalidomide and dexamethasone is an effective alternative to cyclophosphamide–vincristine–doxorubicin–methylprednisolone as induction chemotherapy prior to autologous transplantation for multiple myeloma: a case-matched analysis. Leuk Lymphoma 2006;47:2335–8.
[12] Fiserova A, Hajek R, Holubova V, et al. Detection of 13q abnormalities in multiple myeloma using immunomagnetically selected plasma cells. Neoplasma 2002;49:300–6.
[13] Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115–23.
[14] Alexanian R, Weber D, Anagnostopoulos A, et al. Thalidomide with or without dexamethasone for refractory or relapsing multiple myeloma. Semin Hematol 2003;40(4 Suppl. 4):3–7.
[15] Roussou M, Anagnostopoulos A, Kastritis, et al. Pulsed cyclophosphamide, thalidomide and dexamethasone regimen for previously treated patients with multiple myeloma: long term follow up and disease control after subsequent treatments. Leuk Lymphoma 2007;48:754–8.
[16] Kyriakou C, Thomson K, D'Sa S, et al. Low-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma. Br J Haematol 2005;129:763–70.
[17] Hus I, Dmoszynska A, Manko J, et al. An evaluation of factors predicting long-term response to thalidomide in 234 patients with relapsed or resistant multiple myeloma. Br J Cancer 2004;91:1873–9.
[18] Kropff MH, Lang N, Bisping G, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (Hyper-CDT) in primary refractory or relapsed multiple myeloma. Br J Haematol 2003;122:607–16.
[19] García-Sanz R, González-Porras JR, Hernández JM, et al. The oral combination of thalidomide, cyclophosphamide and dexamethasone (ThaCyDex) is effective in relapsed/refractory multiple myeloma. Leukemia 2004;18:856–63.
[20] Morgan G, Davies FE, Owen RG, et al. Thalidomide combination improve response rates; results from MRC IX study. Blood 2007;110:1051A.
[21] Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clin Proc 2005;80:1568–74.
[22] Palumbo A, Rus C, Zeldis JB, et al. Enoxaparin or aspirin for the prevention of recurrent thromboembolism in newly diagnosed myeloma patients treated with melphalan and prednisone plus thalidomide or lenalidomide. Italian Multiple Myeloma Network, Gimema. J Thromb Haemost 2006;4:1842–5.
[23] Mangles SE, Abdalla SH. CTD treatment of myeloma - a single institution's experience. Haematologica 2007;92(Suppl. 2):169.