



Frane Mlinar. *Tranquil Harbor*. Oil on canvas, 35" × 42". Courtesy of The Weatherburn Gallery, Naples, Florida.

*Thalidomide and its derivatives,
given alone or with dexamethasone,
can induce response in patients
with multiple myeloma.*

Thalidomide and Its Derivatives: New Promise for Multiple Myeloma

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Background: *The combination of melphalan and prednisone has been accepted as standard treatment for multiple myeloma (MM) because most studies demonstrate only minimal survival benefit of combination chemotherapy regimens when compared with melphalan and prednisone. Despite modest gains with more intensive myeloablative regimens for certain subgroups, myeloma remains incurable. In 1999, investigators at the University of Arkansas reported the promising results of a phase II study of thalidomide in patients with resistant MM. Since then various trials of thalidomide alone, and in combination, have been tested in patients with resistant, and more recently, untreated MM. In addition, preliminary results of phase I studies of the immunomodulatory derivatives (IMiDs) of thalidomide have recently been reported.*

Methods: *The author reviewed and reports the results of clinical trials of thalidomide and the IMiDs, as well as the pharmacology, mechanism of action, and toxicity of these agents.*

Results: *Thalidomide has demonstrated significant activity in both resistant and previously untreated multiple myeloma. Combination therapy with dexamethasone increases response rate, even in patients previously resistant to both drugs given as single agents, indicating probable synergy. More recent studies of thalidomide-dexamethasone in previously untreated patients are encouraging. IMiD-3 is active in resistant myeloma and has a toxicity profile different from that of thalidomide.*

Conclusions: *Many studies have confirmed the activity of thalidomide in MM, as well as more responses with dexamethasone. Newer thalidomide derivatives with reduced toxicity are promising. Thalidomide-dexamethasone may now represent the treatment of choice for previously untreated patients. Further studies with these and other novel agents early in the course of myeloma, followed by rational programs of dose intensification, may improve complete remission rates and the frequency of long-term control.*

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Introduction

Multiple myeloma (MM) is a malignant proliferation of plasma cells that produce a monoclonal immunoglobulin. Approximately 14,500 cases of MM will be diagnosed during 2003 in the United States, and this disseminated malignancy, although treatable, remains incurable and accounts for 2% of all cancer deaths.¹ While treatment may be deferred in the 20% of patients who are initially asymptomatic at diagnosis, the disease eventually progresses and all patients require systemic therapy.

For decades, intermittent courses of melphalan and prednisone have represented the standard chemotherapy for newly diagnosed patients with symptomatic MM. Despite investigation of many other drug combinations, including those with multiple alkylating agents, vinca alkaloids, and anthracyclines, virtually all trials have failed to show survival superiority over melphalan and prednisone.² Pulse dexamethasone-containing regimens, including vincristine-doxorubicin-dexamethasone (VAD),³ provide rapid responses, and when followed by myeloablative therapy with autologous stem cell support early in the disease, have resulted in modest gains for many patients. However, the disease eventually relapses in all patients and becomes resistant to treatment, accounting for the current median survival of 3 to 5 years for symptomatic patients.

For many years, it has been known that thalidomide has antiangiogenic properties *in vitro*.⁴ Significant vascularization has been demonstrated in the bone marrow of patients with MM, particularly in those with advanced disease.^{5,6} Based on these features, in 1997 investigators at the University of Arkansas initiated a compassionate-use protocol to assess the activity of thalidomide in patients with end-stage MM. One of 5 patients in this pilot study had a near-complete remission. This prompted a phase II trial of thalidomide, which confirmed significant activity of this agent in patients with advanced and refractory myeloma.⁷ The activity of thalidomide alone, as well as in combination, has been confirmed by others, and this review will focus on thalidomide, its actions, and the results of clinical trials with this agent, as well as immunomodulatory derivatives (IMiDs), in MM.

Pharmacology

Thalidomide was originally used as a sedative and subsequently for the treatment of morning sickness in the 1950s but was withdrawn in the early 1960s because of frequent teratogenicity (phocomelia).⁸ The drug is a derivative of glutamic acid that consists of a

chiral center and two amide rings, and it is categorized as an immunomodulatory agent that also has antiangiogenic properties.^{9,10} Thalidomide exists as a mixture of S and R isomers at physiologic pH. While the S isomer appears responsible for teratogenicity, the R isomer results in sedation. At physiologic pH these isomers interconvert, making attempts at isolation of the R isomer in an effort to eliminate teratogenicity unsuccessful.¹⁰

Thalidomide is poorly soluble in water, and thus no intravenous preparation is available. Pharmacokinetic data are therefore not well characterized and appear highly variable. Maximum serum concentration of a 200-mg dose of thalidomide is reached within a mean of 4 hours, and the drug undergoes spontaneous, nonenzymatic, hydrolytic cleavage to numerous metabolites, which are rapidly excreted in urine, while non-absorbed drug is excreted in feces. Mean half-lives ($t_{1/2}$) for a 200-mg dose range from 4 to 9 hours, while a higher dose of 800 mg has a substantially longer $t_{1/2}$ of approximately 8 hours.^{10,12} Pharmacokinetics in renal and hepatic dysfunction are not well established, but moderate doses have been acceptably tolerated with renal failure.

In vitro, thalidomide has demonstrated apoptotic, immunomodulatory, and antiangiogenic effects. It has been postulated that the antiangiogenic effects of thalidomide are due to metabolites that interrupt processes of angiogenesis mediated by basic fibroblast growth factor (bFGF) and/or vascular endothelial growth factor (VEGF).^{4,13,14} In addition, thalidomide inhibits tumor necrosis factor alpha (TNF- α) gene activation by decreasing NF- κ B binding.¹⁵ Despite a previously demonstrated correlation between levels of marrow angiogenesis factors and disease activity in myeloma, and an increase in the angiogenic cytokines bFGF and VEGF in poor prognosis disease, no correlation between increased microvascular density or subsequent posttreatment decrease in neovascularization was noted in patients with disease responding to thalidomide.^{5-7,14,16,17} It seems unlikely that inhibition of angiogenesis alone accounts for the success of thalidomide in controlling MM.

It has been demonstrated *in vitro* that thalidomide and its analogs can directly inhibit growth of plasma cells, perhaps through caspase-8 activation and subsequent apoptosis.^{10,18} Additionally, TNF- α not only stimulates bone marrow stromal cell secretion of interleukin-6 (IL-6), but also induces expression of adhesion molecules on myeloma and marrow stromal cells (LFA-1, ICAM-1, and VCAM-1).^{11,19} Because thalidomide is a potent inhibitor of TNF- α , the expression of these molecules on marrow stromal cells may be decreased by treatment, resulting in inhibition of

myeloma cell adhesion and decrease of TNF- α -stimulated IL-6 secretion.²⁰ Thalidomide may also promote growth of stimulated anti-CD3 T cells, which may increase inhibitory cytokines for myeloma cell growth (interferon- α or IL-12).²¹

While the mechanism of growth inhibition by thalidomide remains unclear, there is an established apoptotic effect in vitro that is enhanced by dexamethasone. This effect may be partially overcome by IL-6, confirming the potential role of IL-6 suppression as a contributing antimyeloma effect of thalidomide.²²

Dose

No phase I trials have formally evaluated the maximum tolerated or most effective dose of thalidomide. Investigators at the University of Arkansas have noted that patients who received ≥ 42 g of thalidomide during a 3 month period (approximately 400 mg/day) had a higher response rate and superior 2-year survival (54% and 63%, respectively) than counterparts who received < 42 g over 3 months (21% and 45%, respectively).²³ The dose of 42 g, however, was not established as a continuous variable, but instead was the median cumulative dose. It is possible that if doses were explored as a continuous variable, or perhaps as a mean daily dose, a different value may be more significant.

At the M. D. Anderson Cancer Center, the response rate with doses of ≤ 400 mg/day was similar to that with higher doses, with side effects at lower doses approximately half of those at doses > 400 mg/day. However, toxicity nearly doubled at daily doses of > 400 mg.^{24,25} Others have reported responses at low doses of thalidomide alone or in combination (clarithromycin, thalidomide, dexamethasone [BLTD regimen]), but as previously noted, no systematic evaluation has occurred, making strict recommendations for dosing of thalidomide difficult.^{26,27}

Toxicity

Thalidomide is a known teratogenic agent, and its use is absolutely contraindicated in pregnant women. All patients must be registered on the System for Thalidomide Education and Prescribing Safety (STEPS) program before thalidomide may be prescribed.²⁸ Women of childbearing potential (< 2 years postmenopausal) must have a negative pregnancy test prior to starting thalidomide, and they must be using two effective forms of birth control and followed every 4 weeks with a pregnancy test. Men receiving thalidomide must practice abstinence or use a latex condom.

Sedation is one of the most frequently noted side effects of thalidomide and therefore the drug is taken at night.^{11,29} Constipation, another common side effect, can often be controlled by a combination of generous fluid intake, stool softeners, and laxatives.^{11,29} Dry skin and pruritus are frequently noted and can be prevented by using non-alcohol-based lubricants and avoiding hot baths. Occasionally, a true skin rash occurs, requiring temporary cessation of thalidomide, with resumption at a lower dose. Rarely, cases of Stevens-Johnson syndrome have been reported in patients treated with thalidomide and concurrent dexamethasone.²⁹ A sensorimotor peripheral neuropathy, usually of hands and feet, may occur, particularly after prolonged exposure or in those with prior neuropathy.^{11,29} We have also rarely noted decreased hearing acuity. Less common effects include peripheral edema, tremors, bradycardia, hypothyroidism and, rarely, neutropenia and hepatic enzyme elevation.²⁹

While thrombotic and embolic events are uncommon with single-agent thalidomide (approximately 5% in our experience), the incidence appears higher (approximately 15%) when thalidomide is used in combination with either corticosteroids or corticosteroid-anthracycline combinations.^{30,31} At our center, 24 patients were given prophylactic warfarin (1 mg p.o. per day), and six thrombotic episodes were noted. Therefore, it appears there is no role for subtherapeutic levels of warfarin as prophylaxis for thromboembolic events related to thalidomide combination therapy. Subsequent prophylactic therapeutic anticoagulation (target International Normalized Ratio, 2-3) has virtually eliminated this problem, but this approach has to be balanced against the risk of bleeding, particularly for those patients who may be at risk for ulcers and gastrointestinal bleeding because of concomitant dexamethasone. Therapeutic anticoagulation should be strongly considered in those patients with other risk factors that place them at higher risk for hypercoagulability.

Clinical Trials

Refractory Disease

Single-Agent Thalidomide: Initially, Singhal et al⁷ reported a phase II trial of thalidomide in patients with advanced refractory MM. Of the 84 patients studied, 76 had previous myeloablative therapy with stem cell support, although some were relapsing off therapy. Patients were treated with an initial dose of 200 mg/day with dose escalation in 200 mg increments every 2 weeks, in the absence of severe side effects, to a maximum of 800 mg/day. The median duration of treatment was 80 days. Twenty-one patients (25%) achieved par-

tial remission by criteria of 50% reduction in monoclonal (M) protein. In a recently published update of that initial report, 169 patients were enrolled and 30% had at least a 50% reduction in paraprotein.²³ Two-year event-free and overall survival rates were 20% and 48%, respectively, in this group of patients with advanced myeloma. Responding patients had a superior 2-year survival rate (69%) compared with nonresponding patients (47%). As expected, patients with normal cyto-

genetics, low plasma cell labeling index, and B-2 microglobulin <3 mg/L had a longer event-free survival.

We confirmed a 25% response rate and projected median remission duration of 15 months in a phase II study of 44 evaluable patients resistant to at least a pulse dexamethasone-containing regimen using criteria of $\geq 50\%$ and $\geq 75\%$ reduction of serum and urine monoclonal paraprotein, respectively.^{24,25} Many other trials

Table 1. — Thalidomide in Resistant Myeloma: Selected Single-Agent and Combination Trials*

	Daily Thalidomide Dose (mg)	No. of Patients	Response Rate* (%)
Single-Agent Trials:			
Barlogie ²³	200-800	169	30
Alexanian ²⁵	100-400	44	25
Juliusson ³²	200-800	20	43
Yakoub-Agha ³³	50-800	83	47
Raza ³⁴	200-800	83	47
Durie ²⁶	50-400	36	25
Rajkumar ³⁵	200-800	36	31
Tosi ³⁶	100-800	32	31
Grosbois ³⁷	200-800	120	17
Hus ³⁸	200-400	53	36
Trials of Combinations:			
Weber ^{24,39}	200-800 + D 20 mg/m ² × 5 d (d1-5, 15-19 × 2 mos, then d1-5 q mos)	47	52
Dimopoulos ⁴⁰	200-800 + D 40 mg × 4 d (d1-4, 9-12, 17-20, q 35 d)	38	52
Palumbo ⁴¹	100 + D 40 mg × 4 d (d1-4 q 28 d)	77	41
Tosi ⁴²	100 + D 40 mg × 4 d (d1-4 q 28 d)	44	48
Coleman ²⁷	50-200 + B 250-500 mg b.i.d. + D 40 mg × 1 d (q 14 d)	24	100
Kropff ⁴³	100-400 + D 20 mg/m ² × 4 d (d1-4, 9-12, 17-20) + C 1.8 g/m ²	14	86
Moehler ⁴⁴	400 + C 400 mg/m ² × 4 d, CI + E 40 mg/m ² × 4 d, CI + D 40 mg × 4 d (CED q 28d)	42	78
Barlogie ⁴⁵	400 + D 40 mg × 4 d + P 10 mg/m ² × 4 d + A 10 mg/m ² × 4 d + C 400 mg/m ² × 4 d + E 40 mg/m ² × 4 d (DPACE d1-4 q 28 d × 2)	135	54
* Studies with >50% M protein reduction. D = dexamethasone B = clarithromycin (Biaxin) C = cyclophosphamide E = etoposide P = cisplatin A = doxorubicin CI = continuous infusion			

have confirmed this approximately 25% response rate of single-agent thalidomide in refractory myeloma (Table 1).^{23-27,32-45} It is important to note that many thalidomide trials have used less stringent criteria (only 25% reduction or stable disease) for determining myeloma response compared to historical data where at least a 50% reduction in monoclonal paraprotein has been required for partial remission.

Thalidomide in Combination With Other Agents:

In 1999, we reported results of a trial of thalidomide (doses as previously described for single-agent thalidomide) in combination with intermittent pulse dexamethasone (dexamethasone 20 mg/m² per day p.o. on days 1-5 and 15-19 repeated on approximately day 30, for a total of two courses, followed by maintenance on days 1-5 only, repeated every 4 weeks).^{24,46} In 47 patients with resistant myeloma, 22 patients (46%) were resistant to both thalidomide and pulse dexamethasone given separately as single agents. The possibility of synergy between thalidomide and dexamethasone was supported by the surprising response rate of 46% in patients resistant to both drugs given previously as single agents. This result was similar to the overall response rate of 52%. A similar response rate of 55% in 44 patients with refractory myeloma was also reported by Dimopoulos et al.⁴⁰

Investigators at the University of Arkansas are evaluating a program of dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) in combination with thalidomide, compared with DCEP alone in patients with relapsing high-tumor-mass disease or with poor prognostic cytogenetics.⁴⁵ At a median follow-up of 17 months, the response rate of 18%, after 3 cycles of DCEP, doubled to 36% with the addition of thalidomide. The same group is investigating the DT-PACE regimen (dexamethasone, thalidomide, cisplatin, doxorubicin, and etoposide) in patients with prior therapy vs intensive therapy with autologous stem cell transplantation. Among the first 179 patients treated with DT-PACE, only 45% were randomized, largely due to low frequency of response.⁴⁵ Eighty patients have been randomized and treated and are currently evaluable. Complete responses were noted in 26 of 39 patients who received tandem transplants and in only 11 of 41 patients continuing on DT-PACE ($P=.0005$). Two-year event-free survival was similar at 73% in both arms, but 33 patients who failed DT-PACE went on to receive tandem transplant, making this result difficult to interpret. Because of the inferior results with continued DT-PACE, the study has been amended to include melphalan 100 mg/m² with peripheral blood stem cell support in the DT-PACE arm.

A study of vincristine, doxorubicin, and dexamethasone (VAD) combined with thalidomide in refrac-

tory patients was terminated prematurely because of a high rate of thrombotic complications that were attributed to the combination of doxorubicin and dexamethasone.^{30,31}

These and other combination studies are summarized in Table 1.

Previously Untreated Disease

Single-Agent Thalidomide: Because of the significant activity of thalidomide in refractory myeloma, we and others conducted trials in previously untreated patients. Since the efficacy of thalidomide as a single agent was previously unknown, we evaluated thalidomide 100-200 mg per day escalating to 400 mg per day in patients with asymptomatic myeloma.⁴⁶ Twenty-eight patients considered at high risk for early progression of disease (median 18 months), as determined by criteria we previously established, were included in this small trial. Partial remission, characterized by a $\geq 75\%$ reduction in serum in protein synthesis and $\geq 95\%$ reduction in urine Bence-Jones protein, was noted in 10 (36%) of the 28 patients.

Rajkumar et al^{47,48} conducted a similar trial noting a response rate of 38% among 16 comparable patients. Given the long period of disease stability for asymptomatic disease, any impact on time to progression or survival will take many years to determine. Since early treatment of asymptomatic patients with other agents has not previously improved survival, use of thalidomide in asymptomatic disease should be restricted to clinical trials until the benefits and long-term side effects are established.

Thalidomide in Combination With Other Agents:

The activity of thalidomide and dexamethasone in refractory disease prompted several investigators to pursue this regimen in previously untreated patients with symptomatic disease. Rajkumar et al⁴⁹ reported 50 patients treated with 200 mg/day of thalidomide with a dose escalation every 2 weeks up to 800 mg/day along with 40 mg/day of dexamethasone on days 1-4, 9-12, and 17-20 on odd cycles and days 1-4 on even cycles. Because 2 of the first 7 patients experienced grade 3-4 skin toxicity, subsequent patients were treated with a fixed thalidomide dose of 200 mg/day. Thirty-two patients (64%) had a $\geq 50\%$ reduction in serum M protein. Stem cell harvest was completed without difficulty in 31 patients, and 26 patients proceeded to myeloablative therapy with stem cell support.

In a similar trial at our center, 40 patients with untreated myeloma were given thalidomide 100-200 mg per day at bedtime with escalations up to 400 mg.³⁹

Dexamethasone 20 mg/m² per day was given on days 1-4, 9-12, and 17-20 for 2 courses followed by dexamethasone on days 1-4 only for maintenance. Twenty-nine patients (72%) had a $\geq 75\%$ reduction in serum M protein synthesis or $\geq 95\%$ reduction in Bence-Jones proteinuria or both. Complete remission was noted in 7 patients (18%). There was no difficulty in subsequent stem cell harvest for patients in whom this was attempted. Thalidomide is also currently being evaluated at the University of Arkansas as part of induction for myeloablative therapy (total therapy III).⁴⁵

Results of current trials in untreated patients are summarized in Table 2.

Consolidation and Maintenance Therapy After Intensive Therapy With Stem Cell Support

Complete remission has been shown to improve survival in patients with MM.⁵⁰ In an attempt to convert residual disease to complete remission, we treated 21 patients with thalidomide-dexamethasone whose disease was in persistent partial remission despite myeloablative therapy with stem cell support.⁵¹ Thalidomide-dexamethasone was given within 15 months after intensive therapy. Thalidomide was initiated at a daily dose of 100 mg and escalated to a maximum dose of 300 mg. Dexamethasone 20 mg/m² was given on days 1-4, 9-12, and 17-20 with resumption of the same schedule on approximately day 35. After 2 to 3 months, dexamethasone was decreased to days 1-4 only. Patients whose disease remained in plateau phase of partial remission continued maintenance therapy with thalidomide alone until disease progression. Fifty-seven percent of patients had marked further reduction of myeloma protein by $\geq 90\%$, including 4 patients in whom disease converted to complete remission.⁵¹ Whether such an

effect may produce longer disease-free survival will need to be addressed in future trials designed to assess the use of thalidomide as maintenance therapy after myeloablative therapy.

Extramedullary Extension or Extramedullary Plasmacytoma

Although thalidomide alone and in combination has demonstrated activity in patients with both untreated and resistant myeloma, as evidenced by both a fall in monoclonal paraprotein levels and marrow plasmacytosis, the activity in patients with extramedullary plasmacytoma appears less encouraging. Juliusson et al³² first described 1 patient who had a rapid response in immunoglobulin A (IgA) paraprotein level but developed paraparesis due to progression of a spinal plasmacytoma. The authors hypothesized that there could be differences in the microvascular supply of marrow and extramedullary plasmacytomas accounting for the difference in response. Similarly, Blade et al⁵² described a lack of response in the extramedullary plasmacytomas of 5 patients despite reduction of the paraprotein in 3 patients. No prognostic significance was attributed to paraprotein type. Myers et al⁵³ also reported a lack of response in the extrasosseous disease of 2 patients treated with thalidomide despite reduction in monoclonal IgA- λ .

In our experience, we also have noted progression of a paraspinal soft tissue mass after treatment with thalidomide-dexamethasone, despite reduction of IgA- λ paraprotein to remission levels. In contrast, we have noted reduction of extramedullary extension of a rib lesion in 1 patient with resistant myeloma and an IgG- κ paraprotein treated with thalidomide-dexamethasone. Clarification of the prognostic significance of extra-

Table 2. — Selected Studies of Thalidomide in Patients With Untreated Myeloma

Disease Status	Daily Thalidomide Dose (mg)	No. of Patients	Response Rate* (%)
Asymptomatic:			
Weber ⁴⁶	100-400	28	36
Rajkumar ⁴⁸	200-800	16	38
Symptomatic:			
Rajkumar ⁴⁹	200-400	50	64
	200** + D 40 mg \times 4 d (d1-4 q 28 d + even cycles: d9-12, 17-20)		
Weber ³⁹	100-400 + D 20 mg/m ² \times 4 d (d1-4 q 28-30 d + courses 1 and 2: d9-12, 17-20)	40	72

* Studies with >50% M protein reduction.
 ** Dose in the first 7 patients escalated up to 400 mg. Because of Stevens-Johnson syndrome in 2 patients, dose was fixed at 200 mg in the next 43 patients.
 D = dexamethasone

Table 3. — IMiD-3 (CC-5013) for Relapsed/Refractory Multiple Myeloma (Response $\geq 50\%$ Reduction in M Protein)

Daily Dose (mg)	Richardson et al ⁵⁴		Zangari et al ⁵⁵		Total	
	No. of Patients	No. of Responsive Patients	No. of Patients	No. of Responsive Patients	No. of Patients	No. of Responsive Patients
5	6	1	3	0	9	1
10	8	1	3	0	11	1
25	6	0	3	1	9	1
50	14	3	6	2	20	5
Total	34*	5 (26%)	15	3 (20%)	49**	8 (23%)

* Number of evaluable patients: 19
 ** Number of evaluable patients: 34

medullary disease and/or IgA- λ paraprotein in future trials with thalidomide is necessary before any definitive conclusions can be made.

Thalidomide Analogs

Due to the encouraging activity of thalidomide in MM, new analogs of this drug have recently been developed. The first class includes selected cytokine inhibitory drugs, which are inhibitors of TNF- α but do not appear to affect T-cell activation.²² The second class of analogs are the IMiDs; phase I studies of IMiD-3 (CC-5013) have recently been reported.^{54,55}

The IMiDs not only are 50,000 times more potent than thalidomide in inhibiting TNF- α secretion, but also stimulate proliferation of anti-CD3-stimulated T cells resulting in increased IL-2 and interferon- γ secretion.²¹ In addition, IL-2-stimulated peripheral blood mononuclear cell lines treated with IMiDs increased myeloma cell line lysis, and depletion of CD56 cells blocked this lysis, suggesting natural killer cell-mediated myeloma cell death.²¹ In vitro studies of IMiDs also indicate direct inhibition of MAPK growth signaling, which supports the role of IMiDs in downregulating the production of IL-6, an important myeloma cell growth factor.²² In addition, in vitro studies indicate inhibition of proliferation in doxorubicin-, melphalan-, and dexamethasone-resistant cell lines and addition of dexamethasone to IMiDs or thalidomide potentiates such antiproliferative activity.^{18,22}

This activity of IMiDs in myeloma not only is seen in vitro, but also is evident in preliminary results of phase I studies of CC-5013 (IMiD-3) in patients with resistant myeloma.^{54,55} Richardson et al⁵⁴ treated 26 patients with relapsing or refractory myeloma in a phase I study of CC-5013 at four dose levels: 5 mg, 10 mg, 25 mg, and 50 mg. Those enrolled had a median of three prior treatment regimens, 16 patients had received prior myeloablative therapy with stem cell sup-

port, 16 had prior thalidomide, and 18 were resistant to prior salvage therapy. Nineteen of 26 patients who received >28 days of treatment were considered evaluable for response. A $\geq 50\%$ reduction in myeloma paraprotein was noted in 5 patients (26%) and 12 patients (63%) had a $\geq 25\%$ reduction in paraprotein. Responses were noted at all dose levels (Table 3). Grade 3 neutropenia was noted in 1 patient (10-mg dose) prior to day 28, and grade 3/4 thrombocytopenia/neutropenia was noted in 2 patients after day 28 (25-mg dose), resulting in study termination for those patients.

A similar schedule of CC-5013 has also been investigated in a phase I study of 15 patients with resistant myeloma.⁵⁵ A $\geq 50\%$ reduction in paraprotein was noted in 3 patients (20%). All responses were noted at doses ≥ 25 mg (Table 3). Five of 6 patients who continue on study have shown $>50\%$ decrease of platelet count, and 1 patient had thromboembolism. In contrast to thalidomide, no significant somnolence, constipation, or neuropathy was noted in either study. Based on these experiences, a multicenter trial with IMiD-3 at a dose of at least 25 mg per day has been proposed.

Conclusions

Thalidomide is an effective agent in the treatment of both resistant and previously untreated MM. Although thalidomide is active, side effects that include constipation, fatigue, neuropathy, and thrombotic/embolic complications may limit its use in some patients. Newer nonteratogenic derivatives, such as the IMiDs, are also effective but with a different spectrum of side effects, and experience remains limited. In the future, combinations of these agents with novel mechanisms of action (thalidomide, IMiDs, proteasome inhibitors, dexamethasone) followed by intensive therapy with stem cell support early in the disease should result in improved response rates, longer remissions, and improved survival for more patients.

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