Effectiveness of Combination Therapy with Thalidomide and Dexamethasone in Patients with Myeloma

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ABSTRACT:

BACKGROND:

Thalidomide is the first in the class of drugs as an immune modulatory drugs (IMiDs). In vitro data suggest that the drug and its metabolites may inhibit angiogenesis, in addition it may modulate adhesion molecules of myeloma cells and their surrounding stroma,.The combination of thalidomide plus dexamethasone is a feasible and active regimen in the treatment of multiple myeloma as It emerge an oral alternative to infusional chemotherapy with vincristine, doxorubicin ,dexamethasone currently used as pretransplantation induction therapy for myeloma.

OBJECTIVE:

To assess the efficacy ,response rate and safety using the combination of thalidomide-dexamehasone as front line therapy and in relapsed , refractory cases of myeloma

MATERIAL AND METHODS:

Between February 2008 up to January 2010, thirty five cases of multiple myeloma received a combination of Thalidomide and Dexamethasone for 4 cycles. Those patients had been followed and evaluated at National Centre of Hematology.All cases of myeloma were staged at diagnosis according to Durie – Salmon Staging system. Response based on criteria by Chronic Leukemia and Myeloma Task force (EBMT criteria) as complete response (CR), good partial response(GPR) and no response(NR) .

RESULTS:

After 4 cycles of therapy , 6(17%) patients achieved complete response,22(62.9%) patients achieved good partial response, 3(8.6%) patients with minimal response and 4 (11.4%) patients fail responded to treatment .Of those who failed treatment, three patients died two of them with heart failure and one with multi organ failure. Concerning the toxicity , The most common side effect was related to neurotoxcity in form of peripheral neuropathy and thromboembolic disease. Otherwise most of the remaining side effects were rated as mild to moderate

CONCLUSION:

Thal-Dex is an effective myeloma treatment in terms of response , easy to use as outpatient clinic and avoid complications related to line access or cardiac toxicity that related to other treatments.

***KEY WORD*:** thalidomid ,dexamethasone in myeloma.

INTRODUCTION:

Multiple myeloma is a plasma cell malignancy that remains incurable with current treatment approaches including high-dose therapy and autologous stem cell transplantation. Thalidomide represents a major advance in the treatment of this disorder, having demonstrated significant activity in all phases of the disease. Corticosteroids have formed the mainstay of myeloma therapy for decades along with the alkylating agents and have demonstrated synergy when used in combination with thalidomide[(1)].

The Salmon-Durie staging system has been used for years ,it relates to myeloma cell mass , extent of bony disease, hemoglobin and calcium levels, and the monoclonal immunoglobulin levels in serum and urine [(2)]

Thalidomide are known to cause peripheral neuropathy in more than a third of patients. The neuropathy associated with thalidomide is an irreversible small-fiber peripheral neuropathy

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that appears to be both time- and dose-dependent[3],in addition to other toxicities associated with thalidomide include fetal malformations, constipation, weakness or fatigue, somnolence, skin problems, there is also an increased risk of thrombosis in patients treated with thalidomide, which appears to be exacerbated by the use of concurrent combination chemotherapy [4,5].

In a randomized study, the combination of thalidomide-dexamethasone increased partial response (PR) rate and 2-year event-free survival when compared with dexamethasone alone without marked survival differences were reported[6] and it was superior in comparison with standard vincristin adriamycine,dexamerhasone(VAD), but with higher rates of deep-vein thrombosis (15%) were reported[7]

Thalidomide-dexamethasone reduced the mean duration of hospitalization before stem cell collection without any negative impact on the amount of stem cell harvest[8]

PATEINTS AND METHODS:

The study was conducted between February 2008 up to January 2010, during this period 35 cases of multiple myeloma were recruited .These patients received Thalidomide(Starting dose of 200 mg/day with increasing dose until maximum tolerable dose) plus dexamethasone in dose of 40 mg/day on days 1 to 4 , 9 to12 and 17 to 20 for 28 days for 4 cycles followed by maintaining these patients with thalidomide (100-200 mg /day).

Patients were evaluated at National Centre of Hematology to assess efficacy of Tha-Dex. regimen for treatment of myeloma. From these 35 patients 20 patients were considered to upfront treatment with Thal-Dexa and 15 other patients were pretreated previously by other regimen like(vincristine, adriamycin, dexamethasone(VAD)or melphalan ,predneslone (MP),whom they are either not responded or refractory myeloma.

The diagnosis of these patients were issued according to the international Myeloma Working Group to diagnose myeloma with one major +one minor or 3 minor criteria:

Staging of these patients was according to Durie – Salmon Staging system(2).

All patients underwent baseline evaluation include history and physical examination, blood count , serum protein electrophoresis, serum Immunoglobulin assay and urine for Bence Jones Protein. The following biochemistry data were recorded :- serum creatinin level , serum calcium level , liver function test , lactate dehydrogenase (LDH) and C-reactive protein (CRP) level. Base line bone marrow aspirate and biopsy was performed as well as skeletal survey and nerve conduction study. Full blood count and basic biochemistry were repeated every 2 weeks up to 24 weeks ,and then every 4 weeks during treatment. Bone morrow aspirate and biopsy was done at the end of induction phase to assess degree of response. Nerve conductive study was performed during follow up and repeated every 3 months for any evidence of neurotoxcity especially to patients who they are symptomatic. Patients receiving at least one cycle of chemo therapy were considered evaluable for response and toxicity assessment.

Response in these patients was assessed by response criteria , based on those of the Chronic LeuKemia and Myeloma Task force
(EBMT criteria).

All data of toxicities were available for these patients. Both mild(grades 1 and 2) and severe(grades 3 and 4) side effects were recorded according to common toxicity criteria (CTC).Overall survival was calculated from the inclusion time point to death while progression free survival was calculated from time of complete remission to the time of disease progression or death. survival data have presented by Kaplan Meir method

RESULTS:

Thirty five patients with M.M were enrolled in this study and there were 22 men and 13 women, with a median age(59 years) .The median duration of follow up from commencement of treatment to the close out data was 18 months (range 6- 20 months).

Characteristics of patients at study entry are shown in table (1).

Table 1: Shows characteristics of 35 patients treated with combination of Thalidomide-Dexamethasone.

Age(range)	(40-80)
Male: female ratio	1.6:1
Median duration of follow up	18 months
No. of patient treated as front line	20(57.1%)
No of patient previously treated	15(42.9%)
Durie – Salmon Stage I	0
Stage II	20(57.1%)
Stage III	15(42.9%)

The overall response rate for naïve and pretreated patients was 88.5% (complete, partial and minimal response) after 4 cycle of therapy which was significantly better for those treated with combination thalidomide-dexamehtasone as front line therapy(95%) than patient previously treated(80.2%) (p –value < 0.00001).

Generally complete remission was in 17% patients, very good partial response in 62.9%,and minimal response in 11.4% of patients.

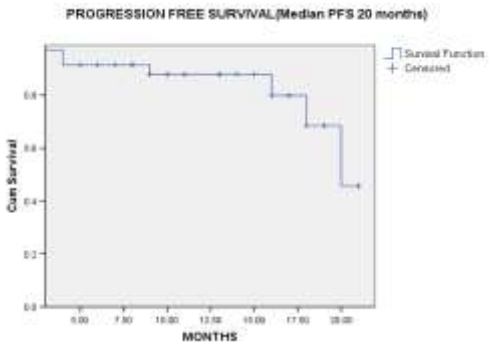
Four patient 4 (11.4%) in this study considered non responder , one of them with frontline therapy other three were pretreated(table 2).

Table 2: Demonstrate type of response after four cycles therapy.

Type of therapy	Frontline therapy	Pretreated	Total %
Complete response CR	4(20%)	2(13.3%)	6(17%)
Very good partial response VGPR	14(70%)	8(53.3%)	22(62.9%)
Minimal response MR	1 (5%)	2(13.3%)	3(8.6%)
No response NR	1 (5%)	3(20%)	4(11.4%)
Total	20 (100%)	15(100%)	35(100%)

The mean duration of remission was12.1 months (minimum 2 months) (maximum 21 months)

The time of progression free survival for all patients were (20 months) (figure I)



FigureI: Overall progression free survival for 35 patients(those with newly diagnosed and pretreated patients)

During treatment 3 deaths occurred, 2(5.7%) with heart failure and one (2.8%)with multi organ failure with overall 2 years survival of these patients was 80%(figure II).

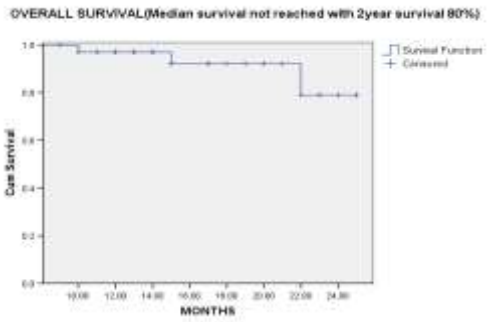


Figure II: Overall survival for 35 myeloma patients treated with Thalidomide-Dexamehasone.

Toxicity assessment in these cases were performed every 4 weeks. The hematological side effects were uncommon with mild anemia and thrombocytopenia (Grade 1) had occur in two patients (5.7%) .Non hematological toxicity with constipation , somnolence , were frequent adverse effects, however, it rated as mild to moderate . Neuropathy was the most common adverse events was documented with(Grade 3) in 7(20%) patients .

Venous thrombotic disease occur in 4(11.4%) patients with three patients had DVT and one (2.8%) had cerebrovenous thrombosis .DVT was documented by Doppler Ultrasound and more frequently developed in the lower extremities with median time of evolving was (2 months) from starting thal-Dex .Anticoogulation therapy consisting of low – molecular weight heparin with or without warfarin was started after the diagnosis of deep vein thrombosis(DVT) was established .

Infection developed in 10(28.5%) patients despite they are non neutropenic ,following the first 3 cycles .No patient experienced serious or opportunistic infections and nobody died due to infections (table 4).

Table 4: Non hematological toxicities according to National Cancer Institute that occurred with combination therapy in those with newly and previously treated by other therapy.

Toxicity	Grade 1 and 2 %	Grade 3 and %	Grade 4 and %
Peripheral neuropatly	10(28.5%)	7(20%)	0
Constipation	9(25.7%)	0	0
Somnolence	6(17.1%)	0	0
Fatigue	10(28.5%)	2(5.7%)	0
Muscular weakness	0	1(2.8%)	0
thromboembolic diseuse	0	3(8.5%)	1(2.8%)
Hypertension	3(8.5%)	0	0
Infection	10(28.5%)	0	0

DISCUSSION:

The combination of thalidomide and dexamethasone has demonstrated remarkable activity in the treatment of both newly diagnosed as well as relapsed myeloma [(1)] and this is reflected with high response rate which was better for naïve than pretreated patients

The efficiency of this combination supported by a report of *Alexian R.et al,* among patients with resistant or relapsing disease treated with a combination of thalidomide and dexamethasone, 47% of patients achieved remission with significant prolongation of survival for responsive patients[(1)],and in those with newly diagnosed myeloma overall response of approximately 40-75%[(1,9,10,11,12)] have been seen with this combination.

Because of high response rate of thalidomide and ease of administration, and using only as oral medications ,without needs of hospitalization, superiority of response, may

make this treatment preferable in comparison with the use of the other frontline therapy such as VAD (as with some pretreated patient in our study) ,with inconvenience of a 4-day continuous infusion via an indwelling central line, the risk of catheter-related complications (eg, infections and thrombosis), and toxicity particularly cardiac, which may preclude patients' eligibility to subsequently receive stem-cell–supported high-dose therapy. However, the risk of thrombosis and other side effects may make the combination of thalidomide and dexamethasone less convenient.

Cavo et al. [13] performed case matching to compare patients treated with thalidomide/dexamethasone (TD) or VAD, there was higher induction response rates were seen (76 vs. 52%). Toxicity profiles were different, with more myelosuppression in the VAD-treated patients, but DVT was more common in the TD patients.

Nonetheless ,despite (28.6%)of our study group more than 60 years and 25.7% more than 70 years, two thirds of older patients achieve stabilization of disease and tolerate treatment albeit for a short time. We believe this information enhances our ability to plan management for patients who they are old or fragile and not tolerate high dose chemotherapy and transplant or who they are failed more standard therapy. However because toxicity of TD may made this treatment unsuitable for elderly patients as shown by *Ludwig et al*. who randomized 350 elderly patients to either thalidomide -dexamethasone or melphalan and prednisone. Preliminary data demonstrate a higher response rate using TD (52 vs. 35%, $p < .05$), but higher rates of neuropathy (25 vs. 8%), psychological problem (20 vs. 8%), skin toxicity (12 vs. 3%), and thrombotic events (8 vs. 3%) while the only toxicity more commonly seen in the MP arm was myelosuppression. Because of this high toxicity rates it does not recommend TD as induction for elderly patients who are not destined for peripheral blood stem cell collection[14],so these patients may benefit from treatment with combination of melphalan, prednisone, and thalidomide (MPT) which is quite promising in elderly patients who are non haemopoitic stem cell transplant candidates. [15]

Good response reflected by high complete remission and very good partial remission(VGPR) with median duration of remission 12 months, which reflected to better progression free survival (20 months) and overall survival 80%within 2 years. This similarly seen with study by *Dingli et al* where 5% of the patient achieved a complete response, and 43% had a partial response with median overall survival and time to progression were 21 months and 18 months, respectively[9].

Thrombotic complications complicated the course of treatment in 4(11.4%) patients , which was nonfatal and in only one patient with DVT mandate treatment discontinuation; in the remaining patients thalidomide was safely continued once full anticoagulation with low–molecular weight heparin, and warfarin was introduced.This increase incidence of hypercoaguble state may related to elevated coagulation factors in myeloma itself rather than to thalidomide therapy with variable increase incidence of DVT from 10% of treated patients(16) up to 28% with the study by *Maurizio etal* ,with all episodes of DVT occurred mainly during the first 3 cycles of induction(17).

In summary, The combination of thalidomide plus dexamethasone is a feasible and effective treatment of multiple myeloma, even as a current treatment of elderly patients without much increase incidence of serious toxicity .The increased risk of thrombosis and irreversible peripheral neuropathy associated with the use of this regimen may raise points of close monitoring in patients with MM treated with this combination .

REFERENCE:

1. Kumar S**,** Rajkumar SV. Thalidomide and dexamethasone: therapy for multiple myeloma. Expert Rev Anticancer Ther. 2005;5:759-66.
2. Rajkumar SV. Current status of thalidomide in the treatment of cancer. Oncology 2001:867–74.
3. Durie BG, Salmon SE: A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 1975;36:842 [PMID: 1182674].

4. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001;98:1614–15.
5. Osman K, Comenzo R and Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 2001;344:1951–52.
6. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR et al.Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial co-ordinated by the Eastern Co-operative Oncology Group. J Clin Oncol 2006;24:431-36.
7. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini Det al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood. 2005;106:35-39.
8. Macro M, Divine M, Uzunhan Y, Jaccard A, Bouscary D,Leblond V et al. Dexamethasone+Thalidomide (Dex/Thal) Compared to VAD as a Pre-Transplant Treatment in Newly Diagnosed Multiple Myeloma (MM): A Randomized Trial.
9. Blood 2006;108:57a[abstract].
10. Dingli D, Rajkumar SV, Nowakowski GS. Combination therapy with thalidomide and dexamethasone in patients with newly diagnosed multiple myeloma not undergoing upfront autologous stem cell transplantation: a phase II trial.
11. Haematologica. 2005 ;90:1650-4.
12. Weber D, Rankin K, Gavino M, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003;21:16–19.
13. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 2002;20:4319–23.
14. Rajkumar SV, Hussein M, Catalano J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of thalidomide plus dexamethasone versus dexamethasone alone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol (Meeting Abstr) 2006;24:7517.
15. Cavo M, Zamagni E, Tosi P, et al. Superior complete remission/very good partial remission rate with peri-transplant administration of thalidomide-dexamethasone for newly diagnosed multiple myeloma. Blood 2005:[5474].
16. Ludwig H, Drach J, Tothova E, et al. Thalidomide-dexamethasone versus melphalan-prednisolone as first line treatment in elderly patients with multiple myeloma: an interim analysis. Session type: oral session. 2005:782.
17. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825–31.
18. Barlogie B, Jagannath S, Desikan KR, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood. 1999;93:55-65.
19. Maurizio Zangari, Elias Anaissie. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy.blood 2001;98:1614-15.