Thalidomide alone or in combination: results in refractory patients

Thalidomide was first marketed in the 1950s for the treatment of pregnancy-related morning sickness and later as a sedative, but was withdrawn because of serious adverse events in pregnant women including teratogenicity and dysmelia. Interest in the drug resurfaced in the 1990s because of its antiangiogenic and immunomodulatory effects. Recently thalidomide has been used to treat multiple myeloma (MM) either alone or in combination with other therapies. This review summarizes study results of thalidomide treatment in patients who have not benefited from conventional therapy.

Pharmacology

Thalidomide, a derivative of glutamic acid, is an equal mixture of (R)- and (S)-thalidomide enantiomers that rapidly interconvert. Thalidomide undergoes rapid pH-dependent hydrolysis to several metabolites that are quickly excreted. The pharmacologic effects of thalidomide on inflammation and angiogenesis require microsomal biotransformation and are therefore stronger in vivo than in vitro. Notably, the biological effects of thalidomide vary substantially by species. In a study designed to determine whether differences in pharmacokinetics could explain species-specific effects, thalidomide administered in equivalent doses to mice, rabbits, and patients with MM revealed that while plasma concentrations over time were similar among species, the area under the curve, elimination half-life, and metabolite profiles were very different among the three species; results, therefore, may differ in different species.

Mechanism of action

It is unclear whether thalidomide modulates immune function and blocks angiogenesis directly or through its metabolites, but its potential effects against MM appear to be extensive (Table 1). Thalidomide inhibits angiogenesis by decreasing the secretion of basic fibroblast growth factor and vascular endothelial growth factor. In addition, thalidomide inhibits the proinflammatory cytokine tumor necrosis factor α and stimulates T-cell proliferation (particularly cytotoxic CD8+ cells), interferon-β, and interleukin (IL)-2 to produce an immunomodulatory effect that inhibits MM cell growth. Thalidomide is believed to increase the number and function of natural killer cells, producing MM cell lysis. An indirect antitumor effect of thalidomide is inhibition of the cytokine IL-6, which is secreted by bone marrow stromal cells and is necessary for the survival and proliferation of myeloma cells. Thalidomide also slows tumor cell proliferation and tumor growth by inducing apoptosis and arresting the G1 growth phase.

Clinical results in refractory multiple myeloma

In 1965, Olson et al. reported slowing of disease progression in one MM patient who was treated with thalidomide. After an initial evaluation of thalidomide administered to five patients with end-stage MM at the University of Arkansas, one of whom achieved a near complete response (CR), a pivotal phase 2 study was initiated, enrolling 169 patients with advanced progressive MM. A dose-escalation protocol was used, beginning with daily doses of 200 mg of thalidomide administered for 2 weeks. The dose was increased by 200 mg every 2 weeks for a maximum of 800 mg. Patients were not excluded for cardiovascular or renal dysfunction. Study end points included serum or urine paraprotein responses (PPRs) of at least 25%, 50%, or 90%. CR was defined as the absence of monoclonal protein. A PPR of at least 25% was observed in 37% of patients (2% CR, 12% near CR, 10%...
Seventy percent of these responses occurred within 2 months, and 90% occurred within 4.5 months. At 22 months, 84 patients who were still living were evaluated. The 2-year event-free survival rate was 20±6%, and the overall survival rate was 48±6%. A dose-response analysis revealed that patients who received a median cumulative dose of more than 42 grams of thalidomide in 3 months had higher response rates and better 2-year survival rates than patients who received lower mean doses. No treatment-related deaths occurred. The most common adverse event was toxicity (58%) affecting the central nervous system (25%), gastrointestinal tract (16%), and peripheral nervous system (9%).

Additional studies have confirmed the efficacy of thalidomide monotherapy in patients with MM who have been refractory to other treatment.14-17 Response rates from studies with more than 50 patients are presented in Table 2 and show an average response rate similar to that of the pivotal phase 2 study (approximately 44% with 29% PR). Certain factors have been shown to influence response rates. In the pivotal phase 2 study, results were inferior for patients with at least one of three risk factors: β2-microglobulin >3 mg/L, plasma cell labeling index >0.5%, or abnormal cytogenetics.13 Two studies have confirmed that cumulative doses of thalidomide >32 grams in 3 months are associated with better outcome,14,18 however, other groups have not found a dose-response correlation.19 A factor that might negatively affect efficacy is the presence of plasmacytomas. Studies generally have found either lower response rates or shorter duration of response from thalidomide treatment when extramedullary disease is present.20 This suggests that thalidomide acts primarily within the bone marrow milieu but not outside of it. Because of the well-known toxicity profile of thalidomide, adverse events have been of concern to researchers. Adverse events are linked to dosage and duration of treatment, with doses of 200 mg/d generally well tolerated.21 The most commonly reported adverse events associated with treatment for MM are constipation (35-60%), weakness or fatigue (29-48%), somnolence (34-43%), peripheral neuropathy (12-30%), and rash (10-25%).22,23

Although deep-vein thrombosis (DVT) is a known risk factor in patients with malignancies, increased risk has been associated with the use of thalidomide.24 Patients treated with thalidomide alone appear to have approximately a 2% risk of developing DVT, but risk increases substantially when combinations of cytotoxic agents are used.25 A study of thrombogenic activity in patients with MM who received thalidomide alone or with combinations of dexamethasone, cisplatin, cyclophosphamide, etoposide, and doxorubicin found a strong correlation between DVT and combination therapy, particularly with doxorubicin.25-27 DVT developed in 2.5% of patients taking combination therapy without doxorubicin and in 16% of patients who were taking doxorubicin, which was a significant difference (p=0.02).

### Table 1. Thalidomide and multiple myeloma: mechanisms of action.

- Antiangiogenesis
- Regulates expression of adhesion molecules
- Inhibits TNF-α production
- Stimulates T-cell proliferation (cytotoxic CD8⁺ cells)
- Induces secretion IFN and IL-2 (Th1 response)
- Induces apoptosis
- Arrests Gi growth


### Table 2. Results with thalidomide alone in relapsed/refractory multiple myeloma.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>% Response*</th>
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<tr>
<td>Dmoszynska</td>
<td>175</td>
<td>56</td>
<td>Hematol J 2003; 4(suppl 1):S34</td>
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<td>Barlogie</td>
<td>169</td>
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<td>Neben</td>
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<td>42</td>
<td>Br J Haematol 2001;115:605-8</td>
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<td>Petrucci</td>
<td>80</td>
<td>63</td>
<td>Hematol J 2003; 4(suppl 1):S59</td>
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<td>Mileskinn</td>
<td>75</td>
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<td>Wu</td>
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<td>Tosi</td>
<td>60</td>
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<tr>
<td>Others</td>
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<td>43</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>1,279</strong></td>
<td><strong>42 (29 PR)</strong></td>
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*Response ≥25% reduction in paraprotein.
Studies of other combinations of thalidomide and various chemotherapy agents report DVT rates as high as 27%.25,26 The reason for development of DVT is unclear, but levels of some prothrombogenic factors appear to increase in patients receiving thalidomide.20,28,29 Patients with increased risk of prothrombogenic factors may benefit from aspirin therapy.

**Thalidomide combination therapy**

Studies suggest that thalidomide may enhance the antitumor activity of dexamethasone.20-33 In studies that compare thalidomide plus dexamethasone with thalidomide alone, response rates are significantly higher with combination therapy. A review of reported studies on thalidomide in combination with dexamethasone (approximately 400 patients) shows an overall response rate of around 60% with 47% PR, which compares favorably with the 42% response rate (29% PR) reported for thalidomide alone.21,23 The dose used for thalidomide ranged between 100 and 400 mg/d, while for dexamethasone 20 to 40 mg for 4 days every 28 days have been used.21

The combination of thalidomide and dexamethasone has generated a response even in patients who are resistant to chemotherapy or dexamethasone regimens. A group of 44 patients with refractory myeloma were treated with an escalating dose (200-400 mg/d) of thalidomide plus intermittent dexamethasone (20 mg/m²/d on days 1 through 4, 9 through 12, and 17 through 20).22 All patients were resistant to chemotherapy, and 77% were resistant to dexamethasone therapy. Within 1.3 months, 55% of patients (24 of 44) achieved partial response. Responses in patients previously refractory to thalidomide alone were also observed. The efficacy of thalidomide plus dexamethasone is believed to be caused by complementary mechanisms of action; ie, thalidomide induces apoptosis in cells that are resistant to dexamethasone, and dexamethasone reduces IL-6 production that inhibits the antitumor activity of thalidomide and its analogs.3,33

Combination regimens of cyclophosphamide and glucocorticoids have been used in Europe for years as palliative therapy. When the efficacy of thalidomide and its apparent synergistic effects with dexamethasone were discovered, it was added to the chemotherapy-glucocorticoids combination. More than 300 patients have been treated with this strategy, achieving a response ranging from 56% to 72% PR (median 60% PR). Garcia-Sanz et al. have evaluated a combination of oral thalidomide, cyclophosphamide, and dexamethasone in 71 patients with relapsed MM.34 Patients were included if they had relapsed after prior or therapy or if they were refractory to treatment. Treatment included oral thalidomide in escalating doses of 200 to 800 mg/d plus cyclophosphamide 50 mg/d as well as pulsed dexamethasone 40 mg/d for 4 days every 3 weeks. Patients were evaluated every 2 weeks during the first 2 months and then monthly thereafter. The primary end points were response at 3 and 6 months, duration of response, and overall survival. Toxicity and adverse events were also analyzed.

**Response rates**

After 3 months of therapy, 89% of patients had responded to the combination regimen. PR was reported in 50% of patients at the 3-month evaluation and 53% at the 6-month evaluation. In addition, CR increased from 2% at 3 months to 10% at 6 months. The overall survival rate at 2 years was 66%, and the event-free survival rate was 57%. Based on multivariate analysis, the independent variables most predictive of favorable response were β2 microglobulin levels ≤ 4 mg/L, high platelet counts, and refractory disease (rather than disease relapse) upon study entry. The best predictors of overall survival were β2 microglobulin levels ≤ 4 mg/L, age < 65 years, and the absence of plasmacytomas.

Interestingly, the incidence of side effects with combination therapy is probably lower than with thalidomide monotherapy because the presence of steroids may mitigate some side effects associated with thalidomide. Notably, the incidence of DVT was low at 7%. Adverse events were generally moderate (constipation in 24%, somnolence in 18%, fatigue in 17%, and neuropathy in 16%). Serious adverse events included five deaths that were not attributable to myeloma progression, including infectious complications in three patients and sudden death due to arrhythmia in two patients who had cardiomyopathy.34

Another interesting study of combination therapy used intermittent administration of thalidomide.25 A total of 53 previously treated MM patients received three 28-day courses of oral cyclophosphamide 150 mg/m² bid (days 1 through 5), oral thalidomide 400 mg qd (days 1 through 5 and 14 through 18), and oral dexamethasone 20 mg/m² qd (days 1 through 5 and 14 through 18). Responding patients went into a maintenance phase with the three drugs administered on days 1 through 5 every 28 days. Among 43 patients who had never received thalidomide, 67% responded to treatment. A total of 32 of 53 patients (60%) achieved PR within an average of 1.5 months; the median time to response was 12 months. Toxicity was mild or moderate, with DVT occurring in 4% of patients and peripheral neuropathy reported in 2%. Median overall survival was 17.5
months. Adverse prognostic factors were high lactate dehydrogenase and poor performance status.

Etoposide added to the combination regimen of thalidomide, cyclophosphamide, and dexamethasone has produced good response rates, but has caused more serious adverse events. In one study of combination therapy with etoposide, the overall response rate was 74.7% (4% CR, 52% PR, 18% MR); however, 60% of patients experienced myelosuppression, and 24% developed infection requiring hospitalization and intravenous antibiotics. Similarly, the combination regimen of thalidomide, vincristine, doxorubicin, and dexamethasone (T-VAD therapy) tested in 50 patients produced a high response rate (89%) with 47% CR, but increased rates of neutropenia, infections, paresthesia, and DVT were observed. Olson et al. have explored the efficacy of the DTPACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) in 236 refractory myeloma patients as part of a total therapy program. After two cycles, 16% achieved a CR or near CR, and a similar proportion achieved PR. Sixty-five percent of patients, however, developed myelosuppression, with neutropenic fever in 12% and DVT in 15%.

### Thalidomide with bortezomib

Bortezomib, a proteasome inhibitor recently approved for MM, was also tested in combination with thalidomide and dexamethasone in a phase 1 two-arm dosing study. Arm 1 included bortezomib 1 mg/m² administered intravenously on days 1, 4, 8, and 11 every 21 days. Thalidomide was added in varying doses (50, 100, 150, and 200 mg) to different cohorts of at least 10 patients each. Patients in study arm 2 received bortezomib 1.3 mg/m² on the same schedule as arm 1 with the addition of thalidomide in the same dose regimen used in arm 1. Dexamethasone 40 mg was added if the response was suboptimal after three cycles.

Patients enrolled in the study had very poor prognostic indicators. Approximately 75% had abnormal cytogenetics, including deletion of chromosome 13 in 50%, prior transplant in 96%, more than one transplant in 63%, and prior treatment with thalidomide in 81%.

After two treatment cycles, there was an overall response rate in 55% of patients, including 40% PR. After eight cycles, the overall response rate increased to 70% with a 22% CR or near CR. Event-free survival duration was 7 months, and the overall survival rate was 21 months. Overall, response was rapid and independent of poor cytogenetics. The side effect profile was similar to that of thalidomide alone or bortezomib alone, but it lacked the synergistic toxicity of myelosuppression and neuropathy. The most common side effects were fatigue, neuropathy, and gastrointestinal symptoms.

Other studies of thalidomide with bortezomib have demonstrated positive early results in refractory myeloma patients receiving the velcade/doxorubicin/thalidomide regimen. These patients received bortezomib 1.3 mg/m² on days 1, 4, 15, and 18 every 28 days; pegylated liposomal doxorubicin 20 mg/m² was administered on days 1 and 15; and an escalating dose of thalidomide up to 200 mg was administered daily. A total of 13 patients were assessable after one cycle and demonstrated an overall response rate of 54%, with 15% CR. Neutropenia was seen in 38% of patients and thrombocytopenia in 22%.

The addition of dexamethasone in a similar study, in which most patients showed prior resistance to bortezomib or thalidomide therapy, or both, produced encouraging results. Patients received bortezomib 1.0 or 1.3 mg/m² on days 1, 4, 8, and 11; doxorubicin 2.5 to 10 mg/m²/d administered in a continuous infusion on days 1 through 4 and 9 through 12; thalidomide 50 or 100 mg/d on days 1 through 12; and dexamethasone 20 or 40 mg/d on days 1 through 4 and 9 through 12. Of 20 patients so far recruited, 16 were assessable, displaying 12% CR, 12% near CR, and 31% PR with manageable toxicities of grade 3 thrombocytopenia in 60% and neutropenia in 30%.

### Conclusion

Used as monotherapy, thalidomide demonstrates efficacy in the treatment of MM, producing response rates of approximately 30%. Response is rapid, occurring within the first 2 to 3 months. While the optimum dose has not been defined, the range that produced the best results with manageable side effects is between 200 and 400 mg. Whether used alone or in combination with other agents, thalidomide dosing regimens should be individualized to patient needs for optimum response vs side effect profile. When used in combination with dexamethasone and chemotherapy, agents such as cyclophosphamide and thalidomide apparently produce better response rates than they do when used alone. The regimen based on thalidomide/cyclophosphamide/dexamethasone represents a convenient oral combination that yields durable responses. Initial results of combination therapy with bortezomib also demonstrate encouraging response rates. Based on these results, thalidomide has become a standard of therapy for patients with relapsed MM or disease that is refractory to treatment.
References


34. Agrawal NR, Hussein MA, Elson P, et al. Pegylated doxorubicin (D)， vincristine (V)， reduced frequency dexamethasone (D) and thalidomide (T) (DVd-T) in newly diagnosed (Nmm) and relapsed/refractory (Rmm) multiple myeloma patients. Blood 2003; 102:831-81.

