

**Toxicity profile of thal-dex regime in patients with multiple myeloma****Dawnji S. R.<sup>1</sup>, Reeja R.<sup>2\*</sup>, Rakesh Praveen Raj M. R.<sup>3</sup>**<sup>1</sup>Department of Pharmacology,  
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medium, provided the original  
work is properly cited.**ABSTRACT****Background:** To study the spectrum, incidence and severity of toxicity among Multiple Myeloma patients receiving Thal-Dex in South Indian population.**Methods:** Between November 2005 and November 2005, 25 adult patients with previously- untreated Multiple Myeloma were assigned to receive Thal-Dex at Regional Cancer Centre, Trivandrum. During chemotherapy, patients were followed-up to detect the development of any toxicity symptoms. The toxicities recorded, were graded according to the criteria of the World Health Organization toxicity-guidelines.**Results:** In the 25 patients who received Thal-Dex, peripheral neuropathy, infection and constipation were significantly seen, while gastrointestinal toxicities were seen to a lesser extent, and haematological toxicities were low.**Conclusions:** The Thal-Dex regimen was tolerated well by majority of the patients and showed favourable toxicity profile, reiterating its acceptability as a front line antimyeloma regimen.**Keywords:** Dexamethasone, Multiple myeloma, Thal-Dex toxicity, Thalidomide**INTRODUCTION**

Multiple myeloma is a neoplastic disease of B- cell lineage causing abnormal proliferation of plasma cells.<sup>1</sup> Multiple myeloma accounts for 10% of all haematological malignancies and 1% of all malignancies.

The standard treatment of myeloma includes conventional chemotherapy, high dose chemotherapy and autologous stem cell transplant. The chemotherapy regimens commonly used in Multiple myeloma include VAD, MP, EP and Thal-Dex. The 1950's ushered in the advent of chemotherapy for Multiple Myeloma with the use of alkylating agents like Melphalan and Cyclophosphamide.<sup>2</sup> Further studies helped in the

development of combination chemotherapy with Melphalan and Prednisolone. This turned out to be the first successful chemotherapy for Multiple Myeloma offering 50% response rate and median survival of 2-3 years.<sup>3</sup>

A new chemotherapeutic regimen-VAD, was developed in the 1980's by Alexanian and colleagues from MD Anderson Hospital in Texas. Vincristine and Adriamycin given as continuous infusion over 4 days with high dose Dexamethasone resulted in a rapid and high response rate, and a median duration of remission of 18 months. A particular advantage noted over other regimens was its utility in patients with renal failure, as a preparation for autologous stem cell transplantation.<sup>4</sup>

Recently, Thalidomide was introduced in the armamentarium against Multiple Myeloma. It was initially used in refractory cases but is now considered as a standard therapy for Multiple Myeloma. Thalidomide as an angiogenesis inhibitor, was first reported by D' Amalo et al in, and used as an antimyeloma agent by Barlogue and colleagues.

Our study focuses on the toxicity profile of Thal-Dex in South Indian population.

The objective of the study was to study the spectrum of toxicities due to chemotherapy with Thal-Dex regime in patients newly-diagnosed with Hodgkin's disease. To study the incidence and the severity of these toxicities by grading them according to WHO guidelines.

## METHODS

This was a prospective unicentric clinical study conducted at the Dept. of Medical Oncology, Regional Cancer Centre, Trivandrum, from November 2005 to November 2006. Patients with newly diagnosed Multiple Myeloma, aged more than 21 years and planned for Thal-Dex regimen were included in the study after obtaining institutional ethics committee approval. After informed consent, a detailed history-taking and clinical examination was performed to assess the extent of disease. Base line laboratory investigations prior to therapy were performed and recorded. The battery of baseline investigations included complete blood count, routine blood biochemistry tests, serum and 24-hour urine electrophoresis, serum Immunoglobulin, beta2 macroglobulin, C-reactive protein, ECHO, complete neurological evaluation etc. All these tests were repeated before each cycle of chemotherapy. X-ray, skeletal survey and bone marrow aspiration were repeated after 6 months of treatment.

Chemotherapy was administered according to the following schedule

Thal-Dex regimen: Thalidomide is started in low doses of 50 mg/day and the dose is increased up to 400-800mg/day depending on patients' tolerability. It is given orally daily throughout the cycle. Dexamethasone-40mg OD orally 1-4, 9-12, 17-20 days in a month, for a total period of 6 months.

Taking into account that the combination of Thalidomide and Dexamethasone is accompanied by increased incidence of DVT, concomitant daily administration of Aspirin 75 mg was given to all patients. Administration of Bisphosphonates was allowed in this regimen. During the course of chemotherapy regimen patients were assessed to detect the development of any adverse drug reactions/ toxicity symptoms. Laboratory test done during the course were reviewed for any abnormality. After recording toxicity, they were graded according to WHO guidelines. The common toxicities looked for in this study were haematological, gastrointestinal, neurological, respiratory, cardiovascular, renal, dermatological, endocrine and infections.

## RESULTS

Twenty-five patients with newly diagnosed multiple myeloma with a median age of 54 years were enrolled in the study, from November 2005 to November 2006. These patients were scheduled to receive Thal-Dex protocol. All patients received Aspirin 75 mg daily and Zoledronic acid 4 mg i/v infusion monthly. The baseline characteristics of 25 patients are shown in Table 1.

The treatment plan used according to the clinical assessment is shown in Table 2. Haematological and non-haematological toxicities are listed in Table 3.

**Table 1: Characteristics of 25 patients with multiple Myeloma.**

Age (Years)	Laboratory parameters			
<b>Range: 27-68</b>				
Median: 54		<b>Median</b>	<b>(Range)</b>	
<b>Sex</b>				
Male	15	Hb(g/dl)	10gm (6-12)	
Female	10	TC cell/mm <sup>3</sup>	7000 (4000-11000)	
<b>Performance status</b>	<b>No. (%)</b>	PL cells/mm <sup>3</sup>	190000 (75000-4 lakh)	
0	1 (4)	RBS (mg%)	110(80-120)	
1	10 (40)		<b>Normal</b>	<b>Increased</b>
2	9 (36)	RFT	20	5
3	3 (12)	LFT	19	6
4	2 (8)	CRP (done 26)	11	4
<b>Myeloma stage (Durie-Salmon)</b>	<b>No. (%)</b>	$\beta_2$ M (done 30)	11	9
Stage-1	1 (4)			
Stage-2	11 (44)	A/G reversal (present 6, absent 19)		
Stage-3	13 (52)			

**Table 2. Treatment Plan with Thal-Dex.**

No. of Patients	6 cycles	3 cycles	<3 cycles	Radiotherapy?	
				Yes	No
Thal-Dex (25)	22	1	2	7	18

**Table 3. Toxicity profile of 25 patients with Multiple Myeloma on Thal-Dex.**

Toxicity profile	Number of patients
<b>Haematology</b>	
Anaemia	15
Leucopenia	2
Thrombocytopenia	2
<b>Gastrointestinal</b>	
Gastritis	19
Constipation	22
Anorexia	3
Nausea	0
Vomiting	0
Stomatitis	03
Foreign body sensation in throat	3
<b>Endocrine</b>	
Hyperglycemia	10
<b>Central Nervous System</b>	
Peripheral neuropathy	15
<b>Dermatology</b>	
Alopecia	0
Pigmentation	0
Oedema	10
<b>Infections</b>	
Deep Vein Thrombosis	0
<b>Hypothyroidism</b>	
Acute Renal Failure	1

## DISCUSSION

The aim of treatment in Multiple myeloma with first-line chemotherapeutic regimens is primarily to achieve high response rate and early reduction of tumour burden, that too, with the least possible toxicity to bone marrow stem cells, since HDT and ASCT in eligible patients is by now the only therapeutic strategy that prolongs overall survival.<sup>4,5</sup> Regimens like VAD, VAD-like regimen, proteasome inhibitors, have replaced MP in the last few decades and have been widely accepted as first line treatment in Multiple myeloma, inducing early objective responses in 55-67% of patients.<sup>6,7</sup> Recently the combination of Thalidomide and Dexamethasone has been proposed as the new initial therapy in Multiple Myeloma.<sup>8</sup> Thal-dex has proved effective in previous studies, yielding response rate of 63-72%, and rapid onset of remission in newly diagnosed Multiple myeloma patients.<sup>9,10</sup> Moreover, Cavo et al in a retrospective matched case control analysis claimed that Thal-Dex is superior to VAD as primary treatment in preparation for ASCT in terms of response rate and myeloma cell mass

reduction and equally as effective as VAD in terms of stem cell collection.<sup>11</sup>

In general, the side-effects of any chemotherapy regimen, limit the effectiveness of therapy substantially. All investigators seek new modalities or combinations that can produce a high response whilst reducing the incidence and severity of side effects. In our study, toxic manifestations of Thal-Dex regimen were, in general, tolerated well and mostly were reversible.

Most of the patients in the present study have a performance status of Grade-1 at presentation. Two patients on Thal-Dex regimen showed worsening of performance status due to progression of the disease. Haematological toxicities were well tolerated, never requiring temporary withdrawal of therapy. Anaemia was the most common haematological toxicity observed. During chemotherapy, most patients had Grade-1 (15 patients) in every cycle, Grade-4 was the maximum toxicity in only 3 patients and required blood transfusion. Leucopenia and thrombocytopenia were not major toxicity issues in this study (>Grade-2=0).

The most common metabolic derangement observed was hyperglycaemia. During therapy 10 patients developed hyperglycaemia (>Grade-2 = 6 patients). All required antidiabetic therapy.

Unlike other chemotherapy regimens, gastrointestinal toxicities were not distressing to patients. The most common GIT toxicities encountered in Thal-Dex were gastritis and constipation. Out of the 25 patients, 20 patients developed gastritis (Grade-1), 20 patients developed constipation. None of the patients progressed beyond Grade-2 toxicity. There was no nausea or vomiting, only three patients had anorexia. Two patients had grade-1 stomatitis. Three patients complained of foreign-body sensation throat.

Regarding pulmonary toxicity 5 patients developed upper respiratory tract infection. Four patients developed pneumonia. Minor toxicities like cough and dyspnoea, were noticed in 6 patients.

No cardiac abnormality was noted in Thal-Dex regimen. There were no cases of alopecia too.

Neurotoxicity was observed in Thal-Dex regimen. Out of 25 patients on Thal-Dex regime n 12 developed Grade-1 and 2 developed Grade-2 sensory involvement. Thal-Dex showed development of peripheral neuropathy even in non-diabetics. After the fifth cycle, one patient developed foot-drop.

Dermatological toxicities were almost absent on Thal-Dex regimen except one patient who developed maculopapular drug eruption all over the body after the first cycle and was managed with temporary stoppage of drug followed by gradually increasing the dose. Oedema

was noticed in 10 patients, 9 with grade-1, and one patient with grade-4. Six patients developed fever (Grade-1). Myalgia and muscle cramps were the minor complaints in this regimen. Ten patients developed grade-1 infection.

Various clinical trials on Multiple myeloma patients treated with Thalidomide at doses ranging from 50-800 mg/day had shown that the most common side effects were sedation (6%-77%), fatigue (27%-67%), constipation (18%-86%), dizziness (4%-28%), dry skin/rash (3%-35%), leucopenia (2%-26%) and peripheral neuropathy (9%-24%).<sup>12</sup> In our study Thal-Dex regimen showed sedation (28%), fatigue (36%), constipation (80%), dizziness (12%), dry skin (36%), and peripheral neuropathy (40%).

One patient developed jaundice and altered liver function in this regimen.

Renal function was satisfactory in all patients except in one who developed acute renal failure after fifth cycle of Thal-Dex and required haemodialysis.

Various studies have shown that Thalidomide depressed the activity of thyroid gland and hypothyroidism has been reported.<sup>13</sup> However in our study thyroid function abnormalities was not reported. Two patients, who were already on treatment for hypothyroidism and were given Thal-Dex regimen, did not show any alteration in thyroid function tests during study period.

In Phase-III Eastern Co-operative Oncology group study of Thal-Dex regimen, 18% patient developed Grade-3 Deep Vein Thrombosis.<sup>14</sup> In our study, none developed Deep Vein Thrombosis. However, all patients in our study were on a daily dose of Aspirin.

In our study one death, due to progression of disease, occurred while on this regime.

## CONCLUSION

Thal-Dex is an effective antimyeloma agent with favorable toxicity profile. Thal-Dex may be considered an effective and relatively well tolerated oral alternative to the more complex VAD regimen as front line therapy for multiple myeloma patients who are candidates for autologous transplantation. Over all, Thalidomide is a very safe drug and relatively high doses can be given for a long duration without any significant side-effects. However, the survival of patients on these regimens could not be assessed and this has to be determined by doing a prolonged period of study. A drawback of this study is the small number of patients studied. By increasing the number of patients and the duration of the study, the toxicity profile and survival can be assessed more.

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