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ORIGINAL ARTICLE

Thalidomide–dexamethasone plus pegylated liposomal doxorubicin vs. thalidomide–dexamethasone: a case-matched study in advanced multiple myeloma

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Abstract

Objectives: Nearly all patients with multiple myeloma (MM) relapse or become refractory to front-line therapy. Several salvage therapies have been explored, but the optimal combination regimen has not been defined. We performed a case-matched study comparing patients with relapsed/refractory MM receiving thalidomide–dexamethasone alone or the combination thalidomide–dexamethasone–liposomal pegylated doxorubicin. *Methods:* Forty-seven patients received thalidomide (100 mg/d), dexamethasone (40 mg p.o. on days 1–4 and 9–12), and pegylated liposomal doxorubicin (40 mg/m^2 on day 1 every 28 d) (ThaDD). Their clinical outcome was compared with that of 47 pair mates selected from patients treated at relapse with thalidomide (100 mg/d) and dexamethasone (40 mg p.o. on days 1–4) (Thal–Dex) and matched for age, β2-microglobulin and previous therapy. *Results and conclusions:* Overall response rate was significantly higher in ThaDD group (92% vs. 63.5%; $P < 0.0001$) as partial response rate (≥PR) (75.5% vs. 59.5%; $P = 0.077$), very good partial response rate (≥VGPR) (36% vs. 15%; $P = 0.018$) and near complete remission rate (≥nCR) (30% vs. 10.5%; $P = 0.002$). Non-hematologic toxicity was similar in the two groups of patients whereas hematologic toxicity and infections were significantly higher in ThaDD patients. Median progression-free survival, event-free survival, and overall survival were significantly longer in patients receiving ThaDD than in those treated with Thal–Dex.ThaDD regimen significantly improved response rate and overall survival in comparison with Thal–Dex. Although the frequency of hematologic toxicity and infections resulted higher in ThaDD group compared with control group, they were not particularly frequent after adequate prophylaxis was added and were easily managed when occurred.

Key words thalidomide; dexamethasone; pegylated liposomal doxorubicin; multiple myeloma

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Introduction

Multiple myeloma (MM) remains a malignant incurable disease and nearly all patients will experience relapse after both conventional chemotherapy and high-dose therapy supported by stem cell transplantation. For these patients a standard salvage therapy has not been defined and traditional therapeutic strategies lead to unsatisfactory results (1–3). Since 1999 thalidomide was found to be effective in relapsed/refractory MM (4). As single agent or combined with dexamethasone, thalidomide induces an overall response rate (ORR) of approximately 30% (5) and 50% (6–8), respectively. Nevertheless, the complete remission (CR) rate is not substantially different from that reported with standard chemotherapy.

Higher ORR and particularly CR rate was achieved when thalidomide was added to chemotherapeutic agents such as cyclophosphamide (9–12), etoposide (13),

melphalan (14, 15), doxorubicin as conventional or pegylated liposomal compound (16) although side effects and complications seem to be more frequent.

In recent phase II studies, we obtained promising results with the combination thalidomide, dexamethasone, and pegylated liposomal doxorubicin both in relapsed/refractory and newly diagnosed elderly MM patients (17, 18). Here, we report the results of a retrospective case-matched study of 94 patients with relapsed/refractory MM receiving thalidomide–dexamethasone (Thal–Dex) alone or the combination thalidomide–dexamethasone–liposomal pegylated doxorubicin (ThaDD).

Patients and methods

Trial design and patients

We compared the clinical outcome of 47 consecutive patients enrolled in the ThaDD regimen from March 2003 to March 2005 in a tertiary care Hematology Department of Ancona University with that of 47 patients with symptomatic myeloma treated with Thal–Dex between July 1999 and September 2005 in a tertiary care Hematology division of Turin University. The two groups of patients met the same eligibility criteria and were pairs matched for age (within 3 yr), β2-microglobulin level at diagnosis (within 1 mg/L), time from first treatment, number of previous regimens (induction and high-dose therapy was considered as a single regimen) and major classes of antimyeloma agents. Moreover, a similar number of patients in both groups had been received autologous stem cell transplant and none had been previously treated with thalidomide. Patients characteristics are shown in Table 1. The two institutional review boards approved the protocol and written informed consent was obtained from all patients.

Assessment of toxicity, graded according to the National Cancer Institute (NCI) criteria version 2 (19) was performed with medical interview, physical examination, and laboratory tests (hematology, clinical chemistry).

Response to treatment assessed at the time of maximal response was defined as per the EBMT criteria (20). Furthermore, we included other two categories: near-complete response (nCR) defined as absence of the monoclonal protein on electrophoresis with positive immunofixation and very good partial remission (VGPR) requiring ≥90% reduction in serum paraprotein. Patients underwent serum and/or urine electrophoreses monthly and bone marrow aspirate after the first 6 months of treatment. Subsequently, patients were followed with history, physical examination and laboratory tests every 3 months, bone marrow aspirates every 6 months and skeletal X-rays every year.

Table 1 Characteristics of patients

Characteristics	ThaDD, *n* (%)	Thal–Dex, *n* (%)	*P*-value
Median age (range)	69 (52–82)	66 (51–84)	0.194
Gender (M/F)	26/21	28/19	0.677
Immunofenotype			
IgG	30 (63)	26 (55)	0.236
IgA	8 (17)	9 (19)	
Light chain	5 (11)	11 (24)	
Not secretory	4 (9)	1 (2)	
Median β2-microglobulin (mg/L) (range)	3.3 (0.5–30)	3.3 (0.5–21.7)	0.650
Median creatinine (mg/dL) (range)	1 (0.5–9.3)	1.1 (0.5–5.7)	0.687
Prior therapy			
2	21 (45)	18 (38)	0.111
3	19 (40)	27 (57.5)	
4	7 (15)	2 (4.5)	
Prior HDT	19 (40)	22 (46)	0.533
Prior anthracyclins	23 (49)	26 (55)	0.536
Time from first treatment (median months)	42 (3–150)	45 (3–142)	0.309
≥3 yr (%)	47	51	0.680
≥5 yr (%)	26	32	0.494
Duration of first remission (median months)	26.4	24.3	0.836

HDT, high-dose therapy; ThaDD, thalidomide, dexamethasone, pegylated liposomal doxorubicin; Thal–Dex, thalidomide, dexamethasone.

Treatment

Forty-seven patients received thalidomide 100 mg each evening, intravenous Caelyx® (Schering-Plough, Heist-op-den-Berg, Belgium) 40 mg/m^2 on day 1 every 28 d, dexamethasone 40 mg p.o. on days 1–4 and 9–12 every 28 d for three courses. Two additional courses were administered if a response ≥VGPR was achieved whereas three additional cycles were given if a response < VGPR was obtained after the first three courses. Thereafter, patients received a maintenance therapy including thalidomide 100 mg/d and dexamethasone 20 mg on days 1–4 every 28 d until relapse or toxicity. The other group of 47 patients were treated with dexamethasone 40 mg p.o. on days 1–4 monthly and thalidomide 100 mg daily continuously until relapse or toxicity.

Supportive therapies of patients received ThaDD consisted of warfarin 1.25 mg/d, vitamin B6, zoledronic acid, erythropoietin, and hypoglycaemic or insulin if glycemic level was more than 180 mg/dL. No antibacterial prophylaxis was initially given to patients. Due to a high incidence of respiratory infections occurred after the first 32 cycles of chemotherapy, we administered ciprofloxacin 250 mg twice daily for all subsequent courses. If patients developed ≥grade 3 neutropenia after a Caelyx® infusion, granulocyte colony stimulating factor (G-CSF) was administered for all subsequent cycles. The dose of Caelyx® was reduced by 25% if ≥grade 3 toxicity occurred

as well as the dose of dexamethasone was reduced to 20 mg or discontinued in case of ≥grade 2 muscular toxicity. Occurrence of ≥grade 3 neurotoxicity required discontinuation of thalidomide. Patients treated with Thal–Dex received, as supportive care, zoledronic acid, erythropoietin, and hypoglycaemic or insulin if necessary. Neither antibacterial nor antithrombotic prophylaxes were used in this group of patients.

Statistical methods

The primary end-point of this study was to compare the response rate and toxicity while the comparison of progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) was a secondary end-point. Paired comparisons of baseline characteristics were performed using the Chi-square test for the categorical variables and by Mann–Whitney test for continuous variables. Outcome was analyzed on an intent-to-treat basis and response was provided by number and rate.

PFS was calculated from the time of enrollment to progression, relapse or the date the patient was last known to be in remission. EFS was calculated from the time of enrollment to progression, relapse, death for any cause, or the date the patient was last known to be in remission. OS was calculated from the time of the enrollment to the date of death for any cause or the date the patient was last known to be alive. All curves were plotted according to the Kaplan–Meier method and compared by log-rank test. For statistical analysis the Statistical Package for Social Science version 11.5 (SPSS, Chicago, IL, USA) was used.

Results

Response to therapy

Overall response rate was significantly higher in the group of patients treated with ThaDD regimen (92% vs. 63.5; $P < 0.0001$) (Table 2). A higher proportion of patients receiving ThaDD obtained a ≥PR (75.5% vs. 59.5%; $P = 0.077$) and a significant difference between the two groups was found in term of ≥VGPR (36% vs. 15%; $P = 0.018$) and ≥nCR rate (30% vs. 10.5%; $P = 0.022$). Response to therapy was more rapid after the ThaDD regimen with a median time to maximum response of 2 months for ThaDD and 4 months for Thal–Dex combination.

Table 2 Response to therapy

Type	ThaDD, *n* (%)	Thal–Dex, *n* (%)	*P*-value
Complete remission	14 (30)	1 (2)	<0.0001
Near complete remission	0	4 (8.5)	
Very good partial remission	3 (6.5)	2 (4)	
Partial remission	19 (40.5)	21 (44.5)	
Minimal response	5 (10.5)	2 (4.5)	
Stable disease	1 (2)	14 (29.5)	
Progression	5 (10.5)	3 (6.5)	
≥Partial remission	36 (75.5)	28 (59.5)	0.077
<Partial remission	11 (23.5)	19 (40.5)	
≥Very good partial remission	17 (36)	7 (15)	0.018
<Very good partial remission	30 (64)	40 (85)	

ThaDD, thalidomide, dexamethasone, pegylated liposomal doxorubicin; Thal–Dex, thalidomide, dexamethasone.

Table 3 Non-hematologic toxicity

Type	ThaDD, *n* (%)	Thal–Dex, *n* (%)	*P*-value
Constipation			
≥Grade 2	9 (19)	2 (4.5)	0.025
Dizziness			
Grade 1	4	1	0.238
Grade 2	2	1	
Grade 3	0	0	
Grade 4	0	0	
Confusion			
Grade 1	2	1	0.947
Grade 2	1	1	
Grade 3	1	1	
Tremors			
Grade 1	4	3	0.067
Grade 2	5	0	
Peripheral neuropathy			
Grade 1	9 (19)	3 (6.5)	0.051
Grade 2	3 (6.5)	10 (21)	
Grade 3	1 (2)	0	
Neutropenia			
Grade 3–4	12 (25)	0	<0.0001
Infections			
Grade 3–4	11 (23)	0	<0.0001
Thrombocytopenia			
Grado 3–4	3	0	0.212
Alopecia			
Grade 1–2	23	0	<0.0001
PPE			
Grade 1	2	0	0.311
Cardiotoxicity	0	3 (1 AF, 2 CHF)	<0.001
Vascular events	6 (5 DVT, 1 PE)	3 (2 DVT, 1 ictus cerebri)	0.293

DVT, deep venous thrombosis; PE, pulmonary embolism; AF, atrial fibrillation; CHF, congestive heart failure.

Toxicity

Adverse events during induction therapy are listed in Table 3. Most side effects were mild or moderate in both regimens. Two patients in ThaDD group and one patient receiving Thal–Dex experienced ≥grade 3 neurological toxicity. The most common side effects observed in the ThaDD group was ≥grade 3 neutropenia (25%) whereas no platelets and/or red cells transfusions were required. Infections occurred in 23% of patients receiving ThaDD

regimen whereas they were not documented in the Thal–Dex group. Of note, in the ThaDD group, the frequency of severe infections dropped below 10% after ciprofloxacin prophylaxis was administered. No significant difference was found in terms of thromboembolic events (6 vs. 3; $P = 0.293$). Cardiac events occurred in three patients in the Thal–Dex group whereas no patients receiving ThaDD developed cardiotoxicity. However, in both group no patients died from the above mentioned side effects although they required thalidomide interruption in four (8.5%; two neurotoxicity and two vascular events) and in five (10.5%; four neurotoxicity, one vascular event) patients treated with ThaDD and Thal–Dex, respectively.

Survival

In the ThaDD group after a median follow-up of 27 months (range 6–46) 27 patients relapsed and 20 died while in the Thal–Dex group, after a median follow-up of 24 months (range 7–71), there were 47 relapses and 44 deaths.

Median PFS, EFS, and OS were 21, 21, and 35.5 months in the ThaDD group whereas they were 11.5, 11.5, and 20 months in the Thal–Dex group ($P = 0.0087$; $P = 0.0376$; $P = 0.0124$, respectively; Fig. 1A–C).

EFS at 2 yr resulted 44% in the ThaDD group and 23% in the Thal–Dex group ($P = 0.0376$; Fig. 1B).

Discussion

Thalidomide represents a greater progress in the treatment of multiple myeloma. After showing antimyeloma activity, thalidomide has proved to be very effective either as single agent and in combination with dexamethasone (4, 6–8). Recently, a randomized study in untreated MM patients demonstrated that thalidomide plus dexamethasone yields superior response rates compared with dexamethasone alone but toxicity is significantly greater with the combination (21). Several trials with chemotherapeutic agents added to thalidomide–dexamethasone reported promising results in patients with relapsed/refractory MM despite the high frequency of side effects mainly peripheral neuropathy, DVT, and infections (9–16). In a recent study including patients with advanced MM receiving the combination thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD) we obtained an ORR of 92% with a nCR rate of 32% and an EFS at 2 yr of 40% (17). Although toxicity has been not negligible, our results seemed superior to those reported with the combination thalidomide–dexamethasone. No studies have reported any comparison between the combination thalidomide–dexamethasone-chemotherapy and thalidomide–dexamethasone. To

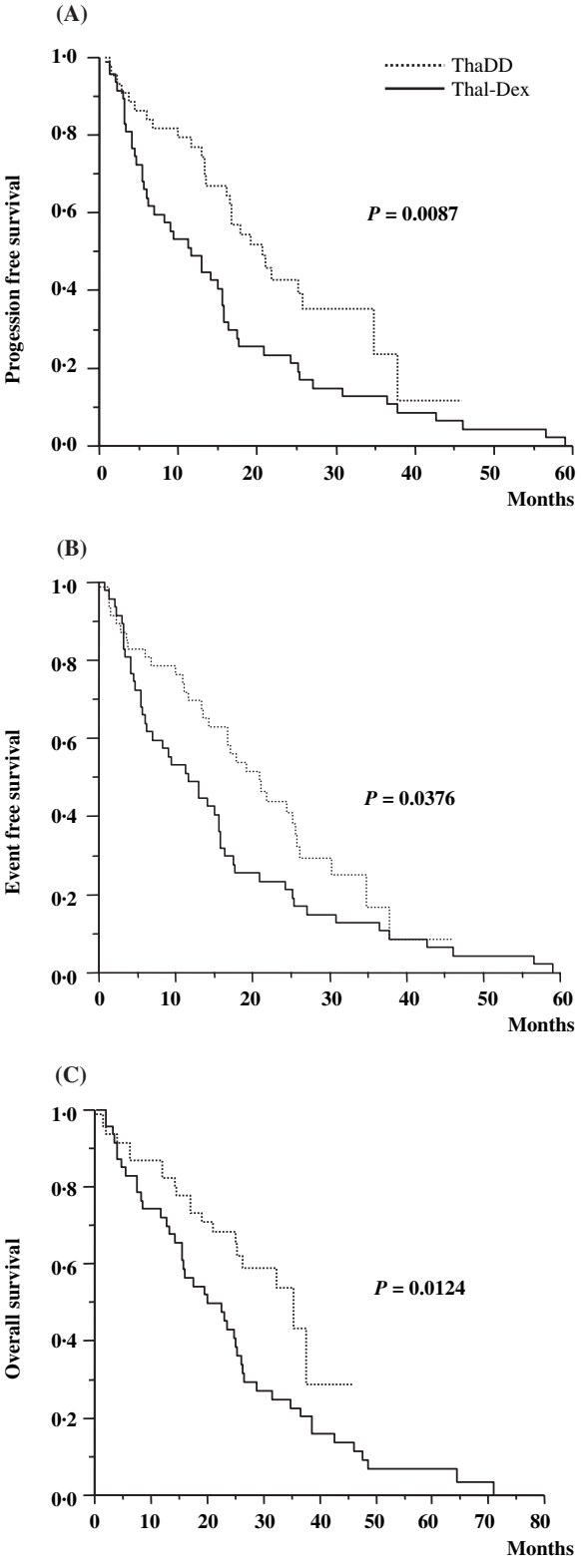

Figure 1 Progression free survival (A), event free survival (B) and overall survival (C) in patients treated with ThaDD (·····) or with Thal–Dex (——).

address this issue, we performed a retrospective study in which 47 patients with advanced MM who had received ThaDD regimen were compared with an equal number of pair mates treated with thalidomide–dexamethasone. ORR and particularly major response categories as VGPR and nCR were significantly higher with the ThaDD regimen. However, it has to be underlined that the dose of dexamethasone in the Thal–Dex group was half of that used in ThaDD one. Nevertheless, studies including relapsed/refractory MM patients treated with Thal–Dex combination in which dexamethasone was given at higher dose (400 mg or 340 mg every 28 d by Dimopoulos *et al.* (6) and Anagnostopoulos *et al.* (7), respectively), ORR rates (57% and 47%, respectively) and CR rates (0 and 13%, respectively) seem lower or similar to those showed in our Thal–Dex study group (ORR = 64% and CR = 10.5%). Moreover, Hussein *et al.* (16) reported results similar to ours (CR + VGPR = 45%) with a regimen including pegylated liposomal doxorubicin, vincristine, thalidomide, and low-dose dexamethasone. Therefore, the higher ORR and particularly CR rate obtained with ThaDD regimen cannot be easily be interpreted as being a reflection of the much increased intensity of dexamethasone administered. A CR + VGPR rate of 36% obtained with ThaDD regimen seems impressive in patients with relapsed refractory MM but this result is reproducible when similar therapeutic scheme is used (16). The 14 patients achieving CR did not result significantly different for the main prognostic characteristics from the 33 who did not although most of them had relapsed after autotransplant. In this setting, we obtained a CR rate of 42% with ThaDD vs. CR + nCR rate of 6% with Thal–Dex (data not shown).

The superiority of ThaDD in reducing tumor burden in comparison with thalidomide–dexamethasone translated into a significantly better PFS, EFS, and OS. Although with ThaDD regimen we obtain a doubling time of survival parameters compared with Thal–Dex, our results should be cautiously interpreted since the study is retrospective.

The non-hematologic toxicities observed after the ThaDD regimen, mainly neurotoxicity and thromboembolic events, were not superior to those of Thal–Dex. The combination thalidomide plus doxorubicin containing chemotherapy is associated with an increased risk of DVT. In our trial we used low-dose warfarin and the rate of DVT we observed was lower than that reported with the same combination in other trials (22) and not significantly higher than that of Thal–Dex. Although no antithrombotic prophylaxis was administered in the Thal–Dex group, vascular events occurred only in 6% of patients. However, this percentage is in agreement with those reported by other studies including patients with relapsed/refractory MM treating with Thal–Dex (6–8) while it results more and more higher in de novo MM patients receiving the same regimen without prophylaxis (23). That the reason why, at that time (1999), antithrombotic prophylaxis was not administered in those 47 patients with relapsed/refractory MM treated with Thal–Dex. At this time, this choice may be questionable as some authors suggest antithrombotic prophylaxis (e.g. aspirin) also in this group of patients.

Severe hematologic toxicity was seen in 28% of patients receiving ThaDD regimen while it was entirely negligible in Thal–Dex group. It mainly consisted of severe neutropenia (25%) although febrile neutropenia was uncommon. Therefore, infectious complications, despite more frequent in ThaDD regimen especially without antibiotic prophylaxis, did not cause fatal events. Moreover, the compliance to therapy and particularly to thalidomide was excellent in both study groups.

In patients with advanced MM the combination thalidomide, dexamethasone, and pegylated liposomal doxorubicin has been found to improve the overall response rate and the quality of response (≥VGPR) if compared with thalidomide–dexamethasone. This translated into a significantly better survival parameters such as PFS and OS. Despite patients receiving ThaDD developed a higher frequency of infections, these complications were prevented with the addition of adequate antibiotic prophylaxis and easily managed when occurred. No significantly differences between the two treatments were found with regard to non-hematologic toxicity, particularly vascular events.

The results in terms of response rates, improvement of outcome and tolerability obtained with ThaDD make this regimen a good candidate for comparison with other combinations in phase III studies.

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