

# Thalidomide: A Review of Approved and Investigational Uses

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## ABSTRACT

**Background:** Thalidomide is best known as a major teratogen that caused birth defects in up to 12,000 children in the 1960s. More recently, this agent has been approved by the US Food and Drug Administration for the treatment of erythema nodosum leprosum (ENL) through a restricted-use program. Its immunomodulatory, anti-inflammatory, and antiangiogenic properties are currently under study in a number of clinical conditions.

**Objective:** This article reviews the pharmacology of thalidomide; its approved and off-label uses in dermatologic, oncologic, and gastrointestinal conditions; and adverse events associated with its use.

**Methods:** Relevant articles were identified through searches of MEDLINE (1966–June 2002), International Pharmaceutical Abstracts (1970–June 2002), and EMBASE (1990–June 2002). Search terms included but were not limited to *thalidomide*, *pharmacokinetics*, *pharmacology*, *therapeutic use*, and *teratogenicity*, as well as terms for specific disease states and adverse events. Further publications were identified from the reference lists of the reviewed articles. Abstracts of recent symposia were obtained from the American Society of Clinical Oncology Web site.

**Results:** Thalidomide is thought to exert its therapeutic effect through the modulation of cytokines, particularly tumor necrosis factor- $\alpha$ . In addition to its approved indication for ENL, thalidomide has been studied in various other conditions, including graft-versus-host disease, discoid lupus erythematosus, sar-

coidosis, relapsed/refractory multiple myeloma, Waldenstrom's macroglobulinemia, myelodysplastic syndromes, acute myeloid leukemia, myelofibrosis with myeloid metaplasia, renal cell carcinoma, malignant gliomas, prostate cancer, Kaposi's sarcoma, colorectal carcinoma, oral aphthous ulcers, Behçet's disease, Crohn's disease, and HIV/AIDS-associated wasting. Adverse events most frequently associated with its use include somnolence, constipation, rash, peripheral neuropathy, and thromboembolism.

**Conclusions:** Use of thalidomide is limited by toxicity, limited efficacy data, and restricted access. Evidence of its efficacy in conditions other than ENL awaits the results of controlled clinical trials. (*Clin Ther.* 2003;25:342–395) Copyright © 2003 Excerpta Medica, Inc.

**Key words:** thalidomide, pharmacology, therapeutic use, adverse events.

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## INTRODUCTION

Thalidomide was introduced in October 1957 by the German company Chemie Grünenthal as a “safe” over-the-counter sedative/tranquilizer. It was subsequently marketed in 46 countries for morning sickness during pregnancy. Severe congenital abnormalities were soon seen in infants born to mothers who had taken thalidomide. (Ironically, the first reported case was a child born without ears on December 25, 1956—10 months before the product was marketed—to an employee of Grünenthal, who had brought samples home to his pregnant wife.<sup>1</sup>) McBride<sup>2</sup> and Lenz<sup>3</sup> published the first reports of an association between the use of thalidomide and birth defects.

Case reports revealed a variety of deformities, most notably amelia (lack of a limb) or phocomelia (seal limb), in thalidomide-exposed children. Also reported were deformities of the heart, kidney, and eyes; absent or abnormal external ears; cleft lip or palate; spinal cord defects; and disorders of the gastrointestinal tract. In all, 8000 to 12,000 infants were affected worldwide.<sup>1</sup> An unknown number of miscarriages also may have been caused by thalidomide.

In the United States, although some infants and adults suffered adverse consequences, thalidomide was used by a limited number of individuals. Its large-scale use was prevented by the action of Dr. Frances Kelsey of the US Food and Drug Administration (FDA), who delayed approval of the drug due to concerns over reports of peripheral neuropathy in adults. Evidence of the teratogenic effects of thalidomide emerged worldwide, and the drug was never approved for general use in the United States.<sup>1</sup> In 1962, thalidomide was withdrawn from the world market (with the exception of Brazil), and the experience with this agent was responsible for many countries' adoption of more stringent guidelines for the testing and approval of medications.

Had it not been for a serendipitous discovery by Jacob Sheskin,<sup>4</sup> the story of thalidomide might have ended at this point. In 1965, Sheskin reported administering thalidomide to an insomniac patient with erythema nodosum leprosum (ENL), an inflammatory complication of leprosy. The patient was able to sleep, and after 3 days of therapy, his symptoms had cleared and his skin lesions healed completely. Sheskin then reported similar results in another 5 patients. Further studies followed,<sup>5</sup> and thalidomide was eventually licensed for the treatment of ENL in Mexico and Brazil. In July 1998, the FDA approved the use of thalidomide for acute management of the cutaneous manifestations of moderate to severe ENL and as maintenance therapy for the prevention and suppression of the cutaneous manifestations of ENL recurrence.<sup>6</sup>

To safeguard patients and prevent fetal exposure, the US manufacturer of thalidomide developed a restricted prescribing and dispensing program called S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety).<sup>6</sup> Under this program, physicians and pharmacists must be registered to prescribe or dispense the drug, and are provided with educational materials concerning the risks of thalidomide therapy. Patients must view an educational video. Women of childbearing potential must use 2 effective methods of contraception and undergo pregnancy testing before and during thalidomide therapy. During thalidomide therapy and for 1 month thereafter, men must use a condom during sexual intercourse with women of childbearing potential.

Interest in the therapeutic potential of thalidomide has increased over the past few years. Investigations into its immunomodulatory, anti-inflammatory, and antiangiogenic properties are ongoing. This article reviews the pharmacology of thalidomide; its approved and off-label uses for dermatologic, oncologic, and gastrointestinal conditions; and adverse events (AEs) associated with its use.

## METHODS

Relevant articles were identified through searches of MEDLINE (1966–June 2002), International Pharmaceutical Abstracts (1970–June 2002), and EMBASE (1990–June 2002). Search terms included but were not limited to *thalidomide*, *pharmacokinetics*, *pharmacology*, *therapeutic use*, and *teratogenicity*, as well as terms for specific disease states and AEs. Further publications were identified from the reference lists of reviewed articles. Abstracts of recent symposia were obtained from the Web site of the American Society of Clinical Oncology.

## CHEMISTRY

Thalidomide— $\alpha$ -(*N*-phthalimido)glutarimide—contains a phthalimide ring and a glutarimide ring. The glutarimide ring has a single asymmetric carbon (chiral center); hence, it possesses a racemic mixture of dextrorotatory (*R*) and levorotatory (*S*) forms in a ratio of 1:1 (figure). The chemical formula of thalidomide is C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>, and it has a molecular weight of 258.2 g.

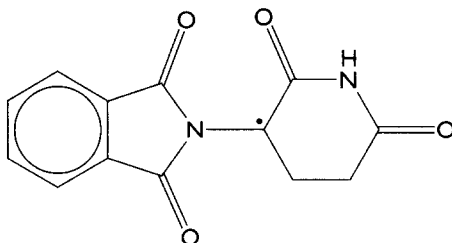


Figure. Structure of thalidomide. Note: • represents an asymmetric carbon atom.

Thalidomide is an off-white to white crystalline powder that is poorly soluble in water and ethanol.<sup>6</sup> The enantiomers of thalidomide are 5 times more soluble in water than the mixture.<sup>7,8</sup> Thalidomide undergoes rapid spontaneous (nonenzymatic) degradation at physiologic pH in an aqueous environment.<sup>9–11</sup> It is available in the United States as a 50-mg capsule whose inactive ingredients include anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

## PHARMACOLOGY

### Absorption

Due to thalidomide's poor aqueous solubility, no IV form is available. Its absolute bioavailability is not known. Although thalidomide is a racemic mixture (the pharmacokinetics of the separate enantiomers have been studied by Eriksson et al<sup>7,12</sup>), the majority of published studies measure total drug. When assaying in vitro and biological samples, special care must be taken to prevent hydrolysis and chiral inversion of thalidomide and its enantiomers.<sup>10</sup>

Teo et al<sup>13</sup> conducted an open-label, single-dose, 3-way crossover study in 15 healthy adults. Subjects received single or multiple capsules of thalidomide as follows: one 50-mg capsule, four 50-mg capsules (200 mg), or eight 50-mg capsules (400 mg). The mean maximum concentrations ( $C_{\max}$ ) of thalidomide with the 50-, 200-, and 400-mg doses were a respective 0.62, 1.76, and 2.82  $\mu\text{g/mL}$ . The times to  $C_{\max}$  ( $T_{\max}$ ) were 2.9, 3.5, and 4.3 hours after the respective doses.  $C_{\max}$  and  $T_{\max}$  were not dose proportional. The product information for thalidomide states that the  $T_{\max}$  varies from 2.9 to 5.7 hours in both healthy subjects and patients with Hansen's disease.<sup>6</sup> The observed decrease in  $C_{\max}$  and increase in  $T_{\max}$  with increasing dose<sup>6</sup> can be explained by the drug's poor solubility. When the area under the concentration–time curve extrapolated to infinity ( $\text{AUC}_{0-\infty}$ ) was calculated, absorption of thalidomide was found to be dose proportional,<sup>13</sup> indi-

cating that the amount absorbed and clearance of thalidomide are independent of dose.

The foregoing results are consistent with the reports of other investigators (Table I<sup>13-20</sup>). Similar findings have been noted in HIV-infected patients receiving multiple doses of thalidomide.<sup>19,20</sup> The lower-than-expected plasma thalidomide concentrations observed in patients with chronic malabsorption syndrome and graft-versus-host disease (GVHD) may be due to a decrease in the amount of drug absorbed.<sup>21,22</sup> The bioavailability of thalidomide has been reported to be increased in patients with Hansen's disease (leprosy) compared with healthy subjects.<sup>6</sup>

Teo et al<sup>18</sup> investigated the effect of a high-fat meal on the absorption of a single 200-mg dose of Thalomid (Celgene Corporation, Warren, New Jersey) in

**Table I. Pharmacokinetic parameters of thalidomide. All formulations studied were products of Celgene Corporation, Warren, New Jersey, with the exception of the formulation in reference 14, which was a product of Andrusis Pharmaceuticals, Greenbelt, Maryland.**

Reference	No. of Subjects	Dose, mg	AUC <sub>0-∞</sub>	C <sub>max</sub> <sup>a</sup> , µg/mL	T <sub>max</sub> <sup>a</sup> , h	t <sub>1/2</sub> <sup>a</sup> , h	V/F, L	Cl/F, L/h
13	15	50	4.9	0.62	2.9	5.5	81.1	10.4
		200	18.9	1.76	3.5	5.5	87.8	10.9
		400	36.4	2.82	4.3	7.3	121.9	11.7
14	10	200	41.1*	3.2*	5.8	6.7*	—	5.4*
			59.6†	4.2†	—	6.8†	—	4.1†
15	12	200	23.0*	2.3*	5.8*	3.0*	39.5*	9.16*
			22.8‡	2.3‡	5.15‡	3.35‡	44.4‡	9.04‡
16	12	100	9.8	1.15	2.5	4.6	69.9	10.4
		200	19.4	1.92	3.3	5.3	82.7	10.8
17	17	200	19.8	2.0	3.2	6.2	89.3	10.5
18	13	200§	24.7	1.99	4.0	5.8	—	—
19	7	200	—	2.1	6.3	5.7	1.15  ¶	5.7
	5¶	—	—	2.0¶	3.9¶	7.3¶	1.24¶#	3.6
20	9**	50	8.8	1.1	2.7	7.1	0.81#	0.08
	8	100	11.3	1.4	2.2	6.3	1.06#	0.13
	5	150	20.9	3.2	2.4	5.7	1.43#	0.16

AUC<sub>0-∞</sub> = area under the concentration-time curve extrapolated to infinity; C<sub>max</sub> = maximum concentration; T<sub>max</sub> = time to C<sub>max</sub>; t<sub>1/2</sub> = terminal half-life; V/F = apparent volume of distribution; Cl/F = apparent total clearance.

\*Day 1.

†Day 21.

‡Day 18.

§Fasted.

||Week 1.

¶Week 4.

#L/kg.

\*\*Week 8.

healthy subjects. Food delayed the onset of absorption by 0.5 to 1.5 hours but caused <10% change in  $AUC_{0-\infty}$  and  $C_{max}$ . According to the study protocol, >20% difference in  $AUC_{0-\infty}$  or  $C_{max}$  between the fasted and fed states was considered significant. The  $T_{max}$  was increased to 6 hours. The study also investigated the Talizer formulation of thalidomide (Serral S.A. de C.V., Col. del Valle, Mexico) and noted differences in the absorption of this product compared with that of Thalomid. The  $C_{max}$  was 2 times higher and the  $AUC_{0-\infty}$  was 10% higher with Thalomid compared with Talizer. The authors emphasized that different products may not have identical bioavailability.<sup>18</sup>

Eriksson et al<sup>23</sup> studied the rectal absorption of suppository and gel formulations of thalidomide compared with the oral form. Rectal absorption was slow and unreliable, and the authors did not recommend this route of administration.

### **Distribution**

After oral administration of thalidomide 50, 200, and 400 mg to healthy subjects, Teo et al<sup>13</sup> reported mean apparent volumes of distribution (V/F) of 81.1, 87.8, and 121.9 L, respectively. The increase in V/F with the 400-mg dose may represent a "flip flop" effect in which the terminal elimination rate constant represents absorption instead of elimination. As a result, the V/F calculation is unreliable. Those studies that included patients' body weight reported a thalidomide V/F of ~1 L/kg body weight (Table I).<sup>19,20</sup>

The degree of plasma protein binding of thalidomide is not known. The mean plasma protein binding of the R- and S-enantiomers has been reported as 55% and 66%, respectively.<sup>9</sup> The volume of the central compartment for the R- and S-enantiomers has been reported as 18 and 24 L, respectively.<sup>7</sup> A pharmacokinetic study in HIV-infected patients reported detectable concentrations of thalidomide in semen from 2 patients that were correlated with plasma levels.<sup>24</sup>

### **Metabolism**

Thalidomide is not appreciably metabolized by the liver.<sup>25</sup> With chronic administration, it does not inhibit or stimulate its own metabolism or that of other drugs.<sup>6,14,15,19,20</sup> Thalidomide undergoes rapid spontaneous nonenzymatic hydrolysis (12 products found in humans) in biological fluids.<sup>6,9-11,26</sup> Temperature and pH affect the rate of hydrolysis in aqueous and biological fluids.<sup>9-11</sup>

### **Elimination**

Teo et al<sup>13</sup> reported a mean half-life of 5.5, 5.5, and 7.3 hours after single 50-, 200-, and 400-mg doses of thalidomide in healthy subjects. These data are consistent with those from other reports (Table I). The half-life of thalidomide was similar after chronic administration in HIV-infected patients.<sup>19,20</sup> The mean elimination half-life of the 2 enantiomers of thalidomide is reported to be 4.7 hours, with an apparent clearance of

10 and 21 L/h for the *R*- and *S*-enantiomers, respectively.<sup>7</sup> Little unchanged thalidomide is excreted in the urine, and the renal clearance of thalidomide is 1.15 mL/min.<sup>6,27</sup>

### **Drug Interactions**

Little is known about the potential for drug interactions with thalidomide. Because the enantiomers have low rates of protein binding, interactions on this basis are unlikely.<sup>9</sup> In vitro studies indicate that thalidomide is not significantly metabolized by the human cytochrome P450 system, making interactions with medications metabolized by this pathway unlikely.<sup>25</sup> Chronic administration of thalidomide in 22 female volunteers did not affect the pharmacokinetics of a single dose of ethinyl estradiol and norethindrone.<sup>14,15</sup> Thalidomide may enhance the sedative effects of alcohol, reserpine, barbiturates, and chlorpromazine.<sup>6</sup> It produces sedation by activating diencephalic sleep centers without depressing central nervous system (CNS) neuronal function.<sup>28</sup>

### **MECHANISM OF ACTION**

Thalidomide is administered as a racemic mixture and has immunomodulatory and anti-inflammatory properties that are most likely mediated by its ability to affect cytokine production and cell function. In vitro and in vivo studies have investigated the effect of the individual enantiomers of thalidomide.<sup>7,9,12</sup> Sedative effects are more closely associated with the *R*-enantiomer, whereas immunologic effects are more closely associated with the *S*-enantiomer. When a specific enantiomer is administered orally or intravenously, it undergoes chiral inversion to the other enantiomer in vivo,<sup>7,12</sup> making total separation of their effects impossible. Many studies have attempted to determine the mechanism of thalidomide and have often yielded conflicting data. Thalidomide decreases production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in monocytes and macrophages by increasing the elimination of TNF- $\alpha$  mRNA, thus decreasing the signaling that induces TNF- $\alpha$  production.<sup>29,30</sup> Usually elevated concentrations of TNF- $\alpha$  were found to be decreased by thalidomide in patients with ENL<sup>31</sup> and HIV disease and tuberculosis.<sup>32</sup> However, concentrations of TNF- $\alpha$  rose in other groups of HIV-infected patients who did not have tuberculosis, despite a response to thalidomide therapy.<sup>33,34</sup> Efforts are under way to create thalidomide analogues that have greater ability to decrease TNF- $\alpha$  production without the toxicity of the parent compound.<sup>35–37</sup>

It is likely that the effect of thalidomide on cellular function depends on the stimulus, the cell line used, and the clinical condition treated.<sup>38</sup> In patients with chronic Crohn's disease who responded to thalidomide therapy, production of TNF- $\alpha$  and interleukin (IL)-12 was decreased in peripheral blood mononuclear cells (PBMCs) and intestinal lamina propria mononuclear cells, whereas IL-1 and IL-6 concentrations did not change significantly.<sup>39</sup> Another research group reported increases in levels of IL-12, soluble IL-2 receptor, and soluble CD8 anti-

gen in HIV-infected patients who received thalidomide.<sup>40</sup> In vitro studies of stimulated PBMCs have shown a decrease in cytokine production (IL-2 and interferon gamma) by type 1 T-helper cells and an increase in cytokine production (IL-4 and IL-5) by type 2 T-helper cells with administration of thalidomide.<sup>41</sup> In contrast, Verbon et al<sup>42</sup> reported that thalidomide increased production of interferon gamma and IL-12p40 by stimulated PBMCs from healthy adults; production of IL-5 decreased, and there was no change in the production of IL-2 or IL-4.

Thalidomide has effects on other components of cell function. It inhibits monocyte and polymorphonuclear leukocyte phagocytosis without cytotoxicity.<sup>43</sup> Inhibition of polymorphonuclear leukocyte chemotaxis has been reported in an in vitro model.<sup>44</sup> Leukocyte migration to inflammatory sites may be affected by downregulation of cell adhesion molecules.<sup>45</sup> Thalidomide has been reported to decrease the ratio of circulating T-helper cells to suppressor T cells in healthy subjects as the result of a decrease in production of helper cells and increase in production of suppressor cells.<sup>46</sup> In HIV-infected patients, thalidomide therapy may exert a beneficial effect by increasing HIV-specific CD8+ T-cell function.<sup>47</sup>

Thalidomide has demonstrated antiangiogenic properties in animal models. Using the rabbit cornea micropocket assay, D'Amato et al<sup>48</sup> found that thalidomide inhibited angiogenesis induced by basic fibroblast growth factor (bFGF). Because this inhibition occurred only after oral administration of thalidomide, it has been hypothesized that an active metabolite is formed in vivo.<sup>48,49</sup> D'Amato et al concluded that inhibition of angiogenesis was independent of thalidomide's effect on TNF- $\alpha$  formation.<sup>48</sup> Kruse et al<sup>50</sup> reported that thalidomide inhibited angiogenesis induced by vascular endothelial growth factor (VEGF).

The results of these animal studies inspired investigation of thalidomide in conditions in which angiogenesis is thought to play a role (eg, cancer). Thalidomide has been evaluated in patients with multiple myeloma (MM), in whom the degree of angiogenesis in bone marrow is correlated with overall survival.<sup>51</sup> Most studies have not found a significant difference in the microvessel density of bone marrow between patients responding and not responding to thalidomide therapy.<sup>52,53</sup> It may be that thalidomide exerts a local effect on the bone marrow environment but does not reverse existing pathology.

Neben et al<sup>54</sup> measured concentrations of angiogenic growth factors in patients with MM who received thalidomide. They found no difference in plasma or bone marrow concentrations of bFGF, VEGF, TNF- $\alpha$ , or IL-6 between responders and nonresponders. Another group of investigators reported a decrease in plasma blood and bone marrow concentrations of FGF, VEGF, TNF- $\alpha$ , and IL-6 in thalidomide responders compared with nonresponders.<sup>55</sup>

Keifer et al<sup>56</sup> proposed that the anti-inflammatory and antiangiogenic effects of thalidomide may be mediated through blockade of NF- $\kappa$ B activation by suppressing the activity of I $\kappa$ B kinase. Other investigators have suggested an effect of



thalidomide by modulation of the number and functions of natural killer cells in MM,<sup>57</sup> inhibition of the expression of cyclooxygenase-2 protein in an MM cell line and stimulated PBMCs,<sup>58</sup> and induction of apoptosis or G1 growth arrest in MM cells.<sup>59</sup> The growth and survival of tumor cells may also be affected by modulation of the profile of adhesion molecules.<sup>45,60</sup>

## CLINICAL USES OF THALIDOMIDE

### ***Dermatologic Conditions***

#### ***Erythema Nodosum Leprosum***

In the United States, thalidomide is approved for management of the acute cutaneous manifestations of ENL and for prevention of recurrences. Patients with moderate to severe neuritis should not receive thalidomide as monotherapy.<sup>6</sup> ENL, or type II lepra reaction, is a complication of multidrug therapy (eg, rifampin/dapsone, rifampin/dapsone/clofazimine) for Hansen's disease (leprosy). Fifteen percent to 25% of patients develop ENL during the first year of therapy.<sup>61</sup> The condition is characterized by painful erythematous nodules of the skin and subcutaneous tissue. Systemic findings may include fever, hepatosplenomegaly, arthralgia, myalgia, neuritis, malaise, anorexia, leukocytosis, weight loss, anemia, epididymo-orchitis, nephritis, iritis, progressive synovitis, and lymphadenitis.<sup>5</sup> Thalidomide is effective in the management of ENL reactions, although it is not active against borderline or tuberculoid reactions.<sup>62</sup> Thalidomide is thought to exert its beneficial action in ENL through its ability to decrease production of TNF- $\alpha$  and its downregulation of cell-surface adhesion molecules that affect white blood cell (WBC) migration.<sup>6,29,31,63</sup>

In a double-blind study in patients with ENL,<sup>5</sup> 92% of thalidomide recipients responded to therapy, compared with 27% of placebo recipients ( $P < 0.001$ ). In another double-blind study,<sup>64</sup> thalidomide was more effective than aspirin in managing cutaneous manifestations of ENL. Skin nodules have been reported to begin resolving within 3 days of initiation of thalidomide treatment and to disappear within 6 to 10 days; systemic symptoms such as fever, neuritic and arthritic pain, and malaise were reported to begin resolving within 24 to 48 hours.<sup>31</sup> The need for corticosteroids may be reduced in patients with ENL who receive thalidomide.<sup>65</sup> Many patients relapse when thalidomide is discontinued.<sup>64–66</sup> AEs associated with thalidomide therapy for ENL are generally mild to moderate and usually do not require discontinuation of the agent. AEs include somnolence, constipation; urticarial, erythematous, and vesicular rashes; edema of the extremities; left-sided facial edema; decreased libido; and increased appetite.<sup>66</sup>

For management of an episode of cutaneous ENL, the manufacturer of thalidomide recommends an initial once-daily dose of 100 to 300 mg taken with water,

preferably at bedtime but at least 1 hour after the evening meal.<sup>6</sup> Therapy in patients weighing <50 kg should begin at the lower end of the dosing range. Moderate to severe neuritis may require concomitant use of corticosteroids.<sup>6</sup> In patients who have required higher doses of thalidomide in the past or who have severe cutaneous ENL, thalidomide may be started at a higher dose (up to 400 mg once daily or in divided doses). Thalidomide should be continued until signs and symptoms resolve (at least 2 weeks). When discontinuing thalidomide, it is recommended that the dose be tapered in 50-mg decrements every 2 to 4 weeks. Patients requiring maintenance therapy should receive the lowest possible dose to prevent a reaction and avoid drug-related AEs. Tapering of the medication should be attempted every 3 to 6 months.<sup>6</sup>

### ***Graft-Versus-Host Disease***

GVHD occurs as a complication of an allogeneic bone marrow transplant (BMT) or peripheral blood stem-cell transplant. Acute GVHD occurs during the first 3 months after BMT, and chronic GVHD (CGVHD) occurs  $\geq 3$  months after BMT. CGVHD may occur in 30% to 60% of patients undergoing human leukocyte antigen (HLA)-matched sibling-donor BMT.<sup>67</sup> Although the pathophysiology of the disease is poorly understood, it is probably a combination of alloimmunity and autoimmunity.<sup>68</sup> The skin, gastrointestinal tract (mouth, chronic diarrhea with or without malabsorption), eyes, joints, lungs, and liver may be involved.

Thalidomide has been investigated in patients with CGVHD after the failure of conventional therapy with corticosteroids, cyclosporine, or tacrolimus. An open-label study by Vogelsang et al<sup>69</sup> involved 23 patients with refractory CGVHD and 21 with high-risk CGVHD (median age, 28 years; range, 3–50 years). The starting dosages of thalidomide were 200 mg QID in adults and 3 mg/kg body weight QID in children. Doses were adjusted to achieve thalidomide concentrations of 5  $\mu\text{g/mL}$  2 hours after a dose. A complete response was defined as complete resolution of active disease in all organs. A partial response was defined as >50% but <100% improvement in all affected organs. Patients with refractory CGVHD continued current medications for GVHD for 3 months after starting thalidomide therapy. Patients with high-risk CGVHD continued prophylactic cyclosporine for acute GVHD for 6 months after transplantation. Immunosuppressive therapy was discontinued at the beginning of thalidomide therapy in the first 4 patients entering the study. Overall survival was 64% (28/44), including 78% (18/23) of patients with refractory disease and 48% (10/21) of patients with high-risk disease. In patients with refractory CGVHD, the rates of complete, partial, and no response were 30%, 48%, and 22%, respectively. In patients with high-risk GVHD, the corresponding rates were 33%, 5%, and 62%. The most common AEs were sedation (91%), constipation (50%), and neuropathy (9%).

Parker et al<sup>70</sup> described their experience with thalidomide in 80 patients with CGVHD who had received an allogeneic BMT from HLA-matched siblings or

matched unrelated donors. The median age of patients was 26 years (range, 6–50 years). Forty-seven percent of patients were categorized as having high-risk disease. A complete response was defined as complete resolution of all clinical manifestations of CGVHD, and a partial response was defined as 50% improvement in objective manifestations of CGVHD. The starting dosage of thalidomide was 100 mg QID, which was increased to 200 and 300 mg QID as tolerated over an unspecified period. Patients also received prednisone alone or prednisone and cyclosporine. Prednisone/cyclosporine could be tapered if improvement occurred. Twenty percent (16/80) of patients responded to thalidomide treatment (9 complete response, 7 partial response). Response rates (complete and partial responses) in patients with CGVHD of the mouth only and those with combined CGVHD of the skin and mouth were 27% (4/15) and 40% (6/15), respectively. The 12 patients with combined skin and liver CGVHD did not respond to therapy, nor did the 5 with gastrointestinal CGVHD (4 lower intestinal and 1 esophageal, with or without mouth, skin, lung, or liver involvement). The median time to response was 3 months, and the median thalidomide dosage was 200 mg QID. Thirty-eight percent (6/16) of responders were able to discontinue all medication for 8 to 36 months. The response to therapy was best in patients with skin involvement that did not include severe sclerodermatous features and in those with isolated liver or mouth CGVHD. Most patients could not tolerate a daily dose >400 to 600 mg. Therapy was discontinued in 36% (29/80) of patients because of AEs. Eight of these patients were responding to thalidomide at the time of discontinuation. Overall, reasons for discontinuation included sedation, constipation, skin rash (including flare of existing rash), neutropenia, and sensory neuropathy.

Browne et al<sup>71</sup> reported on the addition of thalidomide to existing immunosuppressive therapy in 37 patients with refractory CGVHD after allogeneic BMT. The 21 pediatric patients had a median age of 10 years (range, 2–17 years); the 16 adult patients had a median age of 33 years (range, 21–47 years). Thalidomide was started at 50 mg QID and was increased by 200 mg at 2- to 4-week intervals. The maximum target dosages were 800 mg/d for adults and 12 mg/kg daily for children. A complete response was defined as no GVHD in any organ or system, whereas partial response was defined as improvement in  $\geq 1$  affected organ and no progression in any involved organ. One patient had a complete response, and 62% (23/37) had no response. Overall, 25% (4/16) of adults and 48% (10/21) of children had a partial response. Patients with lung involvement did not respond. Improvement was more common in patients with skin involvement. The median duration of response was 18 months (range, 3–42 months). Kaplan-Meier 2-year survival was 41% (95% CI, 24–59). The comparative 2-year survival of children and adults was 51% (95% CI, 27–76) and 27% (95% CI, 4–51), respectively ( $P = 0.07$  adults vs children). Constipation and sedation occurred in 80% of patients. Peripheral neuropathy occurred in 1 patient. Skin rash

necessitated discontinuation in 3 patients. Other investigators have reported a good response in children with GVHD.<sup>72-74</sup>

Chao et al<sup>75</sup> conducted a randomized, placebo-controlled study of thalidomide as possible prophylaxis for GVHD. All patients received acute GVHD prophylaxis after transplantation. Starting 80 days after allogeneic BMT, 28 patients received thalidomide 200 mg BID, and 26 received placebo. There was a nonsignificant higher incidence of GVHD and significantly lower overall survival ( $P = 0.006$ ) in patients receiving thalidomide compared with placebo. These findings did not support use of thalidomide for the prevention of CGVHD.

Arora et al<sup>67</sup> conducted a randomized study comparing the effect of the combination of thalidomide, cyclosporine, and prednisone with that of the combination of cyclosporine and prednisone as initial therapy for CGVHD. Patients were assessed after 2, 6, and 12 months of therapy. Twenty-four patients received thalidomide and 27 patients did not. The median age of the thalidomide group was 44 years (range, 17–60 years); that of the no-thalidomide group was 37 years (range, 12–50 years). The maximum dosage was 200 mg QID in adults and 3 mg/kg QID in children. No differences between patients receiving and not receiving thalidomide were noted in terms of the rate of response at 1 year or in terms of 1- and 2-year survival. Thalidomide concentrations were not measured in this study, and because 70% of patients had gastrointestinal involvement, the adequacy of absorption could not be ensured. However, the investigators felt that adequate absorption was indicated by rates of AEs (somnolence 63%, constipation 52%) in the thalidomide group that were similar to those reported elsewhere.

Koc et al<sup>76</sup> conducted a Phase III, double-blind, placebo-controlled study of thalidomide in patients with extensive CGVHD. Fifty-one patients were enrolled and randomized (25 thalidomide, 26 placebo). All patients also received prednisone and cyclosporine or tacrolimus. Thalidomide was started at 200 mg/d (3 mg/kg QD for children aged <12 years and weighing <67 kg). The dosage was increased as tolerated up to 200 mg QID for adults and up to 3 mg/kg QID for children. Only 16% of patients were able to tolerate the maximum dose. Therapy was discontinued in 92% of thalidomide recipients and 65% of placebo recipients before resolution of CGVHD ( $P = 0.02$ ). Neutropenia occurred in 64% of patients receiving thalidomide and 23% of patients receiving placebo ( $P = 0.003$ ). Thalidomide recipients experienced more frequent numbness (48% thalidomide, 23% placebo;  $P = \text{NS}$ ), sedation (68% thalidomide, 19% placebo;  $P = 0.001$ ), and constipation (40% thalidomide, 8% placebo;  $P = 0.009$ ). The duration of thalidomide therapy was too short to determine efficacy.

Thalidomide may be beneficial in some circumstances; however, the high incidence of AEs at the doses used limits its value in the management of CGVHD. Larger controlled studies are necessary. Consideration should be given to monitoring thalidomide concentrations in the blood to determine the adequacy of absorption and compliance with therapy.

***Cutaneous Lupus Erythematosus***

Chronic discoid lupus erythematosus (CDLE) is confined to the skin, whereas systemic lupus erythematosus (SLE) is a multisystem disease that may involve cutaneous and mucocutaneous tissue. Thalidomide has been investigated as a potential therapy for cutaneous forms of lupus in patients who have failed to respond to conventional therapy. Knop et al<sup>77</sup> reported the results of an open-label study of thalidomide treatment in 60 patients with CDLE who had failed to respond adequately to other therapies, all of which were withdrawn 1 month before commencing thalidomide. The starting dosage of thalidomide was 200 mg BID; once improvement was noted, the dosage was reduced once a month until a maintenance dosage of 50 to 100 mg/d was achieved. Efficacy was assessed in patients who had received therapy for >3 months. Sixty-five percent of patients had complete regression with minimal occasional disease activity, 25% had significant regression (not defined) with some residual activity, and 10% had some regression but no substantial improvement. No statistical analysis was provided. Thirty of 41 (73%) patients relapsed a mean of 3.5 months after discontinuation of therapy. Sixteen patients who relapsed were retreated with thalidomide, and all had a good response. During maintenance therapy, 35% of patients relapsed after being disease free for a mean of 5 months. The incidence of AEs was high. The most common AEs included somnolence (60 patients), constipation (19), rash (7), circulatory disturbances (7), oral dryness (2), lower leg edema (4), and peripheral neuropathy (15). These symptoms disappeared soon after drug discontinuation, with the exception of peripheral neuropathy, which was reported to be present in a few patients 1 year after discontinuation of thalidomide. The authors recommended that lower doses be used in future studies and that a neurologic examination be performed before, during, and after completion of thalidomide therapy.

Kyriakis et al<sup>78</sup> conducted an open-label study in 22 patients who had failed to respond to previous therapy for CDLE. The initial thalidomide dosage was 50 to 200 mg/d, depending on the extent and severity of disease. Previous pharmacotherapy for CDLE was discontinued 1 to 3 months before initiation of thalidomide. Complete (90%–100%) and partial (70%–80%) remission occurred in 55% and 23% of patients, respectively (95% CI, 32.2–75.6). The mean time to complete and partial remission was 65.4 and 68.0 days, respectively. Patients who achieved complete or partial remission received mean daily doses of 116 mg (range, 100–200 mg) and 110 mg (range, 50–200 mg), respectively. Four patients remained disease free at the time of the report, and 67% had  $\geq 1$  relapse after drug withdrawal (mean, 39.4 days). Therapy was withdrawn in 14% of patients due to adverse drug events, whereas 27% of patients experienced no such events. The most common complaints during therapy were drowsiness (41%), somnolence (18%), and constipation (14%). Two patients complained of paresthesias. The au-

thors concluded that lower doses of thalidomide appeared to be an effective alternative in patients failing to respond to conventional therapy for CDLE.

Stevens et al<sup>79</sup> studied thalidomide therapy in 16 patients with cutaneous manifestations of lupus erythematosus that had failed to respond to previous therapy. Thalidomide was initiated at 50 to 100 mg/d. No patient received more than 100 mg/d. Modification of existing therapy was individualized. Complete/almost complete (clearance of rash) or partial remission (improvement in rash, but less than complete clearance) occurred in 44% and 37% of patients, respectively. Responders began to show improvement within 2 weeks, and the maximum response was seen after 16 weeks of therapy. The thalidomide dose was tapered based on the response to therapy. Remission was maintained at daily doses of 25 and 50 mg in 45% and 55% of patients, respectively. Relapse occurred in 75% of patients after discontinuing thalidomide therapy. AEs included drowsiness (32%) and headache (6%). One patient developed peripheral neuropathy after receiving a cumulative thalidomide dose of 22 g.

Walchner et al<sup>80</sup> investigated the activity of thalidomide in 5 patients with SLE, 1 with subacute cutaneous lupus erythematosus and 4 with CDLE. During the first 4 weeks of thalidomide therapy, patients continued to take corticosteroids at their usual doses; doses were then reduced on a weekly basis. The starting dose of thalidomide was 100 mg/d in 9 patients and 300 mg/d in 1 patient. The dose was reduced to 50 mg after 4 months of therapy. Skin lesions began to resolve after 2 to 3 weeks of therapy in all patients. Eight of the 10 patients relapsed within 1 to 3 weeks after discontinuing therapy. Four patients stopped therapy due to development of peripheral neuropathy; symptoms resolved in 3 of 4 patients, and improvement was noted after 1 year in the patient with persistent symptoms. All patients experienced tiredness.

Thalidomide appears to be a valuable second-line agent for the management of cutaneous complications of lupus erythematosus.<sup>78-81</sup> Clinical response (complete/almost complete response and partial response) was reported in 80% to 100% of patients in the studies reviewed, whereas lack of response was reported in 5% to 20% of patients.<sup>80</sup> On discontinuation of therapy, 67% to 80% of patients relapsed.<sup>78-81</sup> Maintenance therapy is necessary to prevent relapse, although it is not always effective.<sup>79</sup> AEs, including peripheral neuropathy, are common even at low doses.

### **Sarcoidosis**

Sarcoidosis is a multisystem disease of unknown etiology. It is characterized by the formation of multiple noncaseating granulomas. It most commonly involves the lungs, lymph nodes, skin, and eyes. In individual case reports,<sup>82,83</sup> thalidomide has had clinical efficacy in this condition.

Oliver et al<sup>84</sup> conducted a 16-week open-label trial of thalidomide in 8 patients with sarcoidosis. The disease involved the skin in all patients. Seven patients had

stage I pulmonary sarcoidosis, and 1 patient had stage IV pulmonary changes. Patients continued stable doses of prednisone or cyclosporine during the study. Thalidomide was initiated at 50 mg/d and was doubled on a monthly basis to a maximum dosage of 200 mg/d. Skin lesions became hyperpigmented in all patients. Lesions became flattened in 5 patients and did not change in size or elevation in 2 patients. In 1 patient, lesions became more elevated and nodular, and central necrosis and ulceration were noted. Seven of 8 patients reported improvement in pulmonary symptoms. One patient experienced a progression of pulmonary disease. When thalidomide was discontinued, disease activity returned to its pre-thalidomide state. AEs included increased inflammation of skin lesions in the first month of therapy (7 patients), dry skin and pruritus (5), transient paresthesias (3), weight gain (2), and maculopapular erythematous rash (1). Increases in eosinophils and decreases in neutrophils were noted; values returned to normal after discontinuation of thalidomide. Pathologic evaluation of skin lesions before and during therapy showed that thalidomide caused granuloma differentiation to a Th1-type cellular immune response.<sup>84</sup> These preliminary data from small numbers of patients are encouraging.

### ***Miscellaneous Dermatologic Uses***

Thalidomide has been used in numerous dermatologic conditions when standard therapies have failed to produce a satisfactory response. It has shown some benefit in scleroderma,<sup>85</sup> actinic prurigo,<sup>86</sup> prurigo nodularis,<sup>87</sup> erythema multiforme,<sup>88</sup> erosive lichen planus,<sup>89</sup> lichen planopilaris,<sup>90</sup> uremic pruritus,<sup>91</sup> pyoderma gangrenosum,<sup>92</sup> Jessner's lymphocytic infiltration of the skin,<sup>93</sup> and adult Langerhans cell histiocytosis.<sup>94</sup> However, the data are based on case reports or studies in small numbers of patients, and further study is necessary.

Toxic epidermal necrolysis should not be treated with thalidomide. Wolkenstein et al<sup>95</sup> conducted a randomized, placebo-controlled study of thalidomide in patients with this condition. The study was terminated early when it was found that the mortality rate was higher in patients who received thalidomide than in those who received placebo. Ten of 12 patients in the thalidomide group died, compared with 3 of 10 in the placebo group (relative risk, 2.78; 95% CI, 1.04–7.40;  $P = 0.03$ , Fisher exact test with Katz's approximation). The mechanism of toxicity may be a thalidomide-induced increase in TNF- $\alpha$  production.

### ***Oncologic Conditions***

#### ***Multiple Myeloma***

MM constitutes ~1% of all cancers and ~10% of all hematologic carcinomas. Therapy involves chemotherapy with or without stem-cell transplantation, but the likelihood of cure is low. Discovery of a correlation between survival and the

degree of angiogenesis in the bone marrow of patients with MM has led to investigation of thalidomide as salvage therapy.<sup>51,52</sup>

Singhal et al<sup>52</sup> were among the first to investigate thalidomide in an open-label study in 84 MM patients with advanced or refractory disease. Thalidomide was initiated at a daily dose of 200 mg; the dose was increased by 200 mg every 2 weeks to a maximum of 800 mg/d, as tolerated. Patients received no other therapy for MM. Eighty-six percent, 68%, and 55% of patients received 400, 600, and 800 mg, respectively. Response was defined in terms of decreases in serum or urine paraprotein of at least 25%, 50%, 75%, and 90% on 2 occasions at least 6 weeks apart. A complete response was defined as the absence of monoclonal protein (M-protein) on immunofixation testing. Thirty-two percent of patients achieved  $\geq 25\%$  decrease in serum or urine paraprotein concentrations, and 2 patients had a complete response. The median time to a  $\geq 25\%$  decrease in paraprotein concentrations was 29 days (range, 4 days–6 months). After a median follow-up of 14.5 months, 12 of 27 responding patients had relapsed and 6 had died.

Barlogie et al<sup>96</sup> continued the preceding study, which has accrued 169 patients. Over a median follow-up of 22 months, 37% of patients achieved  $\geq 25\%$  reduction in serum or urine paraprotein levels, and 14% achieved complete or near-complete remission. Responding patients had a reduction in bone marrow plasmacytosis and serum beta<sub>2</sub>-microglobulin concentrations and an increase in hemoglobin (Hb) levels. Patients with no cytogenetic abnormalities were more likely to achieve a  $\geq 25\%$  reduction in paraprotein levels than were patients with cytogenetic abnormalities (52% vs 28%, respectively;  $P = 0.003$ ); similarly, patients with a low plasma cell-labeling index were more likely to have a better response to therapy than were those with a high plasma cell-labeling index (44% vs 10%, respectively;  $P < 0.001$ ). Patients have discontinued the study due to disease progression (105), toxicity (28), and other reasons (12).

The overall response to thalidomide in patients with MM has varied from 30% to 72% (Table II).<sup>53,59,96–104</sup> Combining thalidomide with pamidronate may be effective in refractory MM, with a resultant decrease in bone pain.<sup>105</sup> Responding patients may relapse quickly or may have a sustained response.<sup>53,97,103–106</sup> In the study by Barlogie et al,<sup>96</sup> median 2-year event-free survival and overall survival were 20% and 48%, respectively ( $N = 84$ ). Another group of investigators reported 50% overall survival at day 360.<sup>97</sup> Hus et al<sup>99</sup> reported a calculated mean survival of 250 weeks in patients who received thalidomide (210 in patients who received chemotherapy) and progression-free survival of 240 weeks in responding patients. In studies of thalidomide as single therapy for MM, daily doses varied from 50 to 800 mg (Table II); the dose was reduced in patients who were unable to tolerate maximal doses because of toxicity.

Most studies of thalidomide in MM used a single daily dose administered in the evening to minimize the effect of sedation; however, divided doses have also



**Table II. Response to thalidomide used as a single agent in patients with refractory/relapsed multiple myeloma, based on percent decrease in levels of serum monoclonal protein and/or urine Bence Jones protein.**

Reference	No. of Patients	Maximum Dose, mg/d*	% Decrease				Complete Response	Overall Response, %
			≥25	≥50	≥75	≥90		
59	44	800 <sup>†</sup>	5 <sup>‡</sup>	11			1	39
96	169	800	12	17	10	20	3	37
97	120	400	18 <sup>§</sup>	14 <sup>§</sup>	4 <sup>§</sup>			30
98	17	800	1	5	5			64
99	53	200 BID	8	12	3		4	51
100	23	400 BID <sup>†</sup>	9	3				52
101	60	800	11	17				47
102	29	200	5	7				41
103	32	800		10				31
104	36	50–400 <sup>  </sup>	7	3	6			44

\*Doses titrated according to tolerance; usually lower than target.

<sup>†</sup>Median dose 400 mg.

<sup>‡</sup>Response defined as stable disease (≤50% decline in serum monoclonal protein level).

<sup>§</sup>Day 180 of therapy.

<sup>||</sup>Dose based on response.

been used to increase tolerability.<sup>99,100</sup> Because of thalidomide's short half-life, Juliusson et al<sup>106</sup> evaluated the use of multiple daily doses compared with a single daily dose. Patient response was defined using the criteria of the European/International Bone Marrow Transplantation Registry. These investigators reported a better response in patients receiving divided doses (50%) compared with those receiving a single daily dose (29%).

Significant AEs occurred in these studies, resulting in discontinuation of medication and drug-related deaths.<sup>96–106</sup> In 1 study,<sup>96</sup> 58% of patients experienced AEs that included sedation, constipation, peripheral neuropathy, and deep-vein thrombosis (DVT). Peripheral neuropathy was a concern with chronic dosing, even at low doses.<sup>104</sup> Other AEs have included skin rash, leukopenia, bradycardia, and cardiac arrhythmias.<sup>98–101</sup> In 2 reports based on a small number of patients,<sup>107,108</sup> no correlation was found between efficacy or toxicity and blood concentrations of thalidomide. Well-controlled studies in larger patient populations are required to determine the potential role of therapeutic drug monitoring of thalidomide in patients with MM.

The combination of thalidomide and dexamethasone has been used to improve the response in patients with relapsed or refractory MM, with reported response rates of 48% to 66% (Table III).<sup>109–113</sup> The response to therapy is usually noted

within 1 to 3 months after the initiation of therapy.<sup>110-112</sup> In 1 comparative study,<sup>112</sup> therapy with thalidomide/dexamethasone yielded an overall response rate of 48%, compared with 44% for melphalan/prednisone. Response was characterized in terms of a reduction in M-protein of >75%, a reduction of 50% to 75%, or no response. Median event-free survival was 12 and 11 months for the thalidomide/dexamethasone and melphalan/prednisone groups, respectively.

Weber et al<sup>114</sup> reported an increased response with the addition of intermittent dexamethasone in patients with MM who had not responded to thalidomide alone. In a compilation of data from a University of Arkansas research group, Barlogie et al<sup>115</sup> compared the response in MM patients receiving thalidomide and dexamethasone with that in patients receiving dexamethasone alone. Fifty-seven percent of patients receiving combination therapy had a  $\geq 50\%$  reduction in para-protein levels, compared with a 27% reduction in patients receiving dexamethasone alone. A complete response (defined as the absence of M-protein on immunofixation analysis) occurred in 29% and 0% of patients receiving combination therapy and dexamethasone alone, respectively ( $P = 0.04$ ). No standard dose of thalidomide or dexamethasone has been determined for use in combination regimens. Improvements in bone pain and Hb concentrations have been reported to accompany the response to combined dexamethasone and thalidomide ther-

**Table III. Response to therapy with thalidomide and dexamethasone in patients with refractory/relapsed multiple myeloma, based on percent decrease in levels of serum M-protein and/or urine Bence Jones protein (or as specified).**

Reference	No. of Patients	Daily Thalidomide Dose, mg*	% Decrease			Response, %†
			$\geq 25$	$\geq 50$	$\geq 75$	
109	77	100‡	19	18	14	66
110	47	800§		24		52
111	44	400		11	13	55
112	44	100‡		7	14	48
113	27	600¶	8	7		56

\*Doses titrated to response; final doses may be lower than target.

†Response criteria were as follows: reference 109, 3% complete response; reference 110,  $\geq 50\%$  decrease in Bence Jones protein; and reference 111,  $\geq 75\%$  decrease in Bence Jones protein.

‡Dexamethasone dose, 40 mg orally on days 1 through 4 of each month.

§Dexamethasone dose, 20 mg/m<sup>2</sup> on days 1 through 5 and 15 through 18 each month until response.

||Dexamethasone dose, 20 mg/m<sup>2</sup> orally on days 1 through 4, 9 through 12, and 17 through 20, and then monthly on days 1 through 4.

¶Dexamethasone dose, 40 mg on days 1 through 4 at 3-week intervals.

apy.<sup>109,112</sup> The combination of thalidomide and dexamethasone has also been used as consolidation therapy in patients with MM.<sup>116</sup>

Thalidomide has been combined with cytotoxic chemotherapy regimens in a number of studies. Barlogie et al<sup>115</sup> reported on a Phase III study in 80 patients with MM who received dexamethasone, cyclophosphamide, etoposide, and cisplatin with or without thalidomide. The patients were in relapse and had a high tumor burden. Response was characterized in terms of a reduction in urine or serum M-protein levels of  $\geq 50\%$ ,  $\geq 75\%$ , or  $\geq 90\%$ , or complete response. The rates of response (partial and complete) to the regimens without and with thalidomide were 18% and 36%, respectively. After 2 years of treatment, event-free survival and overall survival were 38% and 48%, respectively. No difference in event-free or overall survival was noted between those who did and did not receive thalidomide after 2 years.

Another study in patients with MM investigated DT-PACE (regimen consisting of dexamethasone and thalidomide combined with cisplatin, doxorubicin, cyclophosphamide, and etoposide) for 2 cycles (with collection of peripheral blood stem cells), followed by randomization to melphalan-based tandem transplantation or continuation of DT-PACE.<sup>115</sup> The 2-year event-free survival was 73% in both arms. An earlier study on the use of DT-PACE in patients with refractory/relapsed MM reported the deaths of 3 of 43 patients due to drug toxicity.<sup>117</sup> The protocol has since been modified, and patients continue to be accrued for studies of this regimen.

Moehler et al<sup>118</sup> conducted an open-label study of the combination of thalidomide with cyclophosphamide, etoposide, and dexamethasone as salvage therapy in patients with MM. Patient response was defined using the criteria of the European/International Bone Marrow Transplantation Registry, as described in Juliusson et al.<sup>106</sup> The overall response rate was 77%, and the projected 1-year progression-free survival was 60% (95% CI, 0.41–0.75). Garcia-Sanz et al<sup>119</sup> reported an overall response rate of 76% (13/17 patients) and a projected 1-year event-free survival rate of 51% in patients with relapsed/refractory MM receiving thalidomide, cyclophosphamide, and dexamethasone. Among responders, 9 (53%) patients achieved a partial response ( $>50\%$  decrease in M-protein levels), including 2 patients with a complete response (no detectable M-protein, with  $<5\%$  plasma cells in bone marrow). Four (23%) patients had clinical improvement but  $<50\%$  reduction in M-protein. Intermittent thalidomide and dexamethasone have been added to cyclophosphamide therapy, with 50% of previously treated patients achieving a partial response.<sup>120</sup> Previous treatments included high-dose dexamethasone, autologous stem cell transplantation, and pretreatment with thalidomide and dexamethasone. AEs attributed to thalidomide occurred in  $<20\%$  of patients in this study.

Thalidomide has been combined with melphalan and melphalan plus dexamethasone in patients with refractory/relapsed MM, with response rates of 82% (>25% decrease in paraprotein) and 81% (response based on modified Eastern Cooperative Oncology Group criteria), respectively.<sup>121,122</sup> Toxicity was high, with 87% and 62% of patients experiencing leukopenia and neutropenia, respectively. The combination of thalidomide, clarithromycin, and dexamethasone has also been used in patients with MM with a good early response but high toxicity.<sup>123</sup>

Investigations into the potential role of thalidomide as part of first-line therapy for MM are ongoing. A study of a protocol called Total Therapy II is accruing patients, with a final projected size of 660.<sup>115</sup> Patients are being randomized to receive or not receive thalidomide as part of induction, consolidation, and maintenance regimens for MM. The 2-year event-free and overall survival rates for the entire study population to date (309 patients) are 88% and 92%, respectively. The data reflect the entire population due to the blinding protocol. An increased incidence of DVT in the thalidomide group compared with those who did not receive thalidomide (28% vs 6%;  $P = 0.006$ ) has necessitated the addition of prophylactic low-dose warfarin to the protocol. Hypothyroidism has occurred more frequently in the thalidomide group.

Rajkumar et al<sup>124</sup> conducted a Phase II study of the combination of thalidomide and dexamethasone in patients with untreated MM. The initial design called for thalidomide dosing to be increased to a maximum of 800 mg/d, but this was reduced to a final fixed dosage of 200 mg/d due to the occurrence of skin toxicity. Response was defined as  $\geq 50\%$  reduction in serum and urine M-protein levels. The response rate was 64% (95% CI, 49–77).

Thalidomide has been used as single therapy in patients with smoldering MM or indolent MM, many of whom progress to full MM within a few years. Thirty-eight percent (6/16) of patients had a  $\geq 50\%$  decrease in serum and urine M-protein levels.<sup>125</sup> Longer follow-up is necessary to determine whether thalidomide therapy delays progression to MM.

Two Phase I studies of the oral thalidomide derivative CC5013 have been conducted in patients with relapsed/refractory MM. Significant neutropenia, thrombocytopenia, cardiovascular complications (including syncope), and thromboembolism have been reported during therapy.<sup>126,127</sup>

### **Waldenstrom's Macroglobulinemia**

Dimopoulos et al<sup>128</sup> conducted an open-label study of thalidomide in 20 patients with Waldenstrom's macroglobulinemia, 10 of whom had not received previous therapy. Patients received no other medication for their condition during the study. Dosing was initiated at 200 mg/d and increased to 600 mg/d as tolerated. Most patients did not reach the maximum dose due to toxicity or progressive disease. Five patients (25%) experienced a partial response (>50% reduction

in serum M-protein concentration for  $\geq 2$  months and  $>50\%$  tumor reduction at all affected sites). These patients had an increase in Hb concentration, decrease in bone marrow lymphocytosis, and decrease in splenomegaly and lymphadenopathy. Five patients had stable disease ( $<25\%$  change in serum M-protein concentration and no additional complications of macroglobulinemia), and 10 patients had progressive disease. Among responders, the maximum tolerated daily doses were 400 mg in 4 patients and 200 mg in 1 patient. Daily maintenance doses in responders were 200 mg in 3 patients and 100 mg in 2 patients. The duration of response ranged from 3 to  $>16$  months. No patients responded who had  $>2$  years of treated disease or were in refractory relapse. The incidence of AEs was high (75% constipation, 40% mood changes/depression, 25% peripheral neuropathy). Although the results of this preliminary study were encouraging, further studies in larger numbers of patients are necessary.

### ***Myelodysplastic Syndromes***

Myelodysplastic syndromes (MDS) are preleukemic clonal hematopoietic stem cell disorders characterized by peripheral cytopenias.<sup>129</sup> Thalidomide is being investigated in MDS for its anti-TNF- $\alpha$ , immunomodulatory, and anti-angiogenic attributes,<sup>129–131</sup> although its exact mechanism of action in these syndromes is unknown.<sup>131</sup> Raza et al<sup>130</sup> studied thalidomide at a maximum daily dose of 400 mg in 83 patients with MDS who received no other therapy for their condition. Thirty-six patients had refractory anemia (RA), 13 had RA with ringed sideroblasts (RARS), 24 had RA with excess blasts (RAEB), 6 had RAEB in transformation (RAEB-t), and 4 had chronic myelomonocytic leukemia (CMML). Patients were categorized by prognosis: 21 in the low-risk group, 37 in the intermediate-1 (INT-1) group, 12 in the INT-2 group, and 13 in the high-risk group. The criteria for response were based on the report of an international working group.<sup>132</sup> A major erythroid response was defined as an increase in Hb of  $>2$  g/dL when the pretreatment value was  $<11$  g/dL and transfusion independence in previously transfusion-dependent patients. A minor erythroid response was defined as an increase in Hb of 1 to 2 g/dL when the pretreatment value was  $<11$  g/dL and a 50% reduction in transfusion requirement in previously transfusion-dependent patients. Intent-to-treat and efficacy-analyzable (patients who completed  $\geq 12$  weeks of maximally tolerated thalidomide) evaluations were conducted. In the intent-to-treat analysis, 19% (16/83) of patients responded to thalidomide therapy; in the efficacy-analyzable analysis, 31% (16/51) of patients responded. No patient had complete remission. The majority of patients were unable to tolerate the 400-mg dose of thalidomide, and most patients received 150 to 200 mg/d at bedtime. Fifteen patients showed improvement in the erythroid cell line (11 major erythroid responses, 4 minor erythroid responses). Six patients had a 100% reduction in packed red blood

cell (PRBC) transfusion requirement, and 4 had a 100% reduction in PRBC transfusion requirement and an increase in Hb. One transfusion-independent patient had an increase in Hb of  $>2$  g/dL. There were no responders in terms of absolute neutrophil count (ANC). The median duration of response was 306 days in 15 patients, and 4 patients continued to respond to thalidomide at the time of the published report. One transfusion-dependent patient had no response to thalidomide after 12 weeks at the maximum tolerated dosage of 200 mg/d, and thalidomide was discontinued; subsequently, a sustained improvement was seen in all 3 cell lines, and the patient required no transfusion for  $\sim 9$  months. Seventeen of 32 patients who discontinued thalidomide before completing 12 weeks of therapy were in the high-risk or INT-2 categories, whereas 8 of 51 patients who continued therapy were in the high-risk or INT-2 groups ( $P = 0.002$ ). Patients who discontinued therapy also had a higher percentage of blasts in bone marrow pretherapy compared with those who continued therapy (7% vs 2%, respectively;  $P = 0.003$ ). The authors hypothesized that patients with less-advanced disease appeared to tolerate and respond better to thalidomide than patients in higher-risk groups.

Strupp et al<sup>129</sup> conducted an open-label trial in 34 patients with MDS (16 RA, 6 RARS, 4 RAEB, 5 RAEB-t, and 3 CMMoL). Patients were categorized by risk, with 4 classified as low risk, 14 as INT-1, 9 as INT-2, and 7 as high risk. Thalidomide was initiated at a daily dose of 100 mg, which was increased by 100 mg per week until the maximum tolerated dose was reached; the median thalidomide dose was 400 mg. Patients received no other therapy for MDS during the study. Criteria for response were based on the international working group report.<sup>132</sup> Complete remission was defined as Hb  $>11$  g/dL, platelet count  $>100,000$  cells/ $\mu$ L, and WBC count  $\geq 1500$  cells/ $\mu$ L without bone marrow dysplasia for 8 weeks at a stable dose of thalidomide. Partial remission was defined by Hb, platelet count, and WBC count as above, with dysplastic changes in the bone marrow. A major erythroid response was defined as an increase in Hb of 2 g/dL when the pretreatment value was  $<11$  g/dL, and a minor erythroid response was defined as an increase in Hb of between 1 and 2 g/dL. A major platelet response was defined as an increase in platelets of  $\geq 30,000$  cells/ $\mu$ L, and a minor platelet response was defined as an increase of  $>10,000$  but  $<30,000$  cells/ $\mu$ L. A major neutrophil response was defined as an increase in ANC of  $>500$  cells/ $\mu$ L, and a minor response was defined as an increase of  $<500$  cells/ $\mu$ L. Patients' disease was considered stable when neither hematologic improvement nor disease progression was noted for  $\geq 2$  months. A hematologic response was noted after 2 months of therapy. Twenty-nine patients were evaluable for response, of whom 19 had a response to therapy, including 9 with partial remission. All patients achieved a normal peripheral blood count. The median duration of response was 10 months. Four patients had a major response, and 6 had a minor response. Patients with a partial response

and those with a major response became transfusion independent, whereas patients with a minor response had a 50% decrease in transfusion requirement. Four patients had stable disease, and 6 had disease progression during therapy. In contrast to the results of a study by Raza et al,<sup>130</sup> this trial reported a better response in patients with more advanced disease; however, these patients tended to relapse, whereas those with lower-risk disease were still responding to therapy at the time of the published report.

Two studies have evaluated the combination of thalidomide with other agents for the treatment of MDS.<sup>133,134</sup> Patients received no other therapy during these studies. In 1 study by Raza et al,<sup>133</sup> 51 patients received the combination of thalidomide (maximum tolerated daily dose, 300 mg), pentoxifylline 400 mg TID, ciprofloxacin 500 mg BID, and dexamethasone 4 mg/d for 5 days every 4 weeks. The criteria for response were based on the international working group report.<sup>132</sup> Of 25 evaluable patients, 9 showed hematologic improvement, 6 had stable disease, and 10 had no response. All responders were in the categories of low to intermediate risk. Three patients became transfusion independent.

Another study by Raza et al<sup>134</sup> investigated the combination of thalidomide with etanercept. Twenty-six patients received thalidomide at a maximum daily dose of 300 mg and etanercept 25 mg by subcutaneous injection twice weekly. Eighteen patients completed the 16-week trial. Ten patients were in the low-risk category and 8 in the intermediate-risk category. Three patients became transfusion independent, with a major erythroid response. One patient had an improvement in all 3 cell lines, and 1 had disappearance of dysplastic features. Five patients had stable disease or minimal improvement. The use of combination therapy for MDS appeared to be well tolerated.

### ***Acute Myeloid Leukemia***

Steins et al<sup>135</sup> administered thalidomide to 20 patients with acute myeloid leukemia. Patients were not candidates for intensive cytotoxic chemotherapy or stem cell transplantation, or were refractory to induction chemotherapy. Thalidomide was initiated at 200 mg/d and increased to a maximum of 800 mg/d. Seven patients dropped out of the study due to drug intolerance, progressive disease, or personal reasons. Thirteen patients remained in the study for >4 weeks and received daily doses of between 200 and 400 mg. Partial response was defined as  $\geq 50\%$  decrease in blast cell infiltration of the bone marrow. Hematologic improvement was defined as a  $>10\text{-g/dL}$  increase in Hb concentration, a platelet count  $>30,000$  cells/ $\mu\text{L}$  during treatment, and no requirement for transfusion. Four patients had a partial response, and 1 patient had hematologic improvement. The median duration of response was 3 months. Responding patients had significantly lower microvessel density in the bone marrow compared with non-responders ( $P = 0.014$ ).

### ***Myelofibrosis with Myeloid Metaplasia***

Myelofibrosis with myeloid metaplasia (MMM) is a chronic myeloproliferative disease with the hallmark findings of bone marrow fibrosis and extramedullary hematopoiesis (ie, hepatosplenomegaly). Barosi et al<sup>136</sup> investigated the efficacy of thalidomide in 21 patients with MMM, of whom 13 were evaluable. Patients remained on their current therapy (8 patients hydroxyurea, 1 danazol, 4 red blood cell [RBC] transfusions) during the study. The daily thalidomide dose was titrated to a maximum of 400 mg. Nineteen patients discontinued therapy due to AEs before the planned 6-month mark. Eight patients showed a response that included an improvement in anemia and thrombocytopenia, a decrease in leukocytosis, and/or a decrease in spleen size. Effective dosages ranged from 100 to 200 mg/d. Three (23%) patients had an unwanted increase in WBC count, and 5 (38%) had an unwanted increase in platelet count. Such paradoxical increases in WBC and platelet counts in patients receiving thalidomide for the management of MMM have been reported elsewhere.<sup>137</sup>

Elliott et al<sup>138</sup> reported the results of an open-label study of thalidomide in 15 evaluable patients with MMM. The initial daily dose was 200 mg, with a planned maximum daily dose of 1000 mg. Patients were receiving no other therapy for MMM. Only 2 patients were able to tolerate a daily dose of 400 mg, and 12 patients discontinued therapy due to AEs. The median daily dose was 200 mg (range, 50–400 mg). Response was defined in terms of the effects of therapy on anemia and palpable splenomegaly. For anemia, a complete response was defined as an increase in Hb concentration to >11 g/dL, whereas a partial response was defined as a  $\geq 2$ -g/dL increase in Hb concentration or no requirement for RBC transfusion. For splenomegaly, a partial response was defined as a  $\geq 50\%$  decrease in palpable splenomegaly. Two patients had a complete response for anemia and 1 had a partial response. Each of these patients had a dosage reduction to 50 mg/d. One patient had a partial response for splenomegaly. Twelve (80%) patients had an increase in platelet count, and 3 (20%) developed serious thrombocytosis. One patient developed pericardial extramedullary hematopoiesis with tamponade, which the authors felt to be drug related.

Thalidomide appears to have benefit in selected patients with MMM. Increased thrombocytosis and leukocytosis are a concern and bear closer study. Patients were not able to tolerate thalidomide at the doses studied, and lower doses (eg, 50 mg/d) are under investigation.

### ***Renal Cell Carcinoma***

Renal cell carcinoma (RCC) accounts for 2% of all cancers.<sup>139</sup> It is resistant to chemotherapy and radiotherapy, and the likelihood of long-term survival is poor. RCC is a highly vascular tumor, and thalidomide is being investigated in this disease because of its antiangiogenic properties. Stebbing et al<sup>140</sup> reported on the ef-



fect of thalidomide in 25 patients (22 evaluable) with advanced RCC. Patients could not have received any therapy for RCC within 4 weeks of study admission and could not have undergone surgery within 3 weeks. The criteria for response were based on standards issued by the International Union Against Cancer. The target maximum dosage was 300 mg BID. Most patients did not reach this dosage because of toxicity (lethargy, constipation, neuropathy) or death due to progressive disease. Eleven patients who reached the target dose required a dose reduction due to toxicity. Two (9%) patients who received thalidomide 200 mg BID for  $\geq 12$  months had a partial response (95% CI, 1–29). Two (9%) patients had stable disease for  $\geq 12$  months (95% CI, 1–29), 5 (23%) had stable disease for 6 to 12 months (95% CI, 8–45), and 5 (23%) had stable disease for 3 to 6 months (95% CI, 8–45). In an intent-to-treat analysis, the median survival was 9 months and the response rate was 8% (2/25). This research group is currently investigating a maximum daily dose of 400 mg.

Motzer et al<sup>141</sup> reported on the use of thalidomide at the target maximum daily dose of 800 mg in 26 patients with advanced RCC, of whom 25 were evaluable. Thalidomide was the only treatment allowed during the study. Response was based on bidimensional measurements. Sixteen (64%) patients had stable disease (95% CI, 43–82), and 9 (36%) had progressive disease. The median duration of stable disease was 6 months (range, 3–18 months). Progression-free survival at 6 months was 32% (95% CI, 14–50). Fifty-seven percent of patients were alive at 1 year (95% CI, 34–76). Only 5 of 26 (19%) patients achieved the maximum dose. Toxicities included fatigue, constipation, neuropathy, bradycardia, and DVT. Motzer et al<sup>141</sup> noted an overall response rate of 6% in their review of compiled data. Based on the results to date, thalidomide's effect is minimal as a single agent for the treatment of RCC.

A study of the combination of thalidomide (maximum, 400 mg/d) with interferon alfa-2a (9 mU administered subcutaneously 3 times weekly) found significant toxicity and no response to therapy in patients with metastatic RCC.<sup>142</sup> Toxicity included seizures and visual disturbances. An ongoing Phase III study comparing the activity of low-dose interferon alfa with and without thalidomide should provide some insight into the role of thalidomide in combination therapy for RCC. Studies of the tolerability and efficacy of thalidomide combined with IL-2 in patients with metastatic RCC are under way.<sup>143</sup>

### ***Malignant Gliomas***

Malignant gliomas are vascular tumors of the brain and include glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA). Thalidomide is being studied for its ability to block tumor angiogenesis. Fine et al<sup>144</sup> investigated the benefit of thalidomide in an open-label study in patients with GBM (n = 25), AA (n = 12), and anaplastic mixed glioma (n = 2). Thirty patients had undergone tumor

resection, and 9 had undergone biopsy, and their disease had recurred after radiotherapy with or without chemotherapy. Patients had to have completed radiotherapy or chemotherapy  $\geq 3$  weeks (6 weeks from last nitrosurea treatment) before entering the study. Dexamethasone and antiseizure therapy could be continued during the study. Thalidomide was initiated at a daily dose of 800 mg and was increased to a maximum of 1200 mg/d. The response to therapy was evaluable in 36 patients. Partial response was defined as a  $\geq 50\%$  reduction in the size of enhancing tumors on magnetic resonance imaging (MRI). Two (6%) patients had a partial response and 12 had stable disease. The time to tumor progression was 10 weeks for the entire population, 15 weeks for patients with stable disease, and 33 weeks for patients with a radiologic response. Median survival was 28 weeks for the entire population, 30 weeks for patients with stable disease, and 74 weeks for patients with a radiologic response. The authors found no correlation between tumor histology and the response to therapy, although the number of patients was too small to draw definitive conclusions.

Marx et al<sup>145</sup> reported the results of an open-label study in 38 evaluable patients with grade IV GBM and radiographic evidence of recurrent disease after radiotherapy with or without chemotherapy. Chemotherapy or radiotherapy had to have been completed  $\geq 4$  weeks before study entry. Thalidomide was initiated at 100 mg/d and titrated to a maximum of 500 mg/d (median tolerated dosage, 300 mg/d). Complete response was defined in terms of resolution of contrast enhancement on MRI or computed tomography; a partial response was defined as a  $\geq 50\%$  decrease in size of enhancing tumor, and progression of disease was defined as a  $\geq 25\%$  increase in size of enhancing tumor, a new tumor, or deteriorating neurologic symptoms requiring an increase in corticosteroid dose. Two (5%) patients had a partial radiographic response, 16 (42%) had stable disease, and 20 (53%) had disease progression. The median time to progression for the entire group was 11 weeks, and the duration of response ranged from 5 to 38 weeks. Median survival was 31 weeks for the entire group and 74 weeks for patients with stable disease. The 6-month progression-free survival rate was 18%. The 2 patients with a partial response survived for 27 and 32 weeks.

Short et al<sup>146</sup> reported the results of an open-label, nonrandomized trial in 18 patients with recurrent gliomas treated with thalidomide at a maximum daily dose of 100 mg. All patients had received previous radiotherapy and chemotherapy for gliomas, but received only thalidomide during the study. Partial response was defined as  $\geq 50\%$  reduction in maximum tumor diameter on radiography, with improved or stable neurologic status; stable disease was defined by a lesser degree of radiologic change. One (6%) patient had a partial response after 6 months of therapy; 2 (11%) patients had stable disease for 4 and 2 months. Median survival was 2.5 months.

Fine et al<sup>147</sup> studied the combination of thalidomide and BCNU (carmustine) in 38 patients with recurrent high-grade gliomas (histologic diagnosis of GBM, AA,

or mixed glioma) and disease progression after radiotherapy. The maximum daily dose of thalidomide was 1200 mg, and each patient received BCNU 200 mg/m<sup>2</sup> every 6 weeks. One evaluable patient had a complete response, 4 had a partial response, 1 had a minimal response, and 16 had stable disease. Twenty-five percent of patients with recurrent GBM had 6-month progression-free survival.

These studies showed minimal benefit for thalidomide as a single agent in the treatment of recurrent gliomas, with partial responses noted in 5% to 6% of patients. Results of the study with BCNU were encouraging, indicating a need for further investigation of thalidomide combination therapy for malignant gliomas.

### ***Prostate Cancer***

Prostate cancer is the most common malignancy in American men. Figg et al<sup>148</sup> investigated the effect of thalidomide in a Phase II open-label study in patients with androgen-independent prostate cancer who had failed to respond to previous therapy. Patients were randomly assigned to the low-dose group (200 mg/d) or the high-dose group (1200 mg/d). Therapy with a luteinizing hormone–releasing hormone agonist could be continued, but other forms of antitumor therapy were not permitted. Enrollment in the high-dose group was discontinued at 13 patients because of inability to achieve the desired dose due to toxicity and lack of benefit. In the low-dose group, 18% of patients had a  $\geq 50\%$  decrease in prostate-specific antigen (PSA) level, compared with none in the high-dose group. The time to treatment failure was the same in both groups, and the overall median survival was 15.8 months.

Dahut et al<sup>149</sup> and Figg et al<sup>150</sup> published progress reports on a study in which patients with androgen-independent prostate cancer were randomly assigned to receive docetaxel with or without thalidomide. Patients had not received prior chemotherapy for prostate cancer. A  $\geq 50\%$  decrease in PSA level was noted in 37% of patients receiving docetaxel alone and 51% of patients receiving docetaxel and thalidomide. No statistical analyses were provided. Ten patients receiving combination therapy developed a venous thromboembolism. Because of the risk of thromboembolism, patients receiving the combination of thalidomide and docetaxel for prostate cancer are now started on prophylactic low-molecular-weight heparin. Thalidomide combined with granulocyte colony-stimulating factor has shown some clinical benefit (overall response rate, 38%; 95% CI, 17–65).<sup>151</sup> However, more data are necessary to determine the value of this combination.

### ***Kaposi's Sarcoma***

Because of its ability to inhibit production of TNF and its antiangiogenic properties, thalidomide has been investigated in patients with HIV infection and Kaposi's sarcoma (KS). The incidence of KS as an AIDS-defining condition has decreased in the era of highly active antiretroviral therapy (HAART).<sup>152</sup> In an

open-label Phase II study, Fife et al<sup>153</sup> administered thalidomide 100 mg nightly to 17 patients with HIV infection and cutaneous KS. Patients continued anti-retroviral therapy, which included a protease inhibitor in 1 patient. Six patients were withdrawn from the study due to drug-induced AEs. A partial response was defined as  $\geq 50\%$  decrease in the number and/or size of existing lesions for  $\geq 4$  weeks. Progressive disease was defined as the presence of new lesions, a  $\geq 25\%$  increase in size of existing lesions, or a change in  $\geq 25\%$  of lesions from macular to nodular. Stable disease was defined as not meeting the criteria for either partial response or progressive disease. In the intent-to-treat analysis, 6 of 17 (35%) patients achieved a partial response (95% CI, 10–61), 7 (41%) had progressive disease (95% CI, 15–67), and 4 (24%) had stable disease (95% CI, 1–46). The duration of response varied from 6 to  $>19$  weeks. Overall, human herpesvirus 8 (HHV-8) DNA was detected in 10 of 17 patients; the HHV-8 DNA load decreased in 4 of the 6 responding patients.

Little et al<sup>154</sup> studied the use of thalidomide in an open-label study in 20 patients with KS. The planned maximum daily dose was 1000 mg, although the median achievable dosage was 500 mg/d. Seventeen patients were receiving HAART that included a protease inhibitor or nonnucleoside reverse-transcriptase inhibitor. A partial response was defined as no disease progression and a 50% decrease in the sum of the cross-products of the lesions, 50% reduction in the total number of lesions, or flattening of  $\geq 50\%$  of nodular lesions for  $\geq 4$  weeks. Progressive disease was defined as a  $\geq 25\%$  increase in the measures of partial response or the onset of new or increasing edema or effusion (tumor associated) that interfered with daily activities. Stable disease was defined as not meeting the criteria for either partial response or progressive disease. Of 17 evaluable patients, 8 (47%) achieved a partial response (95% CI, 23–72), 7 (41%) had progressive disease during therapy, and 2 (12%) had stable disease. Overall, the median time to treatment failure was 7.3 months. Although these results are encouraging, it is known that HAART therapy can have beneficial effects on KS<sup>155</sup>; therefore, randomized comparative studies are necessary to determine thalidomide's effect on this disease.

### ***Colorectal Carcinoma***

Govindarajan et al<sup>156</sup> and Govindarajan<sup>157</sup> have presented progress reports on an open-label Phase II study of the combined use of thalidomide and irinotecan in 20 evaluable patients with metastatic colorectal carcinoma. Irinotecan was administered at a dose of 350 mg/m<sup>2</sup> IV every 3 weeks in patients aged  $<70$  years; those aged  $\geq 70$  years received 300 mg/m<sup>2</sup> every 3 weeks. All patients received thalidomide 400 mg/d at bedtime. Two (10%) evaluable patients had a complete response, 4 (20%) had a partial response, and 5 (25%) had stable disease. The response criteria were not described. AEs were manageable, and late-onset diarrhea caused by irinotecan was reduced by the concomitant thalidomide.

### **Miscellaneous Cancers**

Studies in small numbers of patients have found single therapy with thalidomide ineffective in patients with advanced melanoma,<sup>158</sup> ovarian carcinoma,<sup>158</sup> breast cancer,<sup>158,159</sup> and squamous cell carcinoma of the head and neck.<sup>160</sup> The results of studies of thalidomide combined with temozolomide<sup>161,162</sup> or DTIC (dacarbazine)<sup>163</sup> in patients with metastatic melanoma justify further investigation. Beneficial responses have been noted in Hodgkin's disease relapsing after autotransplantation (thalidomide combined with low-dose vinblastine),<sup>164</sup> Langerhans cell histiocytosis,<sup>165</sup> epithelioid leiomyosarcoma,<sup>166</sup> small-cell lung cancer (thalidomide combined with carboplatin/etoposide),<sup>167</sup> and unresectable hepatocellular carcinoma (thalidomide combined with celecoxib<sup>168</sup> and thalidomide alone<sup>169</sup>). Thalidomide may be beneficial in some patients with cancer cachexia.<sup>170</sup>

### **Gastrointestinal Conditions**

#### ***Oral Aphthous Ulcers in HIV-Positive Patients***

An AIDS Clinical Trials Group protocol described in 1997 by Jacobson et al<sup>33</sup> was designed to compare the effectiveness of thalidomide and placebo in the treatment of oral aphthous ulcers in HIV-positive patients. Enrolled patients had had aphthous ulcers for  $\geq 2$  weeks, with no infectious or neoplastic cause revealed on biopsy. Among the exclusion criteria were acute neutropenia (ANC  $< 500$  cells/ $\mu$ L) or thrombocytopenia (platelet count  $< 50,000$  cells/ $\mu$ L), bilateral peripheral neuropathy, and pregnancy. Fifty-seven patients were randomized in a double-blind manner to receive thalidomide 200 mg orally once daily or placebo for 4 weeks. Ulcer healing, health-related quality of life (eg, general health, pain, and ability to eat), and drug-related toxicity were assessed after 4 weeks of therapy. Complete healing of ulcers was seen in 55% of the thalidomide group, compared with 7% of the placebo group (95% CI, 1.8–499;  $P < 0.001$ ). The median time to complete healing was 3.5 weeks (95% CI, 2–4). At week 4, partial or complete healing was seen in 90% of the thalidomide group, compared with 25% of the placebo group (95% CI, 5.2–162;  $P < 0.001$ ). Quality-of-life scores for the thalidomide group improved in all categories ( $P < 0.03$ ) except general health. Thalidomide-related AEs included rash (24% thalidomide, 4% placebo) and somnolence (24% and 7%), with 6 patients requiring early discontinuation of therapy due to toxicity and 52% requiring a dose reduction. Three patients in the thalidomide group and 2 in the placebo group had grade 3 or 4 neutropenia. Peripheral neuropathy was no more prevalent in the thalidomide group than in the placebo group. No deaths or opportunistic infections were recorded during the 4 weeks of therapy.

The same research group later conducted a study of the effects of thalidomide on aphthous ulcers of the esophagus in HIV-positive patients with baseline CD4+

lymphocyte counts of  $<200$  cells/mL.<sup>171</sup> Both studies were designed to measure outcomes at 4 weeks, when therapy remained active. Twenty-four patients were randomly assigned to receive thalidomide 200 mg/d orally or placebo for 4 weeks. As measured by esophagoscopy at 4 weeks, 73% of the thalidomide group had complete ulcer healing, compared with 23% of the placebo group (OR 13.82; 95% CI, 1.16–823.75;  $P = 0.033$ ). Quality-of-life scores improved by a median of 1.7 in the thalidomide group, compared with  $-0.1$  in the placebo groups ( $P = 0.022$ ). AEs attributed to thalidomide were somnolence (4/11), peripheral sensory neuropathy (3/11), and rash (2/11), none of them occurring significantly more often than with placebo.

Ramirez-Amador et al<sup>172</sup> conducted an 8-week study comparing the efficacy of thalidomide and placebo in 16 adult HIV-infected patients with recurrent oral aphthous lesions. Compliance was measured by weekly pill counts, and 2 of the initially enrolled patients were removed from the study due to noncompliance. Patients randomized to receive thalidomide received 400 mg/d for 1 week, followed by 200 mg/d for 7 weeks. Nine of 10 (90%) patients in the thalidomide group had complete healing of ulcers at 8 weeks, compared with 2 of 6 (33.3%) patients in the placebo group ( $P = 0.03$ ). Rash was the most common (80%) drug-related AE in the thalidomide group, compared with 17% in the placebo group ( $P = 0.03$ ). Somnolence was also reported more often in the thalidomide group than in the placebo group (70% vs 33%), but the difference was not statistically significant. Neuropathy occurred in 1 patient in each group. Although this study extended assessment of the treatment response through 8 weeks, the effects of drug discontinuation were not addressed.

Two observational case studies have been published. Radeff et al<sup>173</sup> described the treatment of a 50-year-old HIV-positive man with multiple oral aphthous ulcers. Cultures of the ulcers were negative for bacterial, fungal, and herpes simplex virus infection. Topical lidocaine, steroids, oral antibiotics, acyclovir, and analgesics, both alone and in combination, produced limited results. After 2 weeks of oral thalidomide 100 mg/d, improvement was noted and the dosage was reduced to 50 mg twice weekly. After 7 months, transient paresthesias occurred and therapy was stopped. Ulcers recurred 2 to 3 weeks after drug discontinuation but abated 1 to 2 weeks after rechallenge.

In another case study, Diz Dios et al<sup>174</sup> described the use of thalidomide in a 39-year-old man with HIV-associated aphthous ulcers that had been refractory to previous therapies. The patient had received oral acyclovir therapy for 2 weeks and had a large oral ulcer and later multiple ulcers. Oral prednisone was initiated at 1 mg/kg daily, and 2 weeks later the ulcers continued to enlarge. Ulcer cultures were negative for viral, bacterial, or fungal infection. Pentoxifylline 300 mg TID and foscarnet 7000 mg/d were also unsuccessful. Thalidomide was initiated at 300 mg/d; partial ulcer healing was seen within a few days, but the patient died of unrelated causes.

These small comparative trials and case studies suggest a role for thalidomide 100 to 300 mg/d in the treatment of aphthous ulcers in HIV-positive patients. However, AEs may limit its use, and patients should be monitored closely. No trials of >2 months' duration are available for assessment of longer-term outcomes, and patients should be made aware of the relative risk of ulcer recurrence once the drug is discontinued.

### ***Oral Aphthous Ulcers in Non-HIV-Infected Patients***

Oral aphthous ulcers are also common in immunocompetent, non-HIV-infected patients. Thalidomide has been investigated for the treatment and prevention of recurrent oral aphthous ulcers in immunocompetent patients.<sup>175</sup> At least 4 to 8 weeks of therapy with thalidomide 100 to 150 mg/d may be required before ulcer healing. For prophylaxis, thalidomide doses of 100 to 150 mg every 48 to 72 hours have been investigated. In a randomized, double-blind, crossover trial by Revuz et al,<sup>176</sup> 73 adult patients with severe recurrent aphthous stomatitis received thalidomide 100 mg/d for 2 months followed by placebo for 2 months, or the reverse. Seventeen of 38 (45%) patients who received thalidomide first experienced complete remission by 1 month, compared with 1 of 35 (3%) patients who received placebo first ( $P < 0.001$ ). Thirteen patients with an initial response had a recurrence within a mean (SD) of 19 (9) days when switched to placebo.

Grinspan et al<sup>177</sup> reported a case series of 100 patients with oral aphthous ulcers treated with thalidomide 100 to 300 mg/d for  $\geq 3$  months. Patients' median age was 40 to 49 years, and 59% were men. The cure rate was 34%, and the partial cure rate was 100%. Two of 100 (2%) patients experienced peripheral paresthesias that abated on drug discontinuation. None of the ulcers recurred during treatment. Common side effects were somnolence (33%), increased appetite (24%), constipation (11%), and dry mouth (11%).

Buno et al<sup>178</sup> conducted a prospective, nonrandomized, case-control study in patients with recurrent aphthous stomatitis. Biopsy specimens from 21 patients were compared with mucosal specimens from 7 control patients. Patients with recurrent aphthous stomatitis had significantly elevated levels of IL-2 ( $P < 0.05$ ), interferon gamma ( $P < 0.04$ ), and TNF- $\alpha$  ( $P < 0.05$ ). Thalidomide's action as a downregulator of TNF- $\alpha$  production may explain its relative efficacy in patients with recurrent aphthous stomatitis.

### ***Behçet's Disease***

Nasca et al<sup>179</sup> conducted an in vitro study of the effect of therapeutic concentrations of thalidomide on human keratinocyte cells obtained from neonatal foreskin. They found that rates of cell proliferation and migration more than doubled in the presence of thalidomide compared with control samples. Increased migra-

tion was postulated to be secondary to an observed increase in keratinocyte-derived IL-8, a promigratory cellular autocrine factor. The authors suggested that this increased epithelial proliferation and migration secondary to thalidomide exposure may better explain the improved healing of skin ulcers in Behçet's disease.

Hamuryudan et al<sup>180</sup> conducted a randomized, double-blind, placebo-controlled trial of thalidomide in 96 men with oral and genital ulcers as manifestations of Behçet's disease. Patients were randomized to receive thalidomide 100 mg/d, thalidomide 300 mg/d, or placebo for 24 weeks. A complete response was defined as the absence of ulcers during treatment. Complete responses were observed in 2 of 32 (6%) patients receiving thalidomide 100 mg/d (95% CI, 0.8–20.8), 5 of 31 (16%) patients receiving thalidomide 300 mg/d (95% CI, 5.5–33.7), and 0 of 32 (0%) patients receiving placebo (95% CI, 0–10.9). With both doses of thalidomide, healing of oral ulcers was noted at 4 weeks ( $P < 0.001$ ), and healing of genital ulcers ( $P < 0.001$ ) and follicular lesions ( $P < 0.008$ ) was noted at 8 weeks. The number of erythema nodosum lesions increased during the first 8 weeks of therapy with both doses ( $P = 0.03$ ). AEs noted with thalidomide included decreased libido in 5 patients, peripheral neuropathy in 4, weight gain in 4, and oversedation in 3.

Through a retrospective medical record review, Gardner-Medwin et al<sup>181</sup> identified 59 patients (38 women) with severe oral or genital ulcers, all of whom had failed to respond to previous therapies and 23 of whom were diagnosed with Behçet's disease. Previous therapies had included oral or intravenous steroids and undefined cytotoxic agents. In the prospective portion of the study, patients received thalidomide 200 mg/d. The rate of complete ulcer resolution was 81.0% at 4 weeks and 84.7% at 8 weeks. At 4 weeks, 81.0% of patients were completely ulcer free; at 8 weeks, 84.7% were ulcer free. In those with Behçet's disease, 73.9% had complete resolution at 4 weeks and 82.6% had complete resolution at 8 weeks. Forty-five patients underwent measurement of sensory nerve action potential (SNAP) at baseline and after 6 months of treatment or total thalidomide consumption of 10 g, whichever occurred first, to determine the presence of peripheral neuropathy. Symptomatic neuropathy, defined as a 50% decrease in SNAP, was observed in 8 of 59 (14%) patients. The mean duration of therapy before the onset of neuropathy was 1079.5 days. The authors hypothesized that there may be a correlation between the length of therapy and development of neuropathy, but the study was not powered to test this observation.

As Behçet's disease is commonly diagnosed in childhood, there are a number of published case reports and case series concerning the use of thalidomide in children. Shek et al<sup>182</sup> evaluated the effectiveness of thalidomide in an infant with Behçet's syndrome that had been refractory to treatment with intravenous methylprednisolone, intravenous immune globulin, oral cyclophosphamide, and oral chlorambucil. The infant received thalidomide 10 mg/kg per day, and resolution



of oral ulcers and skin lesions was observed at 4 weeks. Pulse steroid and cytotoxic therapy were continued but were tapered over a 9-month period. Nerve conduction tests were performed and produced no evidence of neuropathy. No information was provided on the time of testing or the types of tests used. Thalidomide therapy was continued for 12 months, and oral ulcers and rash recurred 2 weeks after drug discontinuation. Thalidomide was restarted at 5 mg/kg in combination with low-dose oral steroids, and skin manifestations again resolved. No follow-up data were included in this case report, and the ramifications of prolonged thalidomide administration in this population remain unknown.

Kari et al<sup>183</sup> conducted a retrospective review of the cases of 10 pediatric patients with Behçet's disease who received treatment with thalidomide or colchicine. The median age of these patients was 4 years (range, 1.2–12 years) at initial presentation. All had oral lesions, 60% had genital ulcers, and 30% had perianal ulcers. Overall, 5 patients completed thalidomide therapy at dosages ranging from 1 mg/kg per week to 1 mg/kg per day for a median of 2.2 years (range, 1.3–4.3 years). All received concomitant steroids. The median age of these 5 patients was 11.4 years (range, 7–16 years). Three of these 5 had complete ulcer healing, and 2 had partial healing. Neuropathy developed in 2 patients and was permanent in 1 case.

### **Crohn's Disease**

Thalidomide's ability to decrease proinflammatory cytokines (ie,  $\text{TNF-}\alpha$ )<sup>39</sup> has led to its investigation in Crohn's disease. Ehrenpreis et al<sup>184</sup> conducted an open-label study of thalidomide in patients with refractory Crohn's disease. Thirteen patients had refractory perianal fistulas, and 9 had steroid-refractory luminal disease. Patients continued their pre-thalidomide medications, and corticosteroid doses were tapered based on the clinical response. Eighteen and 4 patients received thalidomide 200 and 300 mg/d, respectively, at bedtime. The median daily dose at the end of the study was 100 mg. Clinical response was defined as a >150-point reduction in score on the Crohn's Disease Activity Index (CDAI); clinical remission was defined as a CDAI score <150. Six patients withdrew from the study in the first 4 weeks. Of the remaining patients, 12 had a clinical response (9/13 [69%] fistular, 3/9 [33%] luminal), and 4 were in clinical remission (3 fistular, 3 luminal) after 4 weeks of therapy. Two patients had complete closure of all fistulas at 4 weeks. Fourteen of the original 22 (64%) patients completed 12 weeks of therapy (9 fistular, 5 luminal). These patients' CDAI scores were significantly decreased from the beginning of the study ( $P < 0.001$ ). All 14 patients had a clinical response (9 [69%] fistular, 5 [56%] luminal), and 9 achieved clinical remission (6 [46%] fistular, 3 [33%] luminal). Three patients were able to discontinue prednisone by week 12. The median daily dose of prednisone decreased from 26 to 7.5 mg at the end of the study. Thirty-eight percent of patients had

complete closure of fistulas by 12 weeks, including 2 who had failed infliximab therapy.

Vasiliauskas et al<sup>185</sup> conducted an open-label study in which 12 patients with chronically active steroid-dependent Crohn's disease received thalidomide starting at 50 mg/d (first 6 patients) or 100 mg/d (next 6 patients) at night. Patients continued at stable doses of their current medication for Crohn's disease (eg, mesalamine, 6-mercaptopurine, azathioprine, methotrexate) throughout the study. Clinical response was defined as a  $\geq 100$ -point reduction in CDAI score from baseline to 4 weeks. Clinical remission was defined as a  $\geq 100$ -point reduction in CDAI score from baseline and a score  $< 150$ . At the end of 4 weeks of therapy, clinical response and clinical remission were achieved in 58% and 17% of patients, respectively. Clinical response at 12 weeks was defined as above, with the addition of a  $\geq 50\%$  reduction in steroid dose; clinical remission at 12 weeks was as defined above, with the addition of complete withdrawal of corticosteroids. Ten of 12 patients continued therapy for 12 weeks. A clinical response was observed in 7 (70%) of these patients, and 2 (20%) achieved clinical remission. (Information on the tenth patient was not provided.) The median change in CDAI score for the patients completing 12 weeks of therapy was statistically significant ( $P = 0.002$ ). Four patients were able to stop prednisone therapy completely; overall, patients were able to decrease their steroid dose by  $\geq 50\%$  by the end of the study.

Facchini et al<sup>186</sup> conducted an open-label study in 5 children who were unable to tolerate or were resistant to standard therapy for Crohn's disease. Initial daily thalidomide doses ranged from 1.5 to 2 mg/kg. Patients continued their current steroid therapy, with the dose adjusted according to the clinical findings. One patient dropped out of the study after 6 days due to distal paresthesias in both feet. The remaining 4 patients improved clinically, and all were able to discontinue prednisolone therapy. Clinical remission was confirmed by endoscopy in all patients.

### **Miscellaneous Gastrointestinal Conditions**

There are case reports of benefit for thalidomide in idiopathic colitis and proctitis (in HIV-infected patients),<sup>187</sup> hepatitis C infection,<sup>188</sup> inflammatory pseudotumor,<sup>189</sup> and oral erosive lichen planus.<sup>190</sup> Sharpstone et al<sup>191</sup> conducted an open-label study in 18 HIV-infected patients with refractory microsporidiosis (*Enterocytozoon bieneusi*). Complete remission was defined as cessation of diarrhea (70% reduction in stool frequency or frequency  $< 3$  times/d) and stable or increased body weight. Partial remission was defined as a  $\geq 50\%$  decrease in stool frequency with continued weight loss. A poor response consisted of no response or worsening of symptoms. Thirty-nine percent (7) of patients had complete remission and 17% (3) had partial remission. Stool frequency was significantly de-

creased ( $P < 0.001$ ), with statistically significant weight gain ( $P < 0.02$ ). Forty-four percent (8) of patients had a poor clinical response.

### **Miscellaneous Conditions**

#### ***HIV/AIDS–Associated Wasting***

HIV/AIDS-associated wasting is characterized by loss of  $>10\%$  of body weight, fatigue, fever, and diarrhea. The availability of HAART has essentially eliminated this complication in those who respond to therapy; however, the condition can be a problem in individuals who fail to respond.

Kaplan et al<sup>192</sup> conducted a double-blind, placebo-controlled study of the efficacy and tolerability of thalidomide in the management of AIDS-associated wasting. At study entry, patients were receiving either stable antiretroviral therapy or no antiretroviral therapy. Patients were randomly assigned to receive thalidomide 100 mg ( $n = 36$ ) or 200 mg ( $n = 31$ ) daily at bedtime, or placebo ( $n = 32$ ). Intent-to-treat analysis showed significant weight gain in the thalidomide 100-mg group compared with the placebo group ( $P = 0.021$ ). In 64 patients who completed the study, weight gain was significantly greater in both thalidomide groups than in the placebo group (thalidomide 100 mg,  $P = 0.008$ ; thalidomide 200 mg,  $P = 0.019$ ). About one half of weight gain was in lean body mass in each thalidomide group. Viral load decreased in the placebo group and increased in both treatment arms. AEs were more common and severe in the group that received the higher dose of thalidomide compared with the lower dose.

In the 12-week, randomized, double-blind, placebo-controlled study by Reyes-Terán et al,<sup>193</sup> patients with HIV-associated wasting were assigned to receive thalidomide 100 mg QID or placebo (14 in each group) while continuing current antiretroviral therapy. Five patients (3 thalidomide, 2 placebo) withdrew from the study before 12 weeks and were considered treatment failures. At 12 weeks, 8 thalidomide recipients had gained weight and 3 had stable body weight; 2 failed therapy due to toxicity and 1 due to noncompliance. In the placebo group, 1 patient gained weight, 3 were weight stable, and 10 were therapeutic failures (8 with progressive weight loss, 1 with rash, 1 for noncompliance). At 12 weeks, the change in median weight from baseline was  $+4.05$  kg and  $-1.3$  kg for the thalidomide and placebo groups, respectively ( $P < 0.001$ ). Changes in muscle mass after 12 weeks of treatment were  $+1.0$  and  $-1.01$  kg for thalidomide and placebo, respectively ( $P = 0.001$ ). At 12 weeks, the likelihood of therapeutic failure in the thalidomide and placebo groups was 21% and 64%, respectively ( $P = 0.023$ ). Skin rash occurred in 11 of 14 patients receiving thalidomide and 3 of 14 patients receiving placebo.

Klausner et al<sup>32</sup> conducted a 21-day, randomized, double-blind, placebo-controlled study in patients with HIV-associated wasting with or without tuberculosis. Patients were not receiving any antiretroviral therapy. The daily dose of tha-

lidomide was 300 mg given at night. Of 39 patients enrolled, 32 (16 thalidomide, 16 placebo) completed the study. In the thalidomide group, 2 patients dropped out due to rash and 2 due to development of an opportunistic infection. In the placebo group, 1 patient dropped out due to an opportunistic infection, 1 dropped out due to sepsis, and another was lost to follow-up. Patients receiving thalidomide had significant weight gain compared with those receiving placebo ( $P = 0.02$ ).

Thalidomide appears to be effective for producing weight gain in patients with HIV-associated wasting. Although an exact therapeutic dose has not been determined, it appears that a daily dose of 100 mg given at bedtime is well tolerated and effective in patients with this condition.<sup>192</sup>

### **Other Conditions**

Other conditions in which thalidomide has shown some benefit in case reports or studies in small numbers of patients include tuberculosis,<sup>32,194</sup> reflex sympathetic dystrophy,<sup>195</sup> systemic-onset juvenile rheumatoid arthritis,<sup>196</sup> adult-onset Still's disease,<sup>197</sup> rheumatoid arthritis,<sup>198</sup> and seronegative spondylarthropathy.<sup>199</sup>

## **ADVERSE EVENTS**

Thalidomide's 1998 approval by the FDA for the management of ENL and its off-label use in many conditions has led to renewed concern that deformed infants may be born to patients receiving thalidomide, and the manufacturer of thalidomide has developed the S.T.E.P.S. program to decrease the likelihood of such occurrences.<sup>6</sup> Although the exact mechanism of thalidomide's teratogenicity is unknown, it is likely to be the result of interference with normal angiogenesis during fetal development.<sup>200</sup> As little as a single dose may result in teratogenicity,<sup>6</sup> although thalidomide does not cause second-generation birth defects.<sup>201</sup>

Studies to establish whether the teratogenic effect of thalidomide is specific to 1 of its 2 enantiomers have yielded inconsistent results. Investigations in pregnant mice found that the *S*-enantiomer was the primary teratogen,<sup>200</sup> whereas a study in New Zealand white rabbits reported equal teratogenicity for the 2 enantiomers.<sup>202</sup> These discrepant findings may be due to differences in species susceptibility to the enantiomers. The rapid chiral inversion from one to the other enantiomer *in vivo* makes definitive studies impossible.

Thalidomide was developed as a sedative, and the most common AE associated with its use is somnolence/drowsiness. Thalidomide causes dose-related somnolence by activating diencephalic sleep centers without depressing CNS neuronal function.<sup>28</sup> Sedative effects may be manifested as a morning drug "hangover," dizziness, muscle incoordination, fatigue, unsteady gait, tremulousness, mood changes, confusion, and weakness.<sup>6,16,37,96</sup> To minimize these effects, the drug is usually administered in the late evening or at bedtime. Morning drowsiness may be addressed by decreasing the dose, if indicated, or by moving the dose from

bedtime to late evening. The incidence of significant somnolence/drowsiness varies from 13% to 38%.<sup>6,96,203</sup> World Health Organization (WHO) grade 1 or 2 somnolence occurred in 34% to 43% of patients receiving thalidomide for MM at a daily dose of 200 to 800 mg.<sup>52</sup> Tachyphylaxis to this effect of thalidomide may be noted after the second or third week of therapy (range, 1–3 months).<sup>70,185</sup> However, somnolence/drowsiness may be dose limiting or result in discontinuation of therapy.<sup>70,184,203</sup>

Constipation is a common complication of thalidomide therapy. Its mechanism is unknown but may result from neuromuscular colonic inertia with hypotonia.<sup>28</sup> In clinical studies, the incidence of constipation has varied from 9% to 59% and its severity has varied from mild to severe.<sup>52,69,96,101,203</sup> The incidence of constipation may be greater at higher thalidomide doses. WHO grade 1 or 2 constipation occurred in 35% to 59% of patients receiving daily thalidomide doses of 200 to 800 mg.<sup>52</sup> Constipation may respond to use of cathartics. Some investigators have used laxatives prophylactically to prevent thalidomide-induced constipation.<sup>144</sup>

The occurrence of mild to severe rash in association with thalidomide use may depend on patients' immune status and underlying disease state. The rash is typically pruritic, erythematous, and macular and occurs on the trunk, back, and proximal extremities. It is most likely to occur after 10 to 14 days of thalidomide therapy, and does not appear to be dose related.<sup>203</sup> In a review of studies in HIV-infected patients receiving thalidomide therapy, the incidence of rash was 26%, with a greater incidence in patients with lower CD4+ T-lymphocyte counts.<sup>203</sup> In a study in patients with MM,<sup>52</sup> WHO grade 1 or 2 rash occurred in 16% to 26% of patients receiving daily thalidomide doses of 200 to 800 mg. Another study reported an 11% incidence of rash (WHO grade >2) at a median daily thalidomide dose of 400 mg.<sup>101</sup> Parker et al<sup>70</sup> reported rash in 16% of patients receiving thalidomide for CGVHD. These patients had a flare of existing skin rash or a new-onset rash consistent with CGVHD. One patient developed Stevens-Johnson-like syndrome 2 weeks after beginning thalidomide therapy. Thalidomide has also been reported to cause toxic epidermal necrolysis.<sup>204</sup>

Thalidomide therapy should be discontinued if skin rash occurs. The rash usually resolves when thalidomide is discontinued, but rechallenge should be undertaken cautiously. A severe sepsis-like reaction has been reported in HIV-infected patients after rechallenge with thalidomide.<sup>203,205</sup> Rechallenge should not be attempted if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected.

Thalidomide therapy has been associated with peripheral neuropathy, which may affect 1% to 50% of patients.<sup>52,77,96,101,181,203,206</sup> Neuropathy is characterized by distal axonal degeneration. Sensory symptoms are symmetrical and usually affect the distal lower limbs. Symptoms may include paresthesias of the hands and feet in a stocking-glove pattern, a feeling of "tightness" around the feet, or hy-

peresthesia. Other findings may include muscle cramps, muscle weakness, postural tremor, decreased muscle stretch reflex, palmar erythema, and brittle nails.<sup>207–209</sup> Some studies have indicated an increased risk for neuropathy with greater patient age and a cumulative thalidomide dose >40 to 50 g.<sup>206,210,211</sup> However, peripheral neuropathy can occur at a lower cumulative dose, suggesting that patients' underlying condition or predisposition may play a part.<sup>206,212</sup> Patients with electrophysiologic findings of neuropathy may be asymptomatic, indicating a need for routine testing<sup>213</sup>; conversely, symptomatic patients may have no electrophysiologic findings of neuropathy. Symptoms may improve when thalidomide is discontinued; however, recovery may not be total.<sup>70,210,212,213</sup> Symptoms may also progress after discontinuation of therapy.<sup>207,208</sup> A peripheral neurologic examination should be performed when beginning thalidomide therapy and should be repeated every 3 to 6 months thereafter.

Thromboembolic events have been reported during thalidomide therapy,<sup>6</sup> including DVT, pulmonary embolus, and clotting of central venous catheters.<sup>214–218</sup> Patients with cancer may be at particularly high risk for such events if they receive thalidomide with combination chemotherapy.<sup>96,147,150,214–218</sup> Chemotherapy containing doxorubicin has been reported to increase the risk for thrombosis during thalidomide administration.<sup>216</sup>

In a study in patients with MM,<sup>214</sup> the incidence of DVT was 28% and 4% in patients receiving and not receiving thalidomide, respectively. Each patient was receiving combination chemotherapy that included vincristine, doxorubicin, cyclophosphamide, etoposide, and cisplatin. In a compilation of reports of thromboembolic events during thalidomide administration in patients with cancer,<sup>218</sup> 31% of such events occurred when thalidomide was combined with chemotherapy, 15% when patients were also receiving dexamethasone, and 5% when patients were receiving thalidomide alone. In a study in 169 patients with refractory MM,<sup>96</sup> the incidence of DVT was 1% in patients receiving thalidomide as single therapy. Fine et al<sup>147</sup> reported a 28% incidence of thromboembolic events in patients with recurrent high-grade gliomas receiving thalidomide and BCNU (carmustine). Patients receiving thalidomide should be monitored for the occurrence of thromboembolic events. Some authors have recommended prophylactic anticoagulation if thalidomide is to be given in combination with chemotherapy.<sup>214</sup>

Noormohamed et al<sup>16</sup> reported dose-dependent reductions in supine systolic and diastolic blood pressure in patients receiving thalidomide. Standing systolic and diastolic blood pressure and heart rate were unaffected. Dizziness and orthostatic hypotension have also been reported during thalidomide therapy.<sup>6</sup> In patients with refractory MM, administration of thalidomide 200 to 800 mg/d resulted in dizziness in 17% to 28% of patients.<sup>52</sup> It is recommended that patients receiving thalidomide sit upright for a while before moving from a recumbent to a standing position.<sup>6</sup>

Therapy with thalidomide can have effects on the formed elements of the blood. Neutropenia/leukopenia has been reported, with an incidence that varies according to the underlying condition. Of 84 patients receiving thalidomide for refractory MM, <5% had WHO grade 1 or 2 leukopenia, whereas grade 3 or 4 thrombocytopenia or anemia occurred in 4% (3 patients).<sup>52</sup> In a group of 56 HIV-infected patients receiving thalidomide, severe neutropenia occurred in 1 patient (2%).<sup>203</sup> In a study in patients receiving thalidomide therapy for CGVHD,<sup>70</sup> neutropenia occurred in 18%. Drug therapy was discontinued and the neutropenia resolved. Six patients were rechallenged, and neutropenia recurred. Thalidomide should not be used in patients with an ANC <750/mm<sup>3</sup>. Eosinophilia has also been reported during thalidomide therapy.<sup>85</sup> Patients receiving thalidomide for the management of MMM may experience a sharp rise in platelet and leukocyte counts,<sup>136,137</sup> which may result in serious toxicity.

Among other AEs listed in the thalidomide package insert<sup>6</sup> or reported elsewhere are bradycardia,<sup>99,106</sup> atrioventricular block,<sup>100</sup> seizures,<sup>6</sup> xerostomia (0%–9%),<sup>6</sup> peripheral edema (0%–8%),<sup>53,100,106</sup> hypothyroidism,<sup>106,109,219</sup> hepatitis,<sup>220</sup> amenorrhea<sup>221</sup> or menstrual disturbances (13%),<sup>78</sup> mood changes (eg, confusion, abnormal thinking, agitation, dementia, emotional lability, hostility, psychosis),<sup>6,99,106,109</sup> and impaired glucose uptake and glycogen synthesis in patients with type 2 diabetes.<sup>222</sup>

## CONCLUSIONS

Best known for the catastrophic teratogenic events associated with its use by pregnant women in the 1960s, thalidomide has since been approved for the treatment of ENL and is being investigated in various refractory dermatologic, oncologic, and gastrointestinal conditions. It has shown clinical benefit as a potential second-line agent for cutaneous discoid lupus erythematosus, with a reported clinical response in 80% to 100% of patients. Reports of a 20% response rate from uncontrolled studies in patients with CGVHD have been tempered by the results of controlled evaluations reporting no benefit and high toxicity. Further controlled studies are needed to determine effective and safe doses in these conditions.

Thalidomide has shown benefit in patients with refractory/relapsed MM when used as a single agent and when combined with dexamethasone. Randomized controlled studies are necessary to evaluate its role in early disease and its use in combination with standard chemotherapy for MM. In many studies of thalidomide for other cancers, patients were unable to tolerate the target doses, and high numbers of patients dropped out due to AEs.

Placebo-controlled studies have documented the value of thalidomide in patients with HIV infection and aphthous ulcers of the mouth and esophagus, as well as in non-HIV-infected patients with these lesions. Resolution of ulcers has been observed during thalidomide therapy in patients with Behçet's disease. How-

ever, the ulcers return on drug discontinuation, leading to concerns about long-term use of thalidomide and the risk of peripheral neuropathy. The preliminary results of thalidomide use in patients with Crohn's disease are encouraging; however, further studies are necessary. Case reports and studies in small numbers of patients have shown effectiveness for thalidomide in other clinical conditions.

Because thalidomide is highly teratogenic, guidelines for its use must be followed carefully. Thalidomide is a toxic medication, and therapeutic and well-tolerated doses have not been established for any condition except ENL. Because long-term use of thalidomide carries a risk of irreversible peripheral neuropathy and because the neuropathy may be asymptomatic, routine testing is necessary. Efforts to develop agents that retain the efficacy of thalidomide without its unwanted effects are ongoing.

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