Low-dose thalidomide regimens in therapy of relapsed or refractory multiple myeloma

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Received November 7, 2007

Thalidomide has been estimated as a useful drug in therapy of refractory or relapsed multiple myeloma. Recently, several studies have shown very good results in therapy combination of thalidomide, cyclophosphamide and dexamethasone, but still high doses of thalidomide associated with serious adverse events have been used. In our study, we performed low-dose thalidomide regimens; the aim of this study was to verify the effect and to assess their toxicity. For younger patients up to 65 years we used a "CTD-junior" regimen, consisting of oral thalidomide 200 mg daily, pulsed intravenous cyclophosphamide 800 mg on day 1 and pulsed oral dexamethasone 40 mg on days 1-4 and 12-15, for every three weeks. For patients over 65 years, the "CTD-senior" regimen was used, with oral thalidomide 50-100 mg daily (according to tolerability), oral cyclophosphamide 50 mg daily and pulsed dexamethasone 20 mg on days 1-4 and 15-18, for every four weeks. From the group of 97 patients with progressive form of multiple myeloma or with resistance to conventional chemotherapy, 85 patients were evaluated. According to the EBMT criteria, we observed in 8% complete remission (CR), in 50% partial response (PR) and in 22% minimal response (MR). Ten patients (12%) were stabilized and seven patiens (8%) progressed. Toxicity of both regimens was mild and well managable, when weakness, obstipation, neuropathy of lower extremities, glycoregulation worsening and mild leucopenia occured most often. These results showed that low doses of thalidomide are still effective, when combined with other drugs. Both CTD regimens are safe also for patients with advanced and heavily pretreated multiple myeloma.

Key words: multiple myeloma, resistance to therapy, thalidomide, cyclophosphamide, dexamethasone

Despite modern treatment modalities, multiple myeloma still remains an incurable disease. One of the most active and promising new drugs is thalidomide, for its antiangiogenic and immunomodulatory properties. Its effect is probably not only „anti-myeloma", but it can probably help to stimulate the effect of other chemoterapeutics and to overcome the drug resistance [1]. Used as a monotherapy, its activity is about 30% and in combination with dexamethasone it reaches about 40-60% objective response and can be even higher when combined with some other agents [2]. Several studies have shown very good results with the combination of thalidomide, cyclophosphamide and dexamethasone [3–15]. However, when quite high doses of thalidomide (up to 800 mg daily) have been used, severe toxicity such as peripheral neuropathy or deep vein thrombosis were observed.

The "Czech Myeloma Group" (CMG) used low-dosed-thalidomide regimens, with combination of thalidomide, cyclophosphamide and dexamethasone: the "CTD-junior" regimen, for patients up to the age of 65, and the "CTD-senior" regimen, for patients over 65 years of age. The aim of this study was to assess the effectivity and toxicity of both used regimens in patients with refractory or relapsed multiple myeloma.

Patients and methods

In our study, chemotherapeutic regimens based on low doses of thalidomide in combination with continual oral or pulsed intravenous cyclophosphamide and pulsed dexamethasone were performed. Between January 2004 and June 2006, the group of 97 patients with multiple myeloma refractory or relapsing after conventional chemotherapy or high-dose therapy with autologous stem cell transplant (ASCT) were

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Table 1 Basic characteristics of patients

	Number of patients
Male / Female	49 / 48
Age	62,4 *years*
Monoclonal protein: IgG	63
IgA	23
IgD	3
Light chains / non secretory	5 / 3
Kappa / Lambda	69 / 25
Durie-Salmon stage: I A / B	3 / 0
II A / B	31 / 3
III A / B	47 / 13
Relapsed / refractory MM	74 / 23
Number of prior therapy lines	2 (1-6)
ASCT in a history	35
Time from MM diagnosis	34 (3-204) *months*

ASCT = autologous stem cell transplantation

treated with one of the CTD regimens. These regimens were used mostly as a third-line therapy and started on average 34 months (3-204 months) after MM diagnosis. As previous treatment, autologous stem cell transplantation was used in 35 cases, other patiens were treated using conventional chemotherapy, i.e. regimens: VAD (vincristine, adriablastin, dexamethasone), CyVAD (cyclophosphamide +VAD), MP (melphalan, prednisone), VBMCP (vincristine, BCNU/CCNU, melphalan, cyclophosphamide, prednisone), CIDEX (CCNU, idarubicin, dexamethasone), ten patiens were treated also with thalidomide monotherapy. Basic characteristics of the patients are in Table 1.

The treatment was coordinated by the Czech Myeloma Group (CMG) in three centers of the Czech Republic. For younger patients up to 65 years we used a "CTD-junior" regimen, consisting of oral thalidomide 200 mg daily, pulsed intravenous cyclophosphamide 800 mg on day 1 and pulsed oral dexamethasone 40 mg on days 1-4 and 12-15, for every three weeks. For patients above 65 years, the "CTD-senior" regimen was used: oral thalidomide 50-100 mg daily (according to tolerability), oral cyclophosphamide 50 mg daily and pulsed dexamethasone 20 mg on days 1-4 and 15-18, for every four weeks. As a deep venous thrombosis profylaxis, we used low-molecular weight heparine (LMWH) 0.4 ml subcutaneously daily in 63 of 97 patients. On days with dexamethasone, all patients used omeprazol 20 mg 2 times daily as the prevention of stomach ulcers and kalium chloratum 500 mg 1-3 times daily to prevent hypokalemia. Patients without renal impairment were treated also with bisphoshonates (oral clodronat 1600 mg daily).

Patients were treated by the CTD regimen as long as the paraprotein reduction continued and no serious adverse events occured. Seven patients were treated with 4 cycles of CTD-junior only, used as a reinduction therapy before second ASCT. The treatment response was evaluated using the EBMT criteria [16], in patiens with low-secretory form of MM, the serum free light chain analysis was used [17, 18]. With a view to compare our results with other studies, all categories of response were used, although minimal response (MR) is no longer recommended.

Results

The treatment response was evaluated in 85 of 97 treated patients; 8 patients with nonsecretory form of MM and 4 patients with short time from the start of the treatment (1-2 cycles of CTD) could not be evaluated.

In the whole group, objective response rate was achieved in 68 patients (80%): complete remission without measurable monoclonal protein was in 7 (8%) patients: negative immunofixation (CR) was in 1 (1%), positive or unknown result of immunofixation (nCR) was in 6 (7%) patients. Partial response (PR) achieved 42 (50%) patients and minimal response (MR) achieved 10 (22%) patients. Stable disease (SD) was seen in 10 (12%) patients, while 7 (8%) patients progressed. Moreover, seven patients progressed early after achievement of objective response (CR, PR) or MR, between 3rd to 6th month of the treatment. In seven patients with monoclonal protein reduction we observed an extramedullary progression: in 4 patients the soft tissue tumor (plasmocytoma) was observed in the skull (in one woman also with plasmocellular infiltration of meninges), once in the arm and twice in the chest and neck.

The treatment response was very similar in both arms "CTD-junior" and "CTD-senior". In the group treated by the "CTD-junior" regimen, 29 from 37 patients were evaluated; objective response rate (CR + PR) was achieved in 17 (59%) patients: nCR was observed in 2 (7%), PR in 15 (52%), MR achieved 9 (30%) patients, one patient (4%) was stabilized (SD), while 2 patients (7%) progressed. In the arm "CTD-senior", 56 from 60 patients were evaluated; objective response rate was reached in 32 (57%) patients: CR we observed in one (2%), nCR in 4 (7%), PR in 27 (48%), MR in 10 (18%), SD in 9 (16%), but 5 patients (9%) progressed, as shown in Table 2. It is obvious, that MR was slightly more often in the "CTD-junior" group (30% versus 18%), while SD was more often in the "CTD-senior" group (16% vs. 4%).

Both regimens were relatively well tolerated. Side effects are shown in Table 3. Most frequently, we observed signs of peripheral neuropathy: newly developed mild paresthesias or worsening of preexisting neuropathy of lower extremities in 32 (33%), constipation in 29 (30%) and weakness in 26 (27%) patients. In 17 (18%) patients we observed leucopenia of WHO grade 2 or 3, but no patient experienced febrile neutropenia. Infections developed in 26 (27%) patients, most often were respiratory infections (11%) and candidosis (6%), 4 patients (4%) developed urinary infection and 3 (3%) had herpes zoster, only 2 patients (2%) developed pneumonia and in one case appeared sepsis caused by *Salmonella*. Deep venous thrombosis developed in 4 from 34 patients (12%) without LMWH prophylaxis, but only in 2 from 63 patients (2%) with LMWH. In three patients (3%) we observed serious skin reaction after

Table 2 Results of the therapy with regimens „CTD-junior“ and „CTD-senior“

Result	*Total (N=85)*	*100%*	*„CTD-junior“ (N=29)*	*100%*	*„CTD-senior“*	*100% (N=56)*
CR/nCR	1/6	1/7%	0/2	0/7%	1/4	2/7%
PR	42	50%	15	52%	27	48%
OR (CR + PR)	49	58%	17	59%	32	57%
OR´ (CR+PR+MR)	68	80%	26	89%	42	75%
MR	19	22%	9	30%	10	18%
SD	10	12%	1	4%	9	16%
Progression	7	8%	2	7%	5	9%
(Not applicable)	*(12)*	-	*(8)*	-	*(4)*	-

CR = complete remission with negative immunofixation, nCR = near CR, not detectable M-protein (MIG), but positive or unknown immunofixation, PR = partial remission (MIG under 50% of pre-treatment value), MR = minimal response (decrease of MIG from 25-50% of pre-treatment value), SD = stable disease (decrease of MIG less than 25%), OR = objective response (decrease of MIG more than 50%; CR + PR), OR´ = objective response based on EBMT response criteria (decrease of MIG more than 25%; CR + PR + MR)

Table 3 Side effects with CTD regimens treatment

	Total		***„CTD-junior“***		***„CTD-senior“***	
Side effects	97	100%	37		60	
Neuropathy (new or worsened)	32	33%	13	35%	19	32%
Constipation	29	30%	17	46%	12	20%
Weakness	26	27%	11	30%	15	25%
DVT all / with LMWH	6 / 2	7% / 2%	1 / 1	3%	5 / 1	8% / 2%
Dry skin / exanthema	9 / 3	9% / 3%	2 / 1	5% / 3%	7 / 2	11% / 3%
Infections:	*26*	*27%*	*12*	*32%*	*13*	*22%*
– urinary tract	4	4%	1	3%	3	5%
– upper respiratory tract	11	11%	6	16%	5	8%
– pneumonia	2	2%	1	3%	1	2%
– oral candidosis	6	6%	3	8%	3	5%
– herpes zoster	3	3%	1	3%	1	2%
Neutropenia (< 3.0 x10^9/ml)	17	18%	6	16%	11	18%
Gycoregulation or diabetes worsening	8	8%	1	3%	7	11%
Psychical changes	11	11%	2	5%	9	15%
Oedemas	7	7%	1	3%	6	10%
Extramedullary progression	6	6%	2	5%	4	7%

thalidomide. Other side effects were connected with high doses of dexamethasone: 11 patients (11%) developed psychical changes or nervousness, in 8 (8%) we observed tremor, 8 (8%) developed glycoregulation worsening or diabetes and 7 (7%) had oedemas or fluid retention. Incidence of the side effects was very similar in both arms, only bronchitis and constipation were more often in the “CTD-junior” than in the “CTD-senior” group (16% versus 8% for bronchitis and 46% versus 20% for constipation).

Discussion

The effectivity of thalidomide treatment of relapsed or resistant multiple myeloma has been confirmed in several studies [1, 2, 19–25]. With thalidomide monotherapy using doses from 200 to 800 mg of thalidomide, objective response was reached in one third of patients, but high rate of side effects (prevailing neuropathy and DVT) was observed. The combination of thalidomide with dexamethasone has brought the overall response rate up to 40-60%, but still high doses of thalidomide have been used [26, 27]. Because the toxicity of thalidomide depends on the dose, there is a tendency to use as low doses of thalidomide as possible. Some authors have shown that doses about 50-200 mg daily can be sufficient, but these doses have been useful mainly for patients with first relapse of MM [28–30]. For advanced myeloma, the combination of low dose thalidomide with other drugs seems to be more effective and still safe [23, 29].

Recently, several notes about the combination of thalidomide, cyclophosphamide and dexamethasone have appeared. Garcia-Sanz *et al*. used thalidomide 200-800 mg daily, continuous oral cyclophosphamide 50 mg daily and pulsed dexamethasone 40 mg for 4 days in three weeks’ cycle. Objective response rate (CR + PR + MR) was reached in 76% patients, two years later even in 83% patients. Most often side effects were constipation, neuropathy, somnolence, neutropenia and DVT [3, 4, 5]. The study of Dimopoulos *et al.,* published in the same year, used different dosage of the drugs: thalidomide was used in pulses of 400 mg on days 1-5 and 14-18, oral cyclophosphamide 150 mg/m^2 twice daily on days 1-5 and dexamethasone 20 mg/m^2 on days 1-5 and 14-18 in 4 weeks. Objective response rate achieved 60% patients, while

Table 4 Overview of CTD combination regimens used in other studies

	N = patients	Thalidomide	Cyclophosphamide	Dexamethasone
García-Sanz, J.F. San Miguel(3-5)	59	200-800mg daily	50mg daily p.o.	40mg, Day 1-43-weeks' cycle
M.Dimopoulos,A.Anagnostopoulos(6, 7)	53	400mg, D 1-4, 15-18	150mg /m2 i.v.D 1-5	20mg, D 1-5, 15-18,4-weeks' cycle
M.Kropff(9, 14)	60	100-400mg daily	300mg /m2 i.v.D 1-3, twice daily in 12h interval	20mg /m2 D 1-4, 9-12, 17-20
C.Kyriakou(8, 10)	23	50-200mg daily	400mg /m2 i.v. weekly	40mg, D 1-4,4-weeks' cycle
T.Caravita(11)	12	100-200mg daily	500mg i.v.weekly	40mg, D 1-44-weeks' cycle
F.Di Raimondo(12)	40	200mg daily	100mg p.o., daily	40mg, D 1-44-weeks' cycle
G.Sidra,C.D.Williams(13, 15)	62	100-200mg daily	500mg p.o., D 1, 8, 15	40mg, D 1-4, 15-184-weeks' cycle
CMG:„CTD-junior"	37	200mg daily	800mg i.v., D 1	40mg, D 1-4, 15-18, 3-weeks' cycle
„CTD-senior"	60	100mg daily	50mg p.o., daily	20mg, D 1-4, 12-15, 4-weeks' cycle

D = day of the cycle, CMG = the Czech Myeloma Group

18% progressed. The most often side effect was neutropenia in 40% patients, when in 26% reached the WHO grade 3-4 [6, 7]. Several other observations with CTD regimen were published, but the dosage of the drugs were different [8–15] (Tables 4). In all referenced studies, the objective response rate was defined as at least 25% decrease of paraprotein, i.e. CR + PR + MR, according to EBMT criteria, and was reached in 67-88%: CR in 2-4%, PR in 42-83% and MR in 12-21%, while about 20% patients were stabilized and 4-25% progressed [3–14] . Our results are comparable with most of the listed studies: when comparing objective response defined as CR + PR + MR, we observed 80% (68 patients) of OR in all patients, 89% of OR (26 patients) in the "CTD-junior" and 75% (42 patients) in the "CTD-senior" group. In the presented study, overall survival was not evaluated as the median has not been reached yet.

It is obvious, that using intravenous cyclophosphamide we can reach relativelly better results, but also higher occurence of side effects as infections and neutropenia [8-10, 14]. These regimens should be therefore used mainly for younger patients. For elderly people, the fully oral regimen is more suitable and safe. For most patients, low doses of thalidomide (50-200 mg) are sufficient, when combined with cyclophosphamide and dexamethasone.

To prevent serious side effects (as neuropathy, DVT or infections), it is necessary to monitor clinical state and laboratory findings: it is recomended to ask for clinical signs of neuropathy of lower extremities with prompt changes of thalidomide doses. When leucopenia occurs, the intravenous pulses of cyclophosphamide are worse managable for dosage change than oral cyclophosphamide, so that for heavily pretreated patients oral cyclophosphamide is more safe and should be used. To prevent DVT, it is necessary to use some prophylaxis; LMWH is safe and effective, but not acceptable by all patients. The effectivity of aspirin or low dosed warfarin should be verified [8, 10, 31, 32].

In six patient in our study, an extramedullary plasmacytoma developed during thalidomide treatment. These tumors were totally resistant to thalidomide, what may be caused by complete biological changes of kinetic and proliferative parametres of plasma cells in advanced myeloma [33, 34].

Conclusion

The effectivity and tolerability of the drug combination of thalidomide, cyclophosphamide and dexamethasone have been confirmed recently. In our study, we used different dosage of the drugs and established two regimens "CTD-junior" and "CTD-senior". The effectivity and tolerability is similar in both of them. The overall response rate was a bit better in the "CTD-junior" regimen with pulsed cyclophosphamide, however, this regimen is more suitable for younger patients. For erderly and heavily pretreated patients, we recommend to use fully oral regimen with lower doses of thalidomide and continual cyclophosphamide ("CTD-senior"). Both the CTD combination regimens allow to use low doses of thalidomide and are acceptable in routine clinical practice.

Supported by VVZ MSM 6198959205 and IGA CR NR 9500-3

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