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CONTENTS

Original Article

Long term use of thalidomide: Safe and effective

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Abstract

PURPOSE: To assess the efficacy and safety of high dose thalidomide therapy for longer duration of time in relapsed or refractory Multiple Myeloma (MM) patients. **MATERIALS AND METHODS:** Twelve relapsed/refractory MM patients (7 Males, 5 Females), who received thalidomide for more than 2 years were selected from the Out Patient Department of Institute Rotary Cancer Hospital (IRCH), AIIMS, India. Patients received thalidomide beginning at a dose of 200 mg/day with fortnightly increment to a maximum dose of 800 mg/day. Patients were assessed for response on the basis of M proteins (MP), bone marrow biopsy with touch preparation and skeletal X-rays. **RESULTS:** Nine patients tolerated a maximum dose of 800 mg/day whereas three patients were given 600 mg/day. All patients showed ≥ 25-50% decline in serum /urine M proteins. Complete response/ near complete response was seen in 50%, partial response in 17% and minimal response (SD) in 34% patients. Median duration of thalidomide therapy was 47 months (range 29-60 months). Currently 11 patients are alive. **TOXICITY:** Varying degree of constipation and sedation were seen universally. One patient had DVT, which responded to anti-coagulant therapy. Other toxic effects included infections, skin reactions. There was no toxic death. **CONCLUSION:** long-term use of thalidomide is safe, effective and feasible. We feel that this is one of few reports describing safety and efficacy of long-term thalidomide in relapsed and refractory MM.

Key words: Multiple myeloma, relapse, thalidomide

Introduction

Multiple myeloma (MM) accounts for 1% of all malignancies and 10% of malignant hematological neoplasm.[1] Till date no curative treatment has been found and the median survival with standard therapy is approximately three to four years.[2,3] Prognosis of relapsed patients is worse. Thalidomide has emerged as one of the important drug for the treatment of MM in relapsed and first line therapy. In fact, thalidomide is the first new effective drug in the treatment of MM. Even though enough data is available on short term use and toxicity of thalidomide reports describing its efficacy and toxicity over long-term use are not available. We know that MM is not curative and some form of maintenance therapy is often used. Available options for this kind of treatment are interferon, steroids, alkylating agents. It is not clearly known whether use of thalidomide as a maintenance therapy in myeloma is effective. At our center, thalidomide is being used since year 2000. This report describes efficacy and safety of long-term use of thalidomide in relapsed/ refractory myeloma patients.

Materials and Methods

Patients were selected from a cohort of MM patients on thalidomide. Patients were started on thalidomide after relapse or refractoriness to initial therapy. Patients who were using thalidomide for more than two years and who have received 600 or higher dose for at least two months were included in this study. Response assessment has been done as per standard criteria. For dosage of thalidomide the method of Singhal *et al* was followed.[4] Patients were started on thalidomide at a dose of 200 mg/day with fortnightly increments of 200 mg to a maximum tolerated dose of 800 mg/day.

Table 1: Characteristics of patients and Thalidomide therapy

No.	Age/sex	Initial therapy	Max dose and duration in months	Current dose mg.	Total duration in months	Current status
1	55F	VAD	800x1	100	49	CR
2	56F	PBSCT	800x2	100	54	CR
3	42M	VAD	800x5	100	48	CR
4	69M	VAD	800x1	200	41	SD
5	61M	VMCP	800x9	200	47	SD
6	65M	VAD	800x4	100	36.5	CR
7	41M	PBSCT	800x12	100	54.5	CR
8	56F	VMCP	800x3	0	29	DIED
9	61F	VMCP	600x15	100	42	CR
10	55M	VMCP	800x4	200	39.5	SD
11	57F	PBSCT	600x3	200	60	PR
12	74M	MP	600x27	600	48.5	PD

Ethical clearance was taken from the Institute ethical committee. An informed consent (according to WHO guidelines) was obtained from patients before initiating therapy.

Results

Twelve patients fulfilled the criteria for inclusion in this study. Seven were males; median age was 55 years (range 41-74 years). Stage at the time of initial presentation was IIIA in nine patients and III B in remaining three. Initial treatment was PBSCT in three patients, VAD in five patients and oral alkylating based therapy in four patients. Maximum dose received was 800 mg in nine patients for period of 1- 12 (median 4.5) months and remaining received 600 mg for a period of 3-27 months (median 10). Patient's characteristics, frontline therapy and total duration of thalidomide has been shown in Table 1. Thereafter the dose of thalidomide has been reduced in a planned way to minimum required dose to maintain the best response [Table 2]. Median duration at 400 mg dose was 14 months (range 1-27). Median duration of thalidomide therapy was 47 months (range 29-60 months). Best responses achieved with thalidomide were: CR/ nCR (50%), VGPR (17%) and SD (34%). Currently six patients in CR/ nCR are maintaining their response with 100 mg dose and another four (Stable disease/ PR) with 200 mg daily dose of thalidomide [Table 3].

Side effects: Constipation and mild neuropathy were seen in all patients requiring use of laxative and high dose of pyridoxine. One patient had an episode of DVT requiring anti coagulant therapy. Table 4 is showing worst grade of toxicity seen in this group. Dry skin, dry mouth and ankle edema were seen in 6 patients.

Table 2: Duration of thalidomide therapy (n=12)

Duration (months)	Number of patients
>12	12
>24	11
>36	11
>48	5
>60	1

Table 3: Outcome in patients after Thalidomide therapy

Outcome	Number of patients
Maintaining CR/ nCR	06
Maintaining VGPR	01
Maintaining stable disease	03
Progression	01
Death and PD	01

Table 4: Worst grades of Toxicity observed - CTC version 2.0

Grade	Constipation	Sedation	Neuropathy	DVT	Infection
I	0	2	3	0	0
II	9	5	8	0	3
III	3	5	1	1	0
IV	0	0	0	0	0

Three patients had respiratory tract infections requiring oral antibiotics during initial phase of therapy.

Discussion

Thalidomide has shown remarkable efficacy in relapsed and refractory MM patients.[5] It's efficacy was demonstrated by Singhal *et al.*,[4] who reported

a reduction of at-least 25% in serum or urine M proteins in 27 of 84 patients (i.e. 32%) in refractory MM. Still, insufficient recommendations exist with regard to exact dose and duration of thalidomide. Some form of maintenance therapy is often used to prolong the response duration. Available options for this kind of treatment are interferon, steroids, alkylating agents. It is not clearly known whether use of thalidomide as a maintenance therapy in myeloma is effective. Our brief report does suggest role of thalidomide as a maintenance therapy. All our patients had relapse or refractory disease after PBSCT or first line chemotherapy. In a randomized comparison of post autologous transplantation therapy Attal *et al.*,[6] have reported three years PFS of 56% versus 34% for the patients who were put on maintenance thalidomide versus no therapy. The response rate, especially the complete response rate in the present study is considerably higher than earlier reports. The higher complete/ near complete response may be attributed to the higher dose given to the patients for a longer duration of time. Median duration of therapy with 600 mg/day was 10 months and with 800 mg/day was 4.5 months. Median duration of thalidomide in current study was 47 months.

Conclusion

MM is not curable with therapy and some form of maintenance treatment like interferon, alkylating agents and steroids are used to maintain remission status. This small report confirms safety and efficacy of long-term use of thalidomide in maintaining the response in myeloma patients. To the best of our knowledge this is one of the earliest report showing safety and efficacy of long- term use of thalidomide in relapsed/ refractory MM. We feel that maintenance therapy with thalidomide should be an option after initial front line therapy. However, a larger trial can only answer the question of use of thalidomide as a maintenance therapy.

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References

1. Bataille R, Harousseau JL. Multiple myeloma. N Engl J Med 1997;336:1657-64.
2. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998;16:3832-42.
3. Alexanian R, Dimopoulos M. The treatment of multiple myeloma. N Engl J Med 1994;330:484-9.
4. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, *et al*. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-71.
5. Blade J, Esteve J. Treatment approaches for relapsing and refractory multiple myeloma. Acta Oncol 2000;39:843-7.
6. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, *et al*. Maintenance treatment with Thalidomide and Pamidronate after autologous transplantation for myeloma: Second analysis of a prospective randomized study of the "Intergroue Francophone du Myelome (IFM 99 02). Hematol Jr 2005;90:17.

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