Low-dose thalidomide with pegylated liposomal doxorubicin and high-dose dexamethasone for relapsed/refractory multiple myeloma: a prospective, multicenter, phase II study

Massimo Offidani
Laura Corvatta
Monica Marconi
Giuseppe Visani
Francesco Alesiani
Marino Brunori
Piero Galieni
Massimo Catarini
Maurizio Burattini
Riccardo Centurioni
Serena Rupoli
Anna Rita Scortechini
Luciano Giuliodori
Marco Candela
Debora Capelli
Mauro Montanari
Attilio Olivieri
Maria-Novella Piersantelli
Pietro Leoni

The aim of this prospective, multicenter, phase II study was to investigate the combination of pegylated liposomal doxorubicin (Caelyx®) 40 mg/m^2 on day 1 every 28 days, dexamethasone 40 mg p.o. on days 1-4 and 9-12 and thalidomide 100 mg daily in 50 patients with advanced multiple myeloma. Twenty-six percent of patients achieved a complete reponse, 6% a near complete response, 6% a very good partial response, 38% a partial response, 16% a minor response and 8% progressed, for an overall response rate of 92%. The median event-free survival was 17 months and the median overall survival was not reached. Grade 3 non-hematologic toxicity occurred in 12% of patients, thromboembolic disease in 12% and severe infection in 16%. The combination of pegylated liposomal doxorubicin, dexamethasone an thalidomide is safe and very effective in advanced multiple myeloma.

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From the Clinica di Ematologia Polo Ospedaliero-Universitario, Ospedali Riuniti Ancona Università Politecnica delle Marche (MO, LC, SR, ARS, DC, MM, AO, M-NP, PL); Divisione Medicina Fano (MM, MB); Divisione Ematologia Pesaro (GV); Unità di Oncoematologia San Severino Marche (FA); Divisione Ematologia Ascoli Piceno (PG); Divisione Medicina Macerata (MC); Divisione Medicina Jesi (MB); Divisione Medicina Civitanova Marche (RC); Servizio di Oncologia Fabriano (LG); Divisione Medicina Fabriano (MC).

Correspondence:
Massimo Offidani, Clinica di Ematologia Ospedali Riuniti Ancona Via Conca, 71, 60020 Ancona.
E-mail: m.offidani@ao-umbertoprimo.marche.it

Since 1999 thalidomide has been found to be effective in relapsed or refractory multiple myeloma (MM), administered as a single agent,[1] combined with dexamethasone[2-4] or added to chemotherapeutic agents such as cyclophosphamide,[5-8] etoposide,[9] melphalan[10] and pegylated liposomal doxorubicin.[11] This last drug has a longer half-life than standard doxorubicin and it is able to extravasate through abnormal bone marrow vessels, exposing malignant plasma cells for longer times to higher concentrations of the anthracycline and minimizing organ damage.[12] Combined with vincristine, dexamethasone and thalidomide, pegylated liposomal doxorubicin (DVd-T), was found to be very effective but toxic in relapsed/refractory MM.[11] We designed a VAD-like regimen in which vincristine was removed since its role in MM is not well established, conventional doxorubicin was replaced by a pegylated liposomal form of the compound (Caelyx®) and low-dose thalidomide was added with the aim of achieving a good response while minimizing protocol-related toxicity.

Design and Methods

Trial design and patients

From March 2003 to March 2005, 50 consecutive patients from 9 institutions were enrolled in this prospective, multicenter, phase II study. No patients were excluded on the basis of age, performance status (PS) or renal function whereas patients with other active cancer, uncontrolled infections, pre-existing peripheral neuropathy of grade ≥2, organs dysfunction of grade > 2 or psychiatric disorders were not eligible. The study was approved by the local Ethics Committee and all patients signed informed consent to their participation. Response and toxicity were defined according to the EBMT[13] and National Cancer Institute (NCI) criteria.

Treatment

Patients received intravenous Caelyx® 40 mg/m^2 on day 1 every 28 days, dexamethasone 40 mg p.o. on days 1-4 and 9-12, and thalidomide 100 mg each evening continuously. Thalidomide was supplied by a local pharmacy. Three courses of Caelyx® and dexamethasone were administered after which patients with a very good partial response (VGPR) or better received two more courses of therapy whereas those who had achieved a partial response (PR) or less were given three additional cycles. Supportive therapy consisted of warfarin 1.25 mg/day, vitamin B6, zoledronic acid, erythropoietin and hypoglycemic drugs or insulin if the blood glucose level was more than 180 mg/dL. Antibacterial prophylaxis was not initially given to patients; however because of the high incidence of respiratory infections noted 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; the dose of dexamethasone was reduced to 20 mg or discontinued in the case of ≥ grade 2 muscular toxicity. Occurrence of ≥ grade 3 neurotoxicity required discontinuation of thalidomide.

Statistical methods

The primary end-points of this study were response rate and toxicity while progression-free survival (PFS), event-free survival (EFS) and overall survival (OS) were secondary end-points. All curves were plotted according to the Kaplan-Meier method.

A p value < 0.05 was considered statistically significant. The Statistical Package for Social Sciences version 11.5 (SPSS, Chicago, IL, USA) was used for the statistical analyses.

Results and Discussion

Patients' characteristics

The baseline characteristics of the 50 patients are shown in Table 1. It should be highlighted that 44% of patients were over 70 years old, the performance score was ≥2 in 32%, 54% had received more than two chemotherapy regimens, 40% had undergone autotransplantation, 20% were classified as having refractory disease and 14% had impaired renal function.

Response to therapy

Thirteen (26%; 95% CI, 20-32%) out of 50 patients achieved a complete response (CR), three (6%; 95% CI, 3-9%) had a near complete response (nCR), three (6%; 95% CI, 3-9%) had a VGPR, nineteen (38%; 95% CI, 31-45%) had a PR and eight (16%; 95% CI, 11-21%) had a minor response (MR) resulting in an overall response rate of 92% . Four patients (8%; 95% CI, 4-12%) had progressive disease. The maximal response to treatment was achieved after a median of two cycles (range 1-4). Three patients died during treatment, one of tumor lysis syndrome, one of an arrhythmia that developed during a dialysis procedure and the third, suddenly, of unknown cause. Of note, among 20 patients who had relapsed after an autotransplant, ten (50%) achieved a CR, seven (35%) had a PR and three (15%) had a MR. Moreover, all six patients with extramedullary disease responded to therapy (2 CR, 1 nCR and 3 PR). Six out of seven patients with impaired renal function achieved an objective response (1 nCR, 3 PR and 2 MR) and three of them regained normal renal function whereas one patient progressed.

Survival

After a median follow-up of 12 months (range 2-27), 12 patients relapsed and 10 died (3 during treatment; 7 during follow-up, 6 because of disease progression and 1, in remission, from gastric hemorrhage). Three patients underwent autotransplantation and were censored at the time of transplant. The median progression-free, event-free and overall survivals were 22 months, 17 months and not reached, respectively. At 1 year, 79% of patients were alive, 61% were free of events, and 70% were progression-free (Figures 1A, B, C).

Compliance to therapy

Overall, we administered 200 cycles of the combination Caelyx®, dexamethasone and thalidomide (median 4; range 1-6). No patients had to stop the entire protocol because of adverse events. No patients discontinued or decreased the dose of Caelyx®. The dose of dexamethasone was decreased in four patients and one patient discontinued taking this drug because of muscle weakness. Two patients refused to continue thalidomide after the occurrence of a venous thromboembolic event; two stopped taking it because of toxicity (grade 3 tremors and grade 3 peripheral neuropathy).

Table 1. Baseline characteristics of the 50 patients.

Characteristics	*No of patients (%)*
Age (median, range)	68.5 (41-82)
≤70 years	28 (56)
> 70 years	22 (44)
> 75 years	8 (16)
Sex	
Male	28 (56)
Female	22 (44)
Myeloma type	
Ig G	31 (62)
Ig A	9 (18)
Light chain only	5 (10)
Non-secretory	5 (10)
Unfavorable cytogenetics/ assessable cytogenetics	8/26(31)
Stage	
I	2 (4)
II	2 (4)
III	46 (92)
International Staging System	
1	20 (40)
2	17 (34)
3	13 (26)
Performance Status	
≤1	34 (66)
2	9 (18)
≥3	7 (14)
Bone pain	34 (68)
Presence of plasmacytomas	6 (12)
Serum β2-microglobulin ≥3.5 mg/L	19 (38)
Serum C-reactive protein > 3 mg/dL	12 (24)
Serum albumin < 3.5 g/dL	18 (36)
Serum creatinine > 2 g/dL	7 (14)
Hemoglobin ≤11.5 g/dL	22 (44)
Platelet count ≤130×10^9/L	20 (40)
Bone plasmacytosis > 30%	34 (68)
Disease status	
Untested relapse	40 (80)
Refractory	10 (20)
Prior treatment lines	
≤2	23 (46)
> 2	27 (54)
Prior high-dose therapy	20 (40)
Disease history (months)	
Median (range)	32 (5-144)
> 60	13 (26)

Hematologic toxicity and infection

Neutropenia of any grade and grade 3/4 occurred in 50% and 16% of patients, respectively. We recognized 18 febrile episodes (occuring in 9% of the chemotherapy courses and in 36% of patients); these were ≥ grade 3 in 4% of courses (16% of patients). Most episodes (90%) developed in non-neutropenic patients following the first three cycles of chemotherapy (90%). However, during the first 32 cycles (8 patients) given without antibiotic prophylaxis we documented 10 infectious complications (31%) whereas in the subsequent 168 courses, during which we administered ciprofloxacin 250 mg twice daily, only 8 new episodes of infections (5%) occurred.

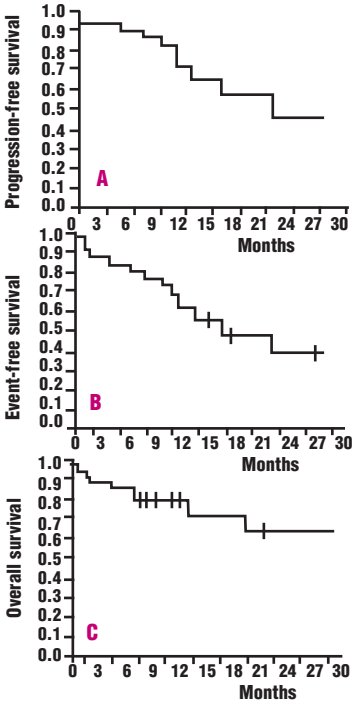

Figure 1. Median progression-free survival (A), event-free survival (B) and overall survival (C) were 22 months, 17 months and not reached, respectively

No patient experienced neutropenic sepsis, herpetic or other opportunistic infections and none died from infections. Thrombocytopenia occurred in 8% of patients but only in 2% it was grade ≥ 3.

Non-hematologic toxicity

Most side effects were mild or moderate (Table 2) but some patients experienced grade 3 adverse events, mainly attributable to thalidomide, such as fatigue, constipation, tremors and peripheral neuropathy, each of which occurred in one patient. Regarding toxicity attributable to pegylated liposomal doxorubicin, only one patient experienced grade 3 mucositis whereas other side effects such as alopecia, palmar-plantar erythrodysesthesia were always ≤ grade 2. Dexamethasone mainly caused moderate-severe muscle weakness (five patients). Venous thromboembolic events occurred in six patients (12%) but only one patient had clinical evidence of pulmonary embolism.

It is very arduous to make a decision on salvage therapy for patients who become refractory or relapse after standard therapy. Fortunately, besides alkylating agents and dexamethasone, the armamentarium for the treatment of advanced MM has been extended by the introduction of thalidomide. In patients with relapsed/refractory MM, thalidomide has been used as a single agent,[1] in combination with dexamethasone[2-4] or with chemotherapeutic compounds, mainly alkylating agents,[5-10] yielding remarkable results. At the end of 2002, we designed a VAD-like regimen comprising low-dose thalidomide instead of vincristine, pegylated liposomal doxorubicin instead of conventional doxorubicin and high-dose dexamethasone. The rationale of this regimen was based on the following assumptions: (i) the uncertain effectiveness of vincristine despite its considerable toxicity; (ii) the increased risk of neurotoxicity when vincristine is associated with thalidomide, limiting its long-term use; (iii) the demonstrated efficacy of thalidomide, especially in combination with dexamethasone and anthracyclines;[14] (iv) the better pharmacokinetic properties, antitumor activity and lesser toxicity of pegylated liposomal doxorubicin when compared with standard doxorubicin; (v) the possibility of administering this regimen on an outpatient basis with only once monthly admission to a day hospital. The overall response rate to this protocol exceeded 90% and most patients achieved their response within 2 months. Moreover, a ≥PR response rate of 76% and ≥VGPR of 38% in this population as well as a CR rate of over 50% in patients who relapsed after high-dose therapy are impressive results. Although each direct comparison should be interpreted with caution, these results are clearly better than those obtained with either VAD[15,16] or thalidomide-dexamethasone.[2-4] They are similar to those obtained by Hussein *et al.* with a regimen containing pegylated liposomal doxorubicin, vincristine, low-dose dexamethasone and thalidomide (DVd-T) although toxicity related to this treatment is quite prohibitive unless intensive supportive care is provided.[11] Our results are also comparable with those obtained with pegylated liposomal doxorubicin plus bortezomib[17] or lenalidomide[11] in phase I trials.

Thalidomide combined with chemotherapy usually produces good results but the different regimens cannot be considered equivalent to each other in terms of either activity (CR rates ranging from 2 to 17%) or toxicity.[5-9,11] Therefore, it is not yet known which is/are the better

Table 2. Non-hematologic toxicity.

	No. of patients (%)
Mucositis	3 (6)
Grade 2	2 (4)
Grade 3	1 (2)
Alopecia	21 (42)
Grade 1	14 (28)
Grade 2	7 (14)
Palmar-plantar erythrodysesthesia	
Grade 1	3 (6)
Rash	
Grade 1	5 (10)
Peripheral neuropathy	13 (26)
Grade < 3	12 (24)
Grade 3	1 (2)
Constipation	26 (52)
Grade < 3	25 (50)
Grade 3	1 (2)
Dizziness	
Grade ≤2	5 (10)
Somnolence	
Grade ≤2	10 (20)
Headache	
Grade 1	1 (2)
Mood changes	
Grade 1	2 (4)
Fatigue	25 (50)
Grade < 3	24 (48)
Grade 3	1 (2)
Confusion	
Grade 1	4 (8)
Tremors	9 (18)
Grade < 3	8 (16)
Grade 3	1 (2)
Muscular weakness	5 (10)
Grade 2	4 (8)
Grade 3	1 (2)
Venous thromboembolic disease	6 (12)
Deep vein thrombosis	5
Pulmonary embolism	1

agent/s or regimen/s to combine with thalidomide-dexamethasone in order to improve efficacy while minimizing the toxicity. Giving a lower dose of thalidomide we obtained a CR rate (26%) superior to that of other schedules containing higher dose of thalidomide, administered continuously[5,7-9,11] or intermittently.[6] Moreover, this result was also superior to that obtained using high-dose thalidomide combined with more than one chemotherapeutic agent.[9,11] Our results were achieved in an unselected group of patients with a high proportion over 70 years old (44%); no patients were excluded because of age,[5,8] performance status,[5,8] life expectancy[7] or renal function.[5,8] Although our protocol induced good responses in each subset of patients, the best results were achieved in patients who had relapsed after high-dose therapy. We, therefore, think that it could play a leading role in such patients. The compliance to the present protocol was very high since no patients were withdrawn from the study and only a few patients discontinued thalidomide or dexamethasone because of toxicity. This is likely due to the low dose of thalidomide administered and to the negligible toxicity of pegylated liposomal doxorubicin. Severe neurologic toxicity and other dose-dependent side effects attributable to thalidomide were negligible in our experience. Muscle weakness due to high-dose dexamethasone was troublesome and sometimes negatively influenced the patients' quality of life. With respect to hematologic toxicity, we observed severe neutropenia in less than 20% of patients and severe infectious complications in 16% of them. Both these percentages are close to the lowest rates reported by other authors (10-86% and 7-36%, respectively).[5-9,11] The introduction of antibiotic prophylaxis in the supportive care of our protocol led to significant reductions in the rate and severity of infections. Of note, our patients did not experience neutropenic sepsis, infections due to herpesvirus or opportunistic pathogens and none died from infections. Similar results were obtained in a study by Kyriakou *et al.,* although in that study, in contrast to ours, it was always necessary to administer G-CSF to prevent severe neutropenia.[8]

When thalidomide is combined with anthracyclines the risk of deep vein thrombosis increases, particularly in patients with *de novo* MM or with high tumor burden.[18] In our study the incidence of deep vein thrombosis was 12%, which is in the range reported for other similar studies (from 7 to 15%).[5-9,11] We observed only one case of pulmonary embolism and all thromboembolic episodes were successfully managed with usual anticoagulation therapy. Although prophylaxis with a low fixed dose of warfarin is widely used, this practice has recently been under discussion since low molecular weight heparin seems to be more effective.[19] Some authors have successfully used low-dose aspirin.[20] Our results and those in general could be improved by better definition of the mechanisms leading to deep vein thrombosis in this setting and by more intensive anticoagulation during the first courses of therapy. Our supportive care (anticoagulation, antimicrobial prophylaxis and erythropoietin) was quite similar to that used for patients treated with thalidomide-dexamethasone but a low amount of G-CSF. Nevertheless, it was very limited compared with that of other protocols including thalidomide-dexamethasone and chemotherapy.

In summary, our study demonstrates that low-dose thalidomide in combination with pegylated liposomal doxorubicin and high dose dexamethasone is a safe and very effective regimen for relapsed MM although adequate antibiotic and antithrombotic prophylaxis is mandatory. We belive that our regimen could be one of the best candidates for comparisons with other combinations in phase III studies.

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