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Efficacy of Low Dose Thalidomide in Multiple Myeloma

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Abstract

Purpose

During 1998 evidence became available that thalidomide is an active anti myeloma agent.[1, 2] The initial study was a rapid (Q 2 week) dose escalation protocol using 200 - 1200 mg of thalidomide daily. Since initial response occurred early and dose escalation significantly increased toxicity it was decided to evaluate the efficacy of less toxic lower doses i.e. thalidomide 50-400 mg daily.

Patients and Methods

Patients with relapsing or progressive multiple myeloma following either standard chemotherapy and/or high dose chemotherapy with transplantation were treated with thalidomide. Doses between 50 mg and 400 mg/day were utilized with dose escalation based upon lack of response. An adequate trial was 8 weeks with myeloma M-protein monitoring every 14-28 days.

Results

Starting in October 1998, 36 patients were accrued, and evaluated for both response and toxicity. Nine patients (25%) achieved partial (PR: 50% partial (PR: >50% regression) or complete (CR: ≥75%) according to Southwest Oncology Group (SWOG) criteria. Of note 2 patients achieved excellent remission with thalidomide 50mg/day and an additional 3 patients with 100 or 200 mg/day. An additional 7 patients (19%) had lesser response or disease stabilization and 11 patients (31%) had progressive disease despite dose escalation to 400 mg/day. Nine patients (25%) were unable to tolerate thalidomide and/or discontinued medication prior to 8 weeks because of progressive disease.

Conclusion

Low dose thalidomide is generally well tolerated and can induce excellent remission in 25% of relapsing or refractory myeloma patients. Response is more likely with kappa subtype disease (81% versus 27%) and may be enhanced by co-administration of glucocorticords such as dexamethasone. Further studies are warranted to more fully assess the efficacy and tolerance of thalidomide used alone and in combination.

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Introduction

There are a limited number of agents which are active in the treatment of multiple myeloma.[3] Preliminary evidence of thalidomide efficacy was therefore very encouraging.[1,2] Because of reports of significant (>50% of ≥ Grade 1) toxicity with thalidomide at doses >400mg/day as well as compassionate use experience indicating excellent responses with thalidomide at doses ≤200 mg/day, it was decided to evaluate low doses of thalidomide in multiple myeloma patients relapsing/ refractory after standard or high dose therapy. It was noted that in patients with leprosy, thalidomide at doses <100 mg/day induced 83% complete responses versus 68.4% at 100-200 mg/day, 67.8% at >200-300 mg/day and 50% at >300 mg-400 mg/day.[4] This obviously implies almost an inverse dose relationship in this setting. The study in myeloma was therefore designed to evaluate thalidomide at doses between 50 mg and 400 mg/day with dose escalation based only upon lack of response.

Patients and treatment

Patients were eligible for thalidomide treatment if they had documented relapsing or refractory myeloma and an M-component marker to allow quantitation of response. Baseline restaging was a prerequisite for study entry and included skeletal radiographs and/or whole body scans, bone marrow aspiration/biopsy, complete blood counts, chemistry panel, serum and urine M-component quantitation, serum β2 micro-globulin and serum creatinine protein.[5,6] Patients had to be at least 3 weeks past their last radiotherapy and/or chemotherapy or 6 weeks from their last treatment with a nitrosourea. Patients were treated with thalidomide at doses between 50 mg and 400 mg/day with testing every 14-28 days and dose escalation (50 mg, 100 mg, 200 mg, 300 mg, 400 mg) only in the absence of response.

All patients were treated with signed informed consent utilizing Thalomid®, provided as 50 mg capsules through the S.T.E.P.S. program from the Celgene Corporation.2 Limiting toxicities were defined as grade 2 peripheral neuropathy, grade 3 sedation, fatigue, dizziness or related neurologic difficulties and grade 4 hematologic toxicity. An adequate trial was 8 weeks with myeloma M-protein monitoring every 14-28 days. All patients were seen and examined at least every 28 days with assessment of toxicity and monitoring of complete blood counts and chemistry panel in addition to myeloma specific marker studies. Because of concerns about achieving rapid response in patients with aggressive disease the starting dose in these instances was 200 mg/day. All responses of ≥ 50% regression had to be sustained for >8 weeks to be considered a «responder». The Southwest Oncology Group (SWOG) criteria were utilized to classify patients into: (i) *Responders*: Partial Response (PR) ≥ 50% regression; Complete response (CR) ≥ 75% regression: (ii) *Stable disease* or response < PR; (iii) *Progressive disease*.[5,6] The point of maximum regression was typically further documented by follow-up bone marrow, biopsy, whole body imaging, and/or other testing.

In an effort to reduce the sedation side effects the full dose of thalidomide was administered as a single dose in the evening. In an effort to reduce constipation, proactive measures were taken to prophylactically manage bowel function.

The study was planned such that if a minimum of 2 patients of the first 15 patients achieved an objective response, an additional 20 patients would be accrued for a total of 35 patients. Since 5 of the first 15 patients responded, the study proceeded and 36 patients were included. The trial design was such there was an 84% power to detect a response rate of 30%.

In addition to routine staging and monitoring, patients had serial testing with whole body FDG/PET imaging. This scanning which detects F18 glucose (FDG) uptake is a very accurate method for detection of any active myeloma either in the bone marrow and/or any extra medullary sites throughout the body.[7] Since several patients had extra medullary disease, this allowed documentation of response at these sites.

Results

A total of 36 patients were accrued to this study. The basic characteristics of the patients are summarized in Table 1. There were 24 men and 12 women. The median age was 56 years with a range of 36-77 years. All patients had received prior therapy of some sort. 29 patients (81%) had received 3 or more types of prior chemotherapy regimens and 9 patients (25%) had received prior stem cell transplant, usually in addition to extensive prior chemotherapy.

Sustained (> 8 weeks) objective response occurred in 9 patients as summarized in Table 1 and detailed in Table 2, which provides more information about the responding patients. Of the 9 patients, 6 achieved «CR» (> 75% regression) and 3 achieved «PR» (≥ 50; ≤ 75%) according to SWOG criteria.[6] As can be seen in the comments section of Table 2, the thalidomide, at doses between 50 mg - 400 mg/day, was well tolerated.

Patient 1 had significant sedation with thalidomide 50 mg daily and herself reduced her dosage to 50 mg every other day. At this dosage she has had no major side effects/difficulties and has achieved an excellent sustained remission. The time course of changes in serum IgGκ M-component and hemoglobin levels in response to thalidomide are summarized in Figure 1. These changes are contrasted with similar changes in Patient 7 who achieved an excellent remission with thalidomide 300 mg daily. In this instance response was after relapse following extensive prior therapy including stem cell transplant. In both instances the drop in serum M-component and improvement in hemoglobin levels parallel each other. Interestingly although patient 7 has now slowly relapsed after 1 year, patient 1 continues to further improve.

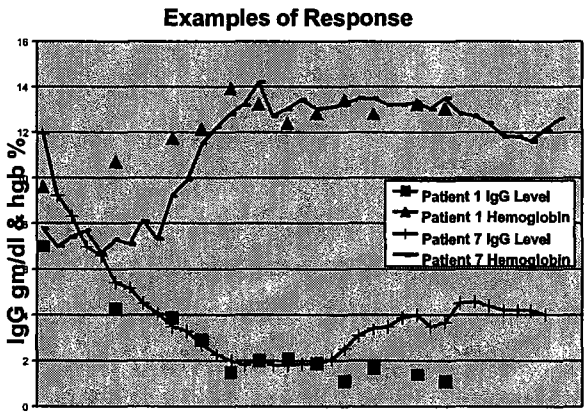

Figure 1: *Examples of hemoglobin and monoclonal component variations in two responding patients*

Table 1. Patient Characteristics

Total Patients	36		
Sex			
Female	12		
Male	24		
Age (years)			
Median	56		
Range	36 - 77		
Prior Chemotherapy (No. of regimens)			
Chemotherapy	0	0	
	1	2	
	2	5	
	≥3	29 (81%)	
Transplant	0	27	
	1	8	25%
	2	1	
Response (SWOG Criteria)*			
CR (> 75% regression		6	25%
PR (≥ 50 - 75%)		3	44%
< PR or «stable»		7	19%
Progressive disease		16	
Not evaluable / resp.***		4	

* *SWOG criteria: see reference 6*

** *5 of the 16 patients had progressive disease, plus toxicity which resulted in discontinuance of thalidomide prior to 8 weeks. 3 had lambda BJ myeloma with increasing serum creatinine (see text).*

*** *Discontinued thalidomide prior to 8 weeks (adequate trial) in absence of clearly progressive disease.*

Of note patient 2, also receiving very low dose thalidomide, (50 mg/day), is also demonstrating continued improvement after 9 months of treatment. Other side effects besides sedation, which has been a WHO grade 1 toxicity at most, have included transient mild rash in patient 2 and 4, mild peripheral neuropathy in patients 3 and 8, plus constipation which required specific management in patient 3 and the development of a rather unusual palmar erythema in patient 7. The erythema disappeared with temporary discontinuation of thalidomide.

Table 2. Patient Outcome: Responders

Ptt	Thalidomide dose / day	Age	Sex	M-Component type	Prior*** Therapy	% Regression	Follow-up (months)	Comments
1	50 mg	77	F	IgGκ	C_3	81%	10	Dose decreased to Q.O.D. with sustained remission
2	50 mg	53		IgAκ	C_3	70%	9	Rash; resolved
3	100-200 mg	55	M	IgGκ	T_1C_3	81%	13	Mild Neuropathy; constipation
4	200 mg	47	M	IgGκ	C_3	53%	10	Rash; resolved
5	200-300 mg	36	M	IgAκ	T_1C_3	75%	12	Best response to any R_x
6	300 mg	52	M	IgAκ	T_1C_3	77%	8**	Extra medullary relapse
7	300 mg	40	M	IgGκ	T_1C_3	86%	12**	Developed palmar erythema Relapse after 1 yr.
8	400 mg	51	M	IgGκ	T_2C_4	75%	13	Mild neuropathy
9	400 mg	66	F	κ (BJ)	C_3	98%*	9	Blood counts improved only with addition of steroids (Pulse dexamethasone 40 mg QDx4 twice/month

* *Kappa BJ protein decreased from 24 grams/24 hours to 0.2 grams/24 hours.*
** *Both relapsed; some restabilization with dose increase and addition of steroids.*
*** *C and T refer to number of prior chemotherapy (C) regimens or transplants (T) previously.*

The benefit of thalidomide was particularly evident in patients who had previously received stem cell transplantation. Patients 3, 5, 7 and 8 have achieved remissions which are better that those obtained with stem cell transplantation. The M-component levels are lower and blood count levels, particularly hemoglobin, are better. Patient 8 has been in remission longer with thalidomide than with prior stem cell transplantation. Five of the responders had previously required erythropoietin by injection to sustain an adequate hemoglobin level, but have now discontinued this treatment.

Other aspects of note include the extra medullary relapse which occurred in patient 6. Retroperitoneal plasmacytoma, evident on whole body FDG/PET, obstructed both ureters. Stents were placed and further response has been achieved with the addition of pulse dexamethasone as was also true for patient 7. Patient 9 with kappa BJ only myeloma had a dramatic reduction in urine BJ protein with thalidomide which was increased to 400 mg/day to achieve this result. The BJ protein level dropped from 24 grams/24 hrs to 0.2 grams/24 hrs. Despite that, severe anemia (7-8 gm/%) and thrombocytopenia (< 50,000/cumm.) persisted. It was elected to add pulse dexamethasone (40 mg daily for 4 days, twice a month) to the thalidomide. Over 2 months, the hemoglobin and platelet counts improved steadily and now at over 8 months later the blood counts are normal. With a current follow up of over 1 year, 2 responders have relapsed at 8 months and 1 year, both having had refractory disease following extensive prior chemotherapy and trans-plantation. Remission duration for the responders (Table 2) is currently 8-13+ months with a median of 9 months. No responders have died.

The 7 patients (19%) who failed to achieve a PR (< 50% regression) as noted in Table 1, represented a mixed group. Table 4 provides additional follow up details. One patient had a brief 30% regression then relapsed and died after 4 months. However 4 patients have been stable or slowly responding over 4 - 9 months. One of these 4 has had improvement in skin amyloidosis of the face, but otherwise stable disease with no reduction in serum IgGκ M-component nor improvement in blood count values. Two of the 4 have been slowly improving over 4-6 months on 50 mg and 100 mg thalidomide daily. The other patient in this group has been completely stable for 9 months on 400 mg thalidomide daily. The final 2 patients out of the 7 «mixed response» group failed to respond with thalidomide at

Table 3. Light Chain Subtype and Thalidomide Response

	Lambda (λ) N° of patients	Kappa (κ) N° of patients	% Kappa	P value
Responders				
• CR (≥75%)	0	7		
• PR (≥50%)	0	2	81%	0.001
• Stable/Mixed	3	4		
Progressive Disease	8*	3	27%	

** Patients with progressive disease **and** adequate trial.*

400 mg/daily, but have since responded with the addition of pulse dexamethasone added as for patient 9, Table 2.

A total of 20 patients had progressive disease on thalidomide and/or were non tolerant of the drug. Of these 20, 11 (55%) patients had progressive disease despite an adequate trial and ability to tolerate thalidomide. Six of these 11 patients have since died with progressive disease. Five patients had progressive disease and non tolerance which led to discontinuation of thalidomide prior to 8 weeks. Three of these 5 had lambda (λ) BJ myeloma and had a progressive increase in serum creatinine (1.7 to 4.3 mg%; 3.6 to 4.3 mg%; and 1.0 to 2.3 mg%) associated with concomitant disease progression which required discontinuation of thalidomide. One of these patients subsequently developed renal failure and died.

Four patients were unable to tolerate thalidomide even at low doses (50 mg, 50 mg, 50 mg, and 100 mg/day). One patient (man, aged 66 years) had extreme dizziness and almost had a fatal fall in the shower. The 3 others all had neurologic toxicity which was limiting including sedation, dizziness, tremor, incoordination and confusion. Of note one patient intolerant with 50 mg thalidomide daily has been rechallenged with 10 mg thalidomide daily which she can tolerate and with which she is manifesting early evidence of response (serum IgGκ M-component reduced from 6 G/DL to 4.5 G/DL).

The different response categories (CR, PR, Mixed, PD) were evaluated with respect to predictors of response. Since advanced, chemotherapy resistance did not preclude response (Table 2) other types of

Table 4. Patient Outcome: Stable Disease and Relapse Patients

Patient Category	Patient Numbers	Outcome	Further Response
[1] Stable/<PR*			
Transient Response	1	Relapse	Subsequently died
Stable/mixed	4	Continued stable	Stable at 4, 6, 6, 9 months
Non response	2	Pulse dexamethasone added (see Table 2)	Now both responders with >50% regression at 2 and 3 months
[2] Relapse Patients**			
Patient 6	-	Pulse dexamethasone added	Transient response: now on alternate treatment
Patient 7	-	Pulse dexamethasone added	Ongoing response.

* *See materials and methods.*
** *See Table 2.*

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