THALIDOMIDE IN ONCOLOGY: THE PERIL AND THE PROMISE

Rod Quilitz, PharmD

From the Pharmacy Service at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.

Introduction and History

From 1956 through 1958, thalidomide was released into the European and Canadian pharmaceutical markets as a rapid-acting, hangover-free sedative without danger of respiratory depression. In 1960, reports of peripheral neuropathy with chronic use began to surface. Growing evidence of severe infant limb defects (phocomelia) and internal organ deformities associated with maternal use of thalidomide soon eclipsed this lesser concern. By late 1961, thalidomide was withdrawn from the world market but not before more than 10,000 "thalidomide babies" were affected. Since that time, thalidomide’s ability to inhibit tumor necrosis factor-alpha (TNF-alpha) activity has been found to be beneficial for the treatment of erythema nodosum leprosum (ENL), chronic graft-vs-host disease (CGVHD), HIV-associated cachexia, oropharyngeal ulcers, and a variety of mucocutaneous disorders. Currently, thalidomide is under study as an angiogenesis inhibitor, with the majority of human data in refractory multiple myeloma.

Because of the teratogenic risks associated with thalidomide, a system has been developed to ensure that fetal exposure to thalidomide does not occur. Thalidomide is commercially available only through the manufacturer-regulated System for Thalidomide Education and Prescribing Safety (STEPS) program, which is discussed later.

Pharmacology

Thalidomide, also known as alpha-(N-phthalimido)glutarimide, consists of a two-ringed structure with an asymmetric carbon in the glutarimide ring (Figure). Thalidomide exists as an equal mixture of S(-) and R(+)-enantiomers that interconvert rapidly under physiologic conditions. Thalidomide is sparingly soluble in water and ethanol, which to date has prevented the availability of an intravenous formulation.

Thalidomide’s mechanism of action is complex and not completely understood. The most frequently cited mechanism is TNF-alpha inhibition. Thalidomide reduces TNF-alpha production by enhancing the degradation of TNF-alpha mRNA. In addition, thalidomide produces a variety of effects on the immune system, including downregulating surface adhesion molecules and major histocompatibility antigens on endothelial and epidermal cells, reducing circulating T-helper cells, increasing circulating T-suppressor cells, and modifying integrin receptors and other surface receptors.

The complexity of this mechanism is demonstrated by the fact that systemic TNF-alpha concentrations have been reported to decline in patients with Hansen’s disease but rise in patients with AIDS. The glutarimide ring probably mediates the sedative/hypnotic effects of thalidomide. This mechanism is distinct from that of barbiturates, and it may result from activation of a forebrain sleep center. Thalidomide acts as a sedative without producing incoordination, respiratory, or narcosis. The exact mechanism of antiangiogenesis is unknown, but it appears to be the result of an as yet unidentified active metabolite rather than the parent compound.

Multiple myeloma requires the presence of interleukin-6, whose production is stimulated by TNF-alpha to circumvent apoptosis. This mechanism in combination with angiogenesis inhibition may explain why the most dramatic clinical results in oncology to date have been seen in refractory multiple myeloma patients.

Pharmacokinetics

Due to poor aqueous solubility, the absolute bioavailability of thalidomide is unknown. Time to maximal concentration (T_{max}) ranged from 2.9 to 5.7 hours in patients with Hansen's disease and healthy volunteers. A similar range of 2 to 7.1 hours was seen in elderly prostate cancer patients. The volume of distribution in prostate cancer patients varied by dose level: 66.93 ± 34.27 L (200 mg/day) and 165.81 ± 84.18 L (1,200 mg/day). The extent of plasma protein binding is unknown. Significant hepatic metabolism has not yet been identified; however, the presence of an antiangiogenic active metabolite is anticipated. Thalidomide does not induce or inhibit its own metabolism.

Renal elimination is minor, with 0.7% of the dose excreted unchanged in the urine. The major route of elimination appears to be non-enzymatic hydrolysis. The elimination half-life is reported to be 5 to 7 hours, based on Hansen’s disease patients who rarely receive more than 400 mg/day. Half-life was shown to be dose-related in prostate cancer patients: 6.52 ± 3.81 hours (200 mg/day) and 18.25 ± 14.08 hours (1,200 mg/day). However, overall clearance was comparable between the two groups (7.41 ± 2.05 L/h and 7.21 ± 2.89 L/h, respectively). Renal dysfunction would be expected to have minimal effects on thalidomide’s pharmacokinetics. Hepatic dysfunction may not produce a major effect on the elimination of thalidomide itself, but it could affect the production of the presumed antiangiogenic metabolite.

Contraindications and Precautions

Several side effects, particularly severe human teratogenicity, are associated with thalidomide therapy and thus have limited its use in specific populations. Some of the adverse effects are listed in Table 1, and a summary of the indications and contraindications of thalidomide use are presented in Table 2.
### Table 1. — Summary of Adverse Effects of Thalidomide

<table>
<thead>
<tr>
<th>Adverse Effect (refs)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratogenecity&lt;sup&gt;1-3,29&lt;/sup&gt;</td>
<td>Even a single dose can produce severe birth defects</td>
</tr>
</tbody>
</table>
| Somnolence/dizziness<sup>1-3</sup> | Most common adverse effect  
Administer at bedtime if possible  
Tolerance usually develops over time  
Gradual dose escalation to prevent excess sedation |
| Constipation<sup>1,3</sup> | Consider routine use of stool softeners  
Use mild laxatives as needed |
| Peripheral neuropathy<sup>1,3</sup> | Can become irreversible if thalidomide not discontinued |
| Neutropenia<sup>1,3</sup> | More common in AIDS and BMT recipients |
| Rash<sup>1,3</sup> | More common in AIDS and BMT recipients |

### Table 2. — Overview of Indications and Contraindications for Thalidomide

**FDA-Approved Indication:**
- Moderate to severe erythema nodosum leprosum<sup>3</sup>

**Literature-Supported Oncology and AIDS Indications:**
- Refractory multiple myeloma<sup>23</sup>  
- Refractory chronic graft-vs-host disease<sup>4,11</sup>  
- AIDS-related cachexia<sup>12</sup>  
- AIDS-related mucocutaneous ulcers<sup>13,14</sup>  

**Potential Oncology Uses (requires additional research):**
- AIDS-related Kaposi's sarcoma<sup>20-22</sup>  
- Plasma cell leukemia<sup>24</sup>  
- Miscellaneous advanced solid tumors (ie, breast, CNS, prostate)<sup>18,19,25,27,28,37,38</sup>  

**Potential Oncology Uses (potential for new phase I research):**
- Cancer cachexia<sup>38</sup>  
- Severe, uncontrollable night sweats<sup>40</sup>  
- Combination therapy with anthracyclines (angiogenesis and cardioprotective?)<sup>16,17</sup>  
- Combination therapy with chemotherapy and/or radiation (angiogenesis and effect on mucositis?)<sup>13,14,16,24</sup>  

**Contraindications:**
- Pregnant women and women capable of becoming pregnant<sup>1-3</sup>  
- Patients with hypersensitivity to thalidomide<sup>3</sup>  
- AlloBMT recipients without CGVHD<sup>33</sup>  
- Toxic epidermal necrolysis<sup>36</sup>
Pregnant Women and Women of Childbearing Potential

The critical period of thalidomide-induced teratogenicity occurs between 34 to 50 days after the last menstrual period. A single dose can cause severe birth defects, including absent or defective limbs, hypoplasia or absence of bones, facial palsy, absent or small ears, absent or shrunken eyes, congenital heart defects, and gastrointestinal and renal abnormalities. Unless incapable of childbirth (greater than 12 months from last menstrual cycle or status posthysterectomy), all women on thalidomide therapy must practice two forms of birth control — one highly effective method (intrauterine device, hormonal contraception, partner’s vasectomy) and one additional effective barrier method (latex condom, diaphragm, and cervical cap). Ideally, these precautions should begin 4 weeks before initiation of thalidomide and then must continue throughout treatment and at least 4 weeks afterwards.

Patients must be advised about emergency contraception options if they undergo unprotected sexual intercourse during this time frame. These women must receive pregnancy testing with a sensitivity of at least 50 mIU/mL within 24 hours before initiation, then every week for the next 4 weeks. Thereafter, patients with regular menstrual cycles should be tested monthly, while patients with irregular cycles should be tested every 2 weeks. Pregnancy testing should also be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. As it is unknown whether thalidomide distributes into the male ejaculate, men receiving thalidomide therapy and for 4 weeks afterwards must wear a latex condom during heterosexual intercourse. All patients must be advised to never share thalidomide capsules with anyone. If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to thalidomide must be reported to the Food and Drug Administration via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corp, the manufacturer of Thalomid.

Nursing Mothers

It is unknown whether thalidomide is excreted in human milk. However, because many drugs are excreted in human milk and because there is the potential for serious adverse reactions from thalidomide in nursing infants, a decision should be made whether to discontinue either nursing or taking the drug, taking into account the importance of the drug to the mother.

HIV-Seropositive Patients With Increased Viral Load

In a randomized, placebo-controlled trial of thalidomide for aphthous ulcers in AIDS patients, plasma HIV mRNA levels were higher in patients receiving thalidomide (median change of 0.42 log10 copies/mL). This information was acquired prior to use of highly active antiretroviral therapy. While the clinical significance is unknown, HIV viral load should be measured in AIDS patients receiving thalidomide after the first and third months of therapy then every 3 months thereafter.

Allogeneic Bone Marrow Transplant Recipients Without Refractory Chronic Graft-vs-Host Disease

Chao et al performed a double-blind, randomized trial with 59 patients to determine whether thalidomide could be used as prophylaxis against CGVHD following allogeneic bone marrow transplantation (alloBMT). Of the 54 evaluable patients, 26 were randomized to placebo and 28 received thalidomide 200 mg po bid beginning on day +80. At the first interim analysis, the thalidomide group surprisingly displayed a higher rate of CGVHD than the placebo group (82% vs 54%, respectively; P=0.06) and a higher mortality (11 in the thalidomide group vs 2 in the placebo group, P=0.0006). Statistical adjustments for possible confounding factors failed to eliminate the negative effect of thalidomide. The authors concluded that thalidomide prophylaxis in alloBMT recipients results in a paradoxical increase in CGVHD.

Patients With Toxic Epidermal Necrolysis

A randomized, placebo-controlled trial of thalidomide 400 mg po qhs for the treatment of toxic epidermal necrolysis demonstrated increased mortality in the thalidomide group (83% vs 30%, P=0.03), possibly due to a paradoxical enhancement of TNF-alpha production.

Other Adverse Effects

The most common adverse effects are dose-dependent somnolence and dizziness. To minimize these complications, thalidomide should be administered as a once-daily dose in the evening. Note that some trials, especially for CGVHD, have studied thalidomide’s effectiveness only with multiple daily doses. For indications requiring higher doses, therapy may need to be initiated at low doses (100 to 200 mg/day) and dose-escalated by 100 to 200 mg/day every 1 to 2 weeks to minimize somnolence. Tolerance to sedative properties usually develops over time. Patients should be warned regarding the risks of driving a car or operating heavy machinery while on thalidomide. Patients also should be advised to sit upright for a few minutes prior to standing from a recumbent position due to possible orthostatic hypotension.

Constipation is a common side effect experienced by 3% to 30% of patients at low doses. The constipation is usually mild and responsive to mild laxatives (eg, milk of magnesia, lactulose, psyllium). Consider routine use of stool softeners (docusate) in patients taking thalidomide at 400 mg or more per day.

Thalidomide-induced pruritic erythematous macular rash, usually involving the trunk and back, has been reported. The rash usually occurs within 2 to 13 days after initiation and reverses after discontinuation with or without the use of antihistamines. Severe, life-threatening epidermal damage has been reported in patients with Hansen’s disease but is more common in patients with CGVHD (16%) and with AIDS (24%).

Chronic thalidomide therapy can produce peripheral neuropathy. The neuropathy results from axonal degeneration without demyelination in the sensory fibers of the lower and occasionally upper extremities. Risk of peripheral neuropathy appears to rise with patient age and cumulative dose of thalidomide, resulting in an incidence of approximately 25% in non-lepromatous patients on chronic thalidomide therapy. This toxicity initially presents as numbness of toes and feet then superficial sensory loss in feet and hands. If therapy is not discontinued, the paresthesias of feet and hands will become permanent and will progress proximally.

Neuropenia is extremely rare in patients with ENL (<1%) but is considerably more frequent in HIV and CGVHD patients (2% to 20%). Thalidomide should not be initiated when a patient’s absolute neutrophil count (ANC) is less than 750 cells/mL. If ANC falls below 750 cells/mL while on treatment, the regimen should be reconsidered. If the ANC falls below 500 cells/mL, thalidomide should be discontinued, with consideration given to filgrastim (G-CSF) therapy.

Drug Interactions

Pharmacokinetic Drug Interactions

Currently, there are no known pharmacokinetic drug interactions with thalidomide. Thalidomide 200 mg/day did not affect the pharmacokinetics of an oral contraceptive containing norethindrone acetate and ethinyl estradiol.

Sedation
Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.3

**Peripheral Neuropathy**

Thalidomide should be used cautiously with medications known to cause peripheral neuropathy (eg, cisplatin, paclitaxel, vinca alkaloids).3

**Important Non-Thalidomide Drug Interactions**

Concomitant use of HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents may reduce their contraceptive efficacy. Other antibiotics such as penicillins, cephalosporins, and tetracyclines may also decrease contraceptive efficacy due to altered estrogen and/or progestin gut metabolism following changes to the intestinal flora.36 Therefore, women requiring treatment with one or more of these drugs must either use two other effective or highly effective methods of contraception or abstain from reproductive heterosexual intercourse.3,29

**Thalidomide Uses**

**Indications Outside Oncology**

Thalidomide has been approved by the Food and Drug Administration for the acute treatment of the cutaneous manifestations of moderate to severe ENL. Thalidomide is not indicated as monotherapy for such ENL treatment in the presence of severe neuritis. Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.3

Tseng et al17 divided the therapeutic uses of thalidomide into two categories: those with efficacy seen in multiple series (ENL, prurigo nodularis, actinic prurigo, discoid lupus erythematosus, aphthous stomatitis, and Behcet’s syndrome) and those with efficacy seen in single series or case reports (palmoplantar pustulosis, sarcoidosis, rheumatoid arthritis, Langerhans cell histiocytosis, pyoderma gangrenosum, uremic pruritus, Jessner-Kanof disease, recurrent erythema multiforme, cold hemagglutination disease, Weber-Christian disease, ulcerative colitis, postherpetic neuralgia, AIDS-associated proctitis, bullous pemphigoid, and cicatricial pemphigoid).

**Neoplasms**

The role of thalidomide in oncology was first addressed in 1965 by two retrospective reports in the medical literature. Grabstald and Golbey37 related their experience in 71 patients with a wide spectrum of advanced metastatic malignancies who received daily doses of thalidomide ranging from 300 mg to 2 g. Of these, only one subject demonstrated clinical response — a patient with renal cell cancer who responded with resolution of pulmonary metastases following nephrectomy and 3 months of thalidomide. As spontaneous regression of pulmonary metastases in renal cell cancer following nephrectomy was already well documented, it was unclear from this report whether even this one patient actually benefited from treatment. A second report by Olson et al15 was slightly more positive. They reported on 21 patients with 14 different types of chemotherapy-unresponsive advanced malignancy. They initiated thalidomide at 200 mg po tid and increased the dose up to 1,400 mg/day as tolerated for 1 to 34 weeks.

No objective evidence of disease regression was obtained. However, 2 patients appeared to benefit from slowing of previously rapid tumor progression. This may have been related to an antiangiogenic effect. Seven patients experienced improved quality of life due to the sedative and antica cachetic effects of thalidomide.

Interest in the use of thalidomide in oncology was revived when D’Amato and colleagues15 demonstrated the ability of orally administered thalidomide to inhibit basic fibroblast growth factor-induced angiogenesis in a rabbit cornea micropocket assay. Experimentation with thalidomide analogs demonstrated that the angiogenesis inhibition correlated with the teratogenicity but not the sedative or immunosuppressive properties of these compounds.

**Breast Cancer**

Preclinical and limited preliminary human data relating to the antiangiogenic activity of thalidomide were reported by Nguyen et al.16 Thalidomide monotherapy failed to suppress tumor growth in a murine breast cancer model. In their second experiment, intraperitoneal cyclophosphamide and doxorubicin were administered on day 0 followed by intraperitoneal thalidomide vs saline 3 times weekly beginning on day 1. Therapy began when tumor volumes were less than 50 mm3. Primary tumor volume at day 25 was significantly lower in the mice treated with either 200 mg/kg or 300 mg/kg of thalidomide vs mice treated with chemotherapy alone (3,812 mm3 and 3,432 mm3 compared with 4,643 mm3, respectively; P=0.0005). After 30 days of treatment, 24% of the mice treated with chemotherapy alone developed pulmonary metastases, while none of the mice treated with chemotherapy plus thalidomide had any detected lung or liver metastases. When they repeated the experiment but delayed initiation of the therapy until the primary tumor was greater than 700 mm3, the addition of thalidomide to chemotherapy failed to show benefit. One limit to the extrapolation of this animal data is the recent discovery that thalidomide must be hepatically activated to exhibit its antiangiogenic effects and that this active metabolite can be formed in humans and rabbits but not rodents.30

After completion of their murine studies, Nguyen et al16 enrolled 7 patients with advanced breast cancer (6 with stage IV) in a phase I trial of thalidomide in combination with conventional cyclophosphamide, doxorubicin, and fluorouracil (CAF). In addition to CAF, these patients received 100 to 300 mg orally at bedtime for 4 weeks. One patient who took 100 mg daily developed a mid rash on her trunk and extremities, while another patient taking 200 mg daily developed worsening constipation; both required early discontinuation. The other 6 patients tolerated therapy well. Three patients had partial responses, 1 had stable disease, 2 progressed, and 1 was lost to follow-up after the rash. Given the limited follow-up time (1 to 6 months) and limited numbers of patients, it is not possible to properly evaluate the response rate of this modality. Of note, thalidomide (and pentoxifylline) may produce cardioprotective effects in subjects receiving doxorubicin according to experimental work with rats by Costa et al.17 Future studies of thalidomide in combination with anthracyclines are needed to assess this phenomenon in humans.

Thalidomide is under study by Long et al18 following STAMP1 high-dose chemotherapy (carmustine, cyclophosphamide, and cisplatin) with stem cell rescue for metastatic breast cancer. Thalidomide is initiated at 200 mg po bid beginning at count recovery and continuing until day +180. Currently, 7 of 30 planned patients have been enrolled. All 7 patients experience fatigue with mild somnolence. In addition, 1 patient developed numbness and tingling in the extremities and another experienced a vaso-vagal fainting episode. Doses for patients who tolerate therapy for the first 20 days will be increased to 400 mg po bid. The investigators plan to monitor for adverse effects, potential markers of angiogenesis activity, response rates, and remission duration.

**Central Nervous System Tumors**

A phase II trial of thalidomide in patients with recurrent high-grade astrocytomas and mixed gliomas was reported in abstract form by Fine et al19 in 1997. Thirty-two patients received 1,200 mg/day orally, although the abstract does not indicate whether the dose was titrated up to this level to reduce adverse effects. Adverse effects of thalidomide included extreme somnolence in 3 patients and drug rash in 2 patients. Seizures occurred in 5 patients (2 with no seizure history), deep venous thrombosis in 1 patient, and unexplained fever in 1 patient. Minimal radiographic responses were seen in the first 10 patients, 1 who had remained on thalidomide for longer than 7 months from tumor recurrence at the time of publication. Complete results of this trial are pending publication.

**Kaposi’s Sarcoma**

Three abstracts have evaluated the use of thalidomide in AIDS-related Kaposi’s sarcoma (KS). Bower et al20 reported on 17 men who were treated with thalidomide 100 mg po.
Politi and colleagues treated 12 patients with AIDS-related KS, 9 with mucosal KS lesions and 3 with edema. Five of the 12 had failed systemic therapy. Thalidomide was administered daily in divided oral doses at four dose levels: 200, 300, 400, and 600 mg (3 patients in each group). The most common toxicity was dose-dependent somnolence, including 2 of 3 patients at 600 mg/day. In addition, 1 patient at 300 mg/day had rash, fever, and dry mouth, 1 patient at 600 mg/day experienced headache, and 1 patient at 400 mg/day for 4 months developed paresthesia. Two partial responses were seen (on 200 mg/day and 400 mg/day), and 7 patients had stable disease (2 each on 200, 300, and 400 mg; 1 on 600 mg/day). Median time to progression was 4 months, and survival ranged from 4 to 18+ months. Further research at doses of 200 to 300 mg/day is planned.

Yarchoan and associates reported on the effect of thalidomide in 13 patients (8 poor risk and 5 good risk) with AIDS-related KS. Thalidomide was initiated at 200 mg/day and was increased by 200 mg/day on a biweekly basis as tolerated to a maximum dose of 1,000 mg/day. Of the 11 evaluable patients, 4 (36%) achieved partial response, 3 at week 4 and 1 at week 8 at daily doses of 300, 400 mg (2 patients), and 600 mg. Two of the partial responders had not progressed at 30 and 50 weeks, while the other 2 partial responders progressed after 16 and 49 weeks. Two patients suffered from progressive disease after 16 and 24 weeks. The remaining 5 patients exhibited stable disease at date of presentation at 12 weeks (2 patients) and at 22, 32, and 52 weeks. Three patients experienced toxicity (grade 3 rash with fever, myositis, and depression) requiring study discontinuation. Neutropenia (grade 3) and sedation requiring dose reduction occurred in 3 and 5 patients, respectively. Thalidomide appears to be a promising agent for the treatment of AIDS-related KS.

### Multiple Myeloma

To date, the best available data on the antiangiogenic activity of thalidomide involve patients with high-risk refractory multiple myeloma. Singh and associates reported on 89 such patients who received 200 mg/day titrated upward by 200 mg/day every 2 weeks as tolerated to a maximum dose of 800 mg/day. The maximum tolerated dose of thalidomide was continued until disease progression or relapse. This was an extremely chemotherapy-refractory multiple myeloma population in which 78% had more than 24 months of prior therapy, 84% had one stem cell transplant, 63% had multiple stem cell transplants, 66% had cytogenetic abnormalities associated with poor prognosis, and all had disease progression prior to thalidomide treatment. Median duration of therapy was 52 days with 80% having received at least 4 weeks of therapy. Table 3 summarizes the response rates, timing, and duration in those patients who received at least 28 days of thalidomide, as measured by at least monthly M protein analysis of serum and urine.

### Table 3. — Thalidomide Use in 89 High-Risk Refractory Multiple Myeloma Patients: Response Rates, Timing, and Duration

<table>
<thead>
<tr>
<th>Degree of Response</th>
<th>Number Responding</th>
<th>Bone Marrow Normalization</th>
<th>Median Time to Response (days)</th>
<th>Median Response Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;75%</td>
<td>10 (11%)</td>
<td>5 of 10</td>
<td>66</td>
<td>20+</td>
</tr>
<tr>
<td>51% - 75%</td>
<td>8 (9%)</td>
<td>4 of 6</td>
<td>44</td>
<td>22+</td>
</tr>
<tr>
<td>21% - 50%</td>
<td>12 (14%)</td>
<td>2 of 8</td>
<td>29</td>
<td>35</td>
</tr>
</tbody>
</table>

Median cytoreduction among the 30 responders was 61%. Responses were consistent between high- and low-risk cytogenetics groups. Patients who did not respond within the first 60 days were unlikely to respond with continued therapy. Adverse effects of moderate severity included neurologic (somnolence, dizziness, confusion, tremors, incoordination, tingling, numbness) in 75% of patients, gastrointestinal (constipation, nausea, vomiting, stomatitis) in 66%, and constitutional symptoms (weakness, weight loss, fever) in 80%. Thalidomide was discontinued secondary to toxicity in 8 patients. These results demonstrated impressive salvage activity for thalidomide in highly refractory patients.

Due to the activity detected in these patients with refractory multiple myeloma, many of the same investigators headed by Barlogie evaluated the use of thalidomide in combination with chemotherapy in patients with plasma cell leukemia and fulminant multiple myeloma. Only preliminary data in 10 patients are currently available. These patients received the novel outpatient regimen of D.T.PACE (Table 4). Of the 5 patients evaluable at the time of abstract release, 3 attained complete response with a single cycle by day 21. Of these, 1 patient had primary refractory plasma cell leukemia with a white blood cell count of >100,000/mm³ and 2 had fulminant relapse after stem cell transplant. The fourth patient had reduction in lesions identified by magnetic resonance imaging, and the fifth displayed resolution of marrow plasmacytosis and reduction in massive amyloidoma lesions. These 5 patients all had unfavorable chromosome 13 abnormalities. Three responses occurred despite prior resistance to the same chemotherapy regimen without thalidomide. The authors are currently investigating tandem treatment with D.T.PACE and high-dose melphalan.

### Table 4. — D.T.PACE Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration (per day)</th>
<th>Route</th>
<th>Days</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>D = dexamethasone</td>
<td>40 mg</td>
<td>oral</td>
<td>1-4</td>
<td>—</td>
</tr>
<tr>
<td>T = thalidomide</td>
<td>400 mg</td>
<td>oral</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>P = cisplatin</td>
<td>10 mg/m²</td>
<td>IVCI</td>
<td>1-4</td>
<td>—</td>
</tr>
<tr>
<td>A = doxorubicin</td>
<td>10 mg/m²</td>
<td>IVCI</td>
<td>1-4</td>
<td>—</td>
</tr>
<tr>
<td>C = cyclophosphamide</td>
<td>400 mg/m²</td>
<td>IVCI</td>
<td>1-4</td>
<td>—</td>
</tr>
<tr>
<td>E = etoposide</td>
<td>40 mg/m²</td>
<td>IVCI</td>
<td>1-4</td>
<td>—</td>
</tr>
</tbody>
</table>

IVCI = intravenous continuous infusion
Figg and colleagues\textsuperscript{25} reported preliminary data on the use of thalidomide in 12 patients with metastatic prostate cancer. These patients had failed combined androgen deprivation, and 7 of 12 had failed secondary hormonal therapy. Patients were divided into low (200 mg/day) and high (titration up to 1,200 mg/day) dose levels — 6 in each group. Two patients had grade 3 complications (neuromotor and constipation), but other toxicities were mild to moderate. Four patients (2 in each group) had 20% to 37% declines in prostate-specific antigen (PSA) — the longest maintained for 84 days. Six patients had progressed at time of publication at 28, 53, 62, 64, 74, and 84 days. The authors plan to enroll 9 patients in each arm of the study with possible extension of one arm based on response. A recent discovery demonstrates that thalidomide use upregulates PSA secretion in the human prostate cell line LNCaP.\textsuperscript{25} Future trials of thalidomide for prostate cancer will need to find alternative methods of evaluating response to therapy.

Other Tumors

A phase II trial by Eisen and associates\textsuperscript{27} investigated the impact of thalidomide 100 mg po qhs in a variety of advanced solid tumors. Of a total of 48 patients enrolled, 17 had ovarian cancer, 16 had metastatic melanoma, 8 had renal cell carcinoma, and 7 had breast cancer. Three patients had "differential response," while 10 patients demonstrated stable disease for 8 to 25 weeks (median = 12 weeks). Eight patients remained on therapy at the time of publication. Data regarding quality of life indicated an improvement in appetite and sleeping. The investigators were able to correlate changes in serum and urinary vascular endothelial growth factor with response to antiangiogenic treatment. The low dose used in this study may have had suboptimal response to thalidomide.

Marx et al.\textsuperscript{28} are conducting a phase III trial of thalidomide in the treatment of advanced brain, melanoma, breast, colon, mesothelioma, and renal cell carcinoma. Initial response data for 33 patients and toxicity data for 45 patients have been reported in abstract form. Thalidomide was initiated at 100 mg/day but increased weekly in 100 mg/day increments as tolerated to a maximum dose of 500 mg/day. There were no complete responders and only 2 (6%) partial responders. More relevant for an antiangiogenic agent was the 30% incidence of stable disease, although the duration was not reported. The most interesting response data were derived from the 5 patients with glioblastoma, which included the only 2 partial responders and 1 of the patients with stable disease. Thalidomide was reasonably tolerated with this dosing schema with no grade 4 toxicities. Additional trials of this agent in a variety of advanced malignancies are required to determine the range of thalidomide’s antioncologic activity.

Chronic Graft-vs-Host Disease

Both animal data\textsuperscript{11} and small case reports\textsuperscript{5-10} have provided evidence that thalidomide can produce responses as salvage therapy for refractory CGVHD following alloBMT. The largest reported experience with thalidomide in this setting included 80 patients.\textsuperscript{11} Eligibility criteria included progressive CGVHD despite at least 1 month of cyclosporine (CSA) and/or prednisone (31 patients), stable but unimproved CGVHD after at least 2 months of treatment (40 patients), CGVHD that initially responded to standard therapy but flared during immunosuppressant taper requiring a daily dose of at least 20 mg of prednisone (7 patients), or prednisone therapy that was medically contraindicated (2 patients). While prior CSA therapy was not required, 67 patients had CSA-resistant disease, while 13 patients were unable to receive further CSA due to excessive CSA-related end-organ toxicity. A total of 38 patients had high-risk CGVHD as indicated by the presence of thromboctopenia, progressive CGVHD, and/or CGVHD of the skin and liver. Thalidomide was initiated at 100 mg po qd, then the dose was gradually escalated to 200 to 300 mg po qd as tolerated. Patients were maintained on prednisone and CSA when thalidomide started, but these were slowly tapered in patients whose condition responded to thalidomide. The overall response rate was 20%, with 9 complete responses (CRs) and 7 partial responses (PRs). High-risk CGVHD responded in 16% of cases (4 CRs and 2 PRs in 38 patients), while standard-risk CGVHD responded in 24% (5 CRs and 5 PRs in 42 patients). Responses were rare for bronchiolitis obliterans with obstructive pneumonia, combined skin and liver CGVHD, and progressive presentation. Most responses were seen in patients with isolated oral or liver CGVHD and skin involvement without severe scleroderma. Sedation was the most common side effect (40%), followed by constipation/nausea (30%), neutropenia (18%), new skin rash (16%), and neutritis (5%). Thalidomide was discontinued in 36% of patients due to toxicity. Side effects also prevented maximal dose escalation; few patients tolerated doses of much greater than 400 to 600 mg/day. Thalidomide has a role in refractory CGVHD due to a dearth of effective therapies for this complication of alloBMT.

Cachexia

Cachexia is a constellation of symptoms encountered in patients with cancer and end-stage AIDS — anorexia, early satiety, chronic nausea, asthenia, and a catabolic state resulting primarily in loss of lean body mass. Cachexia results from a complicated interaction of tumor effects, treatment effects, and host cytokines including TNF-alpha.\textsuperscript{39} Due to its anti-TNF-alpha activity, thalidomide was studied in 28 patients with advanced AIDS with wasting syndrome.\textsuperscript{12} These patients were adult AIDS patients with progressive loss of more than 10% body weight prior to the previous 6 months despite at least 12 weeks of antiretroviral therapy, as well as CD4+ T cells of less than 500 x 10\textsuperscript{3}/L, and a Karnofsky performance index of more than 50%. Patients could not receive concurrent immunosuppressants, megestrol acetate, pentoxifylline, or parenteral or enteral nutrition. Patients were stratified by severity of weight loss and CD4+ T-cell counts and then randomized to receive either thalidomide 100 mg po qhs (14 patients) or placebo (14 patients) for 12 weeks. Clinical efficacy was defined as more than 5% weight gain in at least 3 consecutive measurements or no progression of the wasting syndrome (more than 5% weight decline). Treatment failure included progressive wasting, severe drug toxicity, noncompliance, voluntary withdrawal, or death. After 12 weeks, 71% of the 14 patients in the placebo group failed due to progressive wasting (9 patients) or toxicity (1 patient). In the thalidomide-treated group, 21% of the 14 patients had failed due to progressive wasting (1 patient) or toxicity (2 patients). Also in this group, 8 patients exhibited weight gain compared with only one in the placebo group. Patients with weight gain demonstrated increases in not only fatty tissue, but also muscle mass. Median Karnofsky index remained stable in patients on thalidomide (80%) but fell in placebo subjects (80% to 60%). No effect on HIV viral burden or CD4+ T-cell counts was detected. In the thalidomide-treated group, transient somnolence occurred in 11 patients and skin rash also in 11 patients, whereas in the placebo group, transient somnolence was seen in 5 patients and skin rash in 3. One patient in the thalidomide group experienced a severe skin rash that was life-threatening, and 1 patient developed peripheral neuropathy. Due to similarities in clinical presentation and probable mechanism between AIDS-related and cancer-induced cachexia, clinical trials of thalidomide in patients with cancer cachexia are warranted.

Night Sweats

A 59-year-old man with severe, drenching night sweats induced by mesothelioma was unresponsive to prednisone 25 mg po qd and diclofenac 50 mg po tid. However, he did respond to thalidomide 200 mg po qhs.\textsuperscript{40} The night sweats almost completely ceased within 3 days but rapidly returned within 24 hours of the end of his 14-day trial. He was then restarted at 100 mg po qhs with rapid response. The effectiveness of thalidomide in patients with severe night sweating that results in reduced quality of life should be investigated further.

Stomatitis

Thalidomide has not been evaluated for the prevention or amelioration of chemotherapy- or radiation-induced mucositis. However, thalidomide has demonstrated efficacy in HIV-infected patients with oral aphthous ulcers\textsuperscript{13} and idiopathic esophageal ulcers.\textsuperscript{14} In the oral ulceration trial, 16 (55%) of 29 patients had complete healing after 4 weeks of thalidomide 200 mg po qhs vs 2 (7%) of 28 patients in the placebo group. The thalidomide group also experienced reduced oral pain and improved ability to eat. Twelve patients with idiopathic esophageal ulcers were treated with thalidomide 200 mg po qhs resulting in a 92% complete symptomatic response.\textsuperscript{14} Prospective, double-blind, placebo-controlled trials will need to be performed to evaluate whether thalidomide can reduce chemotherapy- or radiation-induced mucositis in oncology patients.

Dosage and Administration

Erythema Nodosum Leprosum

For an episode of cutaneous ENL, therapy should be continued until signs and symptoms of active reaction have subsided (usually after a period of at least 2 weeks) then tapered off in 50 mg decrements every 2 to 4 weeks. Patients with a documented history of requiring prolonged maintenance therapy should be maintained on the minimal possible dose. Tapering off the medication should be attempted every 3 to 6 months in decrements of 50 mg every 2 to 4 weeks.\textsuperscript{3}
Antitumor Activity

A wide range of doses (100 to 1,200 mg/day) and dosing schedules (qhs to qid) continue to be studied in a variety of tumor types. Whether there is a dose-response relationship for activity is unknown, although there is a relationship for toxicity. Clinicians planning to use thalidomide in this setting are encouraged to enter their patients into clinical trials whenever possible. If study enrollment is not possible, clinicians should use generally the same dosing schema for which safety and efficacy data are available in patients with the same disease state.

Refractory Chronic Graft-vs-Host Disease

While optimal dosing for the treatment of CGVHD was not been established, clinicians should prescribe this agent based on the available literature. One approach is to initiate therapy at 100 mg po qid. The thalidomide dose should then be titrated upward gradually to a goal dose of 200 to 300 mg po qid based on the patient’s tolerance and evidence of clinical response.

Cost Evaluation

Thalidomide is supplied in boxes of 6 prescription packs of 14 capsules consisting of 50 mg each. Currently, the average wholesale price (AWP) for each box of 84 capsules is $630, which equals $7.50 per capsule. Daily costs per dose are shown in Table 5.

<table>
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<tr>
<th>Dose Per Day</th>
<th>Cost Per Day</th>
<th>Cost Per 28 Days</th>
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</thead>
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</tr>
<tr>
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<tr>
<td>1,200 mg</td>
<td>$180</td>
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</tr>
</tbody>
</table>

Table 5. — Costs of Thalidomide Use*

Based on the current average wholesale price (AWP) of $630 for each box of 84 capsules ($7.50 per 50-mg capsule).

Special Requirements

To minimize the substantial risk of thalidomide-induced teratogenicity — and with the approval of the Food and Drug Administration — Celgene Corp requires prescribers, pharmacists, and patients to use a restricted distribution system: the System for Thalidomide Education and Prescribing Safety (STEPS). To prescribe thalidomide, the physician, physician assistant, or advanced registered nurse practitioner must register with the STEPS program. To dispense thalidomide, the pharmacy must also be registered with the STEPS program. Patient education materials on the risks of thalidomide and on contraceptive measures are required to be reviewed with the patient. The patient and the prescriber are then required to review and sign the informed consent form. The consent form informs the patient of necessary contraceptive measures and frequency of pregnancy testing, as discussed previously. Patients are also required to participate in a mandatory and confidential survey on a monthly basis for women and at least every 3 months for men. The registered pharmacy may dispense no more than a 28-day supply of thalidomide after receiving a copy of the informed consent document and after electronically verifying patient and prescriber eligibility with the STEPS Patient Registry. As most inpatient hospital pharmacies are unlikely to participate in the STEPS program, patients should bring their own supply of thalidomide if hospitalization is required.

Conclusions

Thalidomide is a complex immunomodulatory and antiangiogenic agent whose role in oncology practice is as yet not fully clear. Thalidomide has notable salvage therapy in multiple myeloma and CGVHD following alloBMT. To determine its antiangiogenic activity and how best to use this agent, thalidomide needs to be studied in a variety of tumor types, used both alone and in combination with chemotherapy. Whenever possible, patients with refractory malignancies should be enrolled in clinical trials to answer some of these questions. In addition, further research may indicate whether thalidomide has a beneficial role in reducing or preventing cancer cachexia and mucositis. The potential benefits of thalidomide must not blind us to the danger of teratogenicity. Proper patient counseling and monitoring are critical for the safe use of thalidomide in the oncology population.

References
