Palliative Oncology: Thalidomide

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Abstract
After decades of disuse because of its teratogenic effects, thalidomide has had a resurgence of use as a promising therapeutic agent for multiple myeloma. Its mechanism of action involves activation of the immune system, antiangiogenic effects, and inhibition of cytokines. Thalidomide does not interact with the cytochrome oxidase system. It is not significantly metabolized, but it does undergo nonenzymatic hydrolysis in plasma. The resulting products are inactive. Despite the potential adverse effects of peripheral neuropathy, constipation, deep vein thrombosis, somnolence, rash, and orthostatic hypotension, thalidomide is an effective first-line agent for multiple myeloma in combination with dexamethasone or melphalan and prednisone. It has also been studied in the palliative care of patients with cytokine-based syndromes such as anorexia-cachexia syndrome. This review describes its use in oncology, hematology, and palliative care.

Keywords
thalidomide, anorexia-cachexia, cytokines

Introduction
Immunonodulatory drugs such as thalidomide have emerged as a novel and promising class of therapeutic agents. After decades of disuse as a sedative and antiemetic once its teratogenic effects were documented, thalidomide has had a resurgence of use as a potentially promising therapeutic agent. Thalidomide is a racemic glutamic acid that has been shown to regulate components of the cellular immune and cytokine response. Its interference with the tumor growth–promoting effects of cytokines has implications for cancer therapy and palliative care. Thalidomide can also inhibit or interfere with blood vessel formation (ie, angiogenesis), an important component of tumor growth. This article reviews the current applications of thalidomide in cancer care and palliative care.

Mechanisms of Action
Thalidomide’s exact mechanism of action is not known. Thalidomide has an effect on the immune system, angiogenesis, and cytokine production, all of which play an important role in tumor growth.

Immune Modulation
Thalidomide can help stimulate primary human T lymphocytes by increasing the production of interleukin 2 (IL-2) and interferon γ. Thus, its immunologic adjuvant action enhances the otherwise ineffectual immune response of the body under siege from cancer.

Antiangiogenesis
Angiogenesis is the development of new blood vessels. In cancer, this process can nurture the growth of tumors and aid the metastasis of tumor cells. Thalidomide has antiantiogenic properties that act independently of its immunomodulatory effects.

Cytokine Inhibition
Cytokines are soluble glycoproteins released by immune system cells that regulate immune responses by acting nonenzymatically through specific receptors. The proinflammatory cytokine tumor necrosis factor α (TNF-α) is produced by monocytes, macrophages, lymphocytes, and natural killer cells. Cytokine excess plays an important role in the cancer-related anorexia-cachexia syndrome.

Thalidomide inhibits the production of TNF-α by enhancing the degradation of TNF-α messenger RNA (mRNA). It may also bind to and increase the effect of α1-acid glycoproteins that possess intrinsic anti-TNF-α activity. This mechanism differs from that of other drugs that inhibit TNF-α, such as pentoxifylline or glucocorticoids.
Thalidomide can inhibit DNA synthesis in human multiple myeloma cell lines and in cells from patients resistant to melphalan. These results correlate well with the antitumor activity in patients with drug-resistant forms of the disease. Thalidomide enhances programmed cell death in multiple myeloma cells.

**Pharmacology and Metabolism**

**Pharmacokinetics**

Intravenous pharmacokinetic studies have not been performed on thalidomide because of its low solubility in acceptable solvents. Thus, no determinations have been made of its absolute bioavailability, true elimination half-life, systemic clearance, or volume of distribution. Thalidomide is a racemic glutamic acid derivative that interconverts between the R-enantiomers and the S-enantiomers in plasma, with protein binding of 55% and 65%, respectively. No information is available about the difference in enantiomer activity. Within 48 hours, more than 90% of the absorbed drug is excreted in the urine and feces.

In healthy volunteers, absorption of a single 200-mg oral dose (the US-approved formulation) of thalidomide has been found to be slow and extensive, with a peak concentration of 1 to 2 mg/L within 4 hours. Absorption lag time may be 30 minutes, elimination half-life 6 hours, and systemic clearance 10 L/h. The pharmacokinetics of thalidomide are best described as a 1-compartment model with first-order absorption and elimination. Because thalidomide has low solubility in the gastrointestinal tract, it exhibits absorption rate-limited pharmacokinetics, with its rate of elimination actually occurring faster than its rate of absorption. As a result, its apparent elimination half-life of 6 hours represents absorption versus elimination. The actual apparent volume of distribution may be as much as 16 L. Multiple doses of thalidomide (200 mg/d for 21 days) cause no change in pharmacokinetics, with a steady-state peak concentration of 1.2 mg/L. Thalidomide does not accumulate with increasing doses, and its pharmacokinetics are not affected by age, sex, or smoking. The pharmacokinetics of multiple doses are similar for patients with cancer compared with those for healthy patients. In healthy participants, the absorption of thalidomide may increase after a high-fat meal without concomitant changes in maximum concentration, half-life, or area under the curve.

**Metabolism**

The exact metabolic route of thalidomide in humans has not been identified. Hepatic metabolism seems to be minor; however, thalidomide may undergo nonenzymatic hydrolysis in plasma. The byproducts of such hydrolysis are not active.

**Use in Renal Insufficiency**

Thalidomide pharmacokinetics are not well documented in patients who have renal dysfunction. The use of thalidomide has been reported for the treatment of patients who have immunoglobulin D multiple myeloma and associated renal failure, with results comparable to those for patients who have normal renal function. However, precautions must be taken in treating patients with a creatinine concentration of more than 300 μmol/L because it can lead to fatal hyperkalemia.

**Use in Liver Disease**

The low-dose thalidomide has been well tolerated by patients who have hepatitis C and cirrhosis. However, patients with liver disease require close monitoring of liver enzymes. The low-dose thalidomide (200 mg/d) has been found to be well tolerated by patients with cirrhosis who received thalidomide for hepatocellular carcinoma. The pharmacokinetics of thalidomide in patients with hepatic impairment have not been determined.

**Pediatric Population**

No pharmacokinetic data are available on the use of thalidomide in patients younger than 18 years of age.

**Drug Interactions**

There are no known pharmacokinetic interactions between thalidomide and other drugs. Thalidomide can enhance the sedative effects of alcohol and benzodiazepines. When thalidomide is added to a treatment regimen, other drugs that might cause neuropathy or decrease the efficacy of oral contraceptives should be monitored carefully. The use of thalidomide in patients taking chemotherapeutic agents has resulted in an increased incidence of thrombosis, and its use in conjunction with dexamethasone has resulted in severe skin reactions such as toxic epidermonecrosis.

**Adverse Effects**

Adverse effects can occur in the neurologic, cardiovascular, gastrointestinal, and dermatologic systems. In general, thalidomide is well tolerated at doses of less than 400 mg/d. For symptom control, thalidomide has been studied at doses far below those used for solid tumors and multiple myeloma.
Neurologic Effects

Peripheral neuropathy. Peripheral neuropathy is recognized as one of the most significant complications of this medication. Thalidomide-induced neuropathy occurs mainly after therapy lasting 6 months or longer. Its incidence is higher in elderly patients and women, as well as in patients who have preexisting neuropathy or who are treated with neurotoxic chemotherapy, such as vincristine, cisplatin, or paclitaxel. Common measures for neurotoxicity show that the low-grade peripheral neuropathy occurs in more than 80% of patients receiving thalidomide, whereas severe neuropathy occurs in 3% to 5%. The most common presentation of peripheral neuropathy is distal paresthesia or dysesthesia with or without sensory loss. Physical examination results may be normal or may show mildly decreased sensation in the distal limbs. Strength is usually preserved, but reflexes, particularly ankle jerks, may be depressed or absent. These symptoms, which are progressive, usually begin in the distal lower limbs and extend proximally and into the upper limbs. Although some studies have found a relationship between the cumulative dose and the occurrence of neuropathy, others have not. Nerve conduction studies typically show results consistent with a sensory axonal neuropathy. No standard therapy for thalidomide-induced neuropathy exists, but symptoms may improve with the withdrawal of or a reduction in the dose of thalidomide. Other symptomatic therapy for paresthesia includes the low-dose gabapentin and tricyclic antidepressants.

Tremor. The dose-related tremors occur in about 35% of patients receiving thalidomide.

Somnolence. Somnolence or sedation may occur in patients taking thalidomide. Although these effects are usually mild, taking the daily thalidomide dose at bedtime reduces the potential for daytime somnolence.

Gastrointestinal Effects

Constipation. Constipation is a side effect of thalidomide, with up to 80% of patients experiencing a mild decrease in bowel motility. This gastrointestinal complication may reflect autonomic dysfunction due to thalidomide, which is similar to those of vincristine, another neurotoxic chemotherapy agent.

Xerostomia. Thalidomide can cause xerostomia (dry mouth). This adverse reaction affects about 10% of patients treated with thalidomide.

Cardiovascular Complications

Thromboembolic Complications

Thalidomide has been associated with the occurrence of deep vein thrombosis, mainly when it is given in combination with dexamethasone or other chemotherapy agents. Although thalidomide is associated with low rates of thrombosis when used alone; in combination with corticosteroids or other chemotherapy, the risk of thrombosis increases considerably to 17% to 26%. The rate of venous thromboembolism is substantially higher in trials of thalidomide administered in conjunction with the high-dose dexamethasone or doxorubicin hydrochloride in patients with multiple myeloma or in conjunction with docetaxel in patients with prostate cancer. Overall, the median time to the onset of a thrombotic event was about 3 months after initiation of thalidomide therapy. Thromboprophylaxis is indicated in patients prone to these thrombogenic complications. However, the incidence of such complications appears to be low when lower doses of thalidomide are used, such as for symptom control. Thromboprophylaxis may represent an increased burden for palliative care patients.

Other Cardiovascular Complications

In addition to being associated with thrombotic disease, thalidomide has been associated with arrhythmia, hypotension, and edema. Sinus bradycardia, which is usually mild, has been reported in up to 25% of patients. Severe bradycardia is rare. Severe sinus bradycardia occurs in only 1% to 3% of patients receiving thalidomide. Mild peripheral edema has been reported in 15% of patients. Orthostatic hypotension and dizziness have also been reported with thalidomide.

Dermatologic Complications

Skin rash can appear with the administration of thalidomide. Most patients have only a mild rash that resolves with moisturizing lotions and dose adjustments. The rash is typically pruritic and maculopapular, starting on the trunk and extending to the back and proximal limbs. The rash does not appear to be dose related, and onset has been reported within 10 to 14 days after the initiation of treatment. Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with the use of thalidomide. Dermatologic complications seem more likely to occur when thalidomide is combined with dexamethasone. Hall et al reported minor to moderate skin eruptions in more than 40% of patients taking thalidomide alone or thalidomide with dexamethasone.

Systemic Reactions

Fever

Hypersensitivity reactions to thalidomide occur more often in patients infected with the human immunodeficiency virus (HIV) than in other groups; hypersensitivity may manifest as an erythematous macular rash, possibly associated with fever, tachycardia, and hypotension. Rash and fever have been found with thalidomide doses as low as 200 to 300 mg/d for a maximum of 3 weeks; about 50% of patients with rash also had fever. A low CD4 count has been associated with the development of adverse effects such as rash and fever.
Hematologic Effects

Thalidomide can affect both granulocytes and platelets. This medication should not be initiated in patients who have an absolute neutrophil count of less than 750. Thalidomide should also be used with caution in patients who have thrombocytopenia.

Tumor Flare

Tumor flare, or the temporary increase in size of a cancerous lesion not associated with a worsening of cancer, may occur when thalidomide is used to treat chronic lymphocytic leukemia. Patients have subsequently experienced increased lymphadenopathy, enlargement of the spleen, and an increased lymphocyte count.

Teratogenicity

Thalidomide is contraindicated in pregnant women and in women with childbearing potential unless several conditions to avoid pregnancy are met. In women who are not pregnant, the manufacturer recommends the simultaneous use of 2 different reliable forms of contraception while taking thalidomide, unless continuous abstinence from heterosexual contact is the method of choice. Contraception should be used for at least 4 weeks before starting therapy and should be continued during treatment and for 4 weeks after the discontinuation of treatment. Routine pregnancy testing is advisable throughout treatment. In addition, because thalidomide is present in the semen of men treated with the drug, even men who have undergone a successful vasectomy must use a latex condom during any sexual contact with women of childbearing potential.

Therapeutic Role of Thalidomide

The antineoplastic effects of thalidomide have led to its evaluation for use with both hematologic and nonhematologic malignancies. The effect of thalidomide on cytokines has led to its evaluation for palliative care.

Hematologic Malignancies

Thalidomide is an effective first-line treatment of multiple myeloma, in combination with dexamethasone or with melphalan and prednisone for patients not considered candidates for stem cell transplantation. Thalidomide is an alternative to infusional chemotherapy with vincristine, doxorubicin, and dexamethasone. In some patients with myeloproliferative disorders such as agnogenic myeloid metaplasia, thalidomide can improve cytopenia, decrease spleen size, and help achieve transfusion independence. Palliative doses for myeloproliferative disorders are as low as 50 mg/d.

Solid Tumors

No randomized trials have shown thalidomide to be a useful first-line treatment of the management of solid tumors. It has been studied for its effects on various types of solid tumors, but many of these studies were uncontrolled. Thalidomide has neither supplanted traditional chemotherapy agents nor has its addition to current chemotherapy regimens been found advantageous.

Palliation of Symptoms

Nonmalignant Palliation

Congestive heart failure. On the basis of evidence that cytokines such as TNF- and IL-6 bear a direct relationship to the deterioration of cardiac performance in congestive heart failure, compared thalidomide with placebo for the management of congestive heart failure. Patients were randomized to thalidomide (25 mg/d increasing to 200 mg/d) or placebo with follow-up at 12 weeks. Patients receiving thalidomide had increased cardiac ejection fraction and lower end-diastolic volumes and heart rate. Surprisingly, these effects were more pronounced in patients with idiopathic dilated cardiomyopathy than in patients with heart failure due to coronary artery disease. However, the subset of patients with cardiomyopathy tolerated a larger dose of thalidomide. Treatment with thalidomide did not lead to changes in New York Heart Association class or quality of life. Contrary to what was expected, thalidomide was associated with an increase in TNF-.

Anorexia-cachexia. Proinflammatory cytokines are thought to be an important mechanism in the anorexia-cachexia syndrome. Gordon et al evaluated the effects of thalidomide on anorexia-cachexia in patients with pancreatic carcinoma. In their blinded single-center study, they randomized 50 patients who met the criteria for the anorexia-cachexia syndrome to either thalidomide 200 mg/d or placebo. Weight gain and nutritional assessment (arm muscle mass) were the primary end points. Because of dropouts, only 33 patients (16 controls and 17 receiving thalidomide) were evaluated at 4 weeks, and only 20 patients (8 controls and 12 receiving thalidomide) were evaluated at 8 weeks. At 4 weeks, patients in the thalidomide arm had gained an average of 0.37 kg and had developed 1.0 cm³ in arm mass versus the placebo group (no gain weight or increase in muscle mass). At 8 weeks, the thalidomide patients had lost both weight and arm mass but less than those lost by patients in the placebo group. Other benefits of weight gain associated with thalidomide were improvement in strength as assessed by physical functioning.

Khan et al evaluated thalidomide for the treatment of anorexia-cachexia associated with advanced esophageal cancer. In an open-label design, patients were first treated with dietary measures (isocaloric diet) for 2 weeks and then treated with thalidomide 200 mg/d. Weight gain and lean body mass were compared between treatments. Of the 10 patients who completed the study, 9 patients lost weight lean body mass.
during the 2-week diet portion of the study. During the thalidomide treatment portion of the study, patients had both a mean gain in weight (1.29 kg [median, 1.25 kg]) and no loss of body mass. No conclusions could be made regarding other dietary measures (eg, energy expenditure). The authors suggested that thalidomide had a positive effect both on weight gain and on lean body mass of patients with advanced esophageal carcinoma.

**Human immunodeficiency virus wasting.** Thalidomide has been evaluated for the treatment of HIV-associated cachexia. In a randomized and blinded study, Reyes-Teran et al compared thalidomide 100 mg 4 times daily with placebo for patients with advanced HIV disease who had been receiving antiviral therapy at least 6 months. Exclusionary criteria included the presence of an opportunistic infection. Patients had to have had at least a 10% weight loss in the preceding 6 months. Twenty-eight patients entered the 12-week study. The primary end point was weight gain or stabilization. More patients in the thalidomide arm achieved the designated end point (P = .021) with weight gain in 8 of 14 patients receiving thalidomide versus 1 of 14 receiving placebo. Performance status also improved more with thalidomide. Thalidomide therapy did not affect T-cell counts.40

**Aphthous ulcers.** Among patients with HIV or AIDS, mucosal lesions of unknown etiology, such as recurrent aphthous ulcerations, are often unresponsive to standard therapies and result in substantial morbidity. Aphthous stomatitis has been associated with immunologic alteration.41 Thalidomide, because of its immunomodulatory properties, has been studied as a treatment of aphthous ulceration in different sites.

**Esophageal aphthous ulcers.** Jacobson et al evaluated thalidomide for the treatment of esophageal aphthous ulcers. In a multicenter, blinded, randomized, controlled trial of 24 patients, they compared thalidomide 200 mg/d with placebo. After 4 weeks, healing was determined by endoscopic evaluation of HIV-infected patients who had a biopsy-confirmed aphthous ulceration of the esophagus. Of 11 patients in the thalidomide arm, 8 had complete healing of aphthous ulcers compared with 3 (23%) of 13 patients in the placebo arm (odds ratio, 13.82; 95% confidence interval, 1.16-823.75; P = .033). Patients reported that thalidomide improved appetite and reduced pain. Adverse events associated with its use included somnolence (4 patients), rash (2 patients), and peripheral sensory neuropathy (3 patients).

**Aphthous stomatitis.** Thalidomide (100 mg/d) and placebo were compared in a randomized, multicenter, crossover trial for the treatment of aphthous stomatitis.43 Seventy-three patients met the inclusion criteria of having had aphthous stomatitis for at least 6 months. A complete response was obtained in 32 patients who received thalidomide and in 6 patients who received placebo. Of 17 patients who had complete remission with thalidomide, 13 had a recurrence with placebo a mean (SD) of 19 (9) days after discontinuing the drug. The main adverse effects of thalidomide were drowsiness and constipation.

**Pain management.** Thalidomide has been reported to have analgesic properties in a patient with complex regional pain syndrome (CRPS1).44 Evidence supports the involvement of TNF-α in the pathogenesis of CRPS1, and thalidomide has been shown to block neuropathic pain in a rat model of chronic constriction injury.45

**Night sweats.** Thalidomide may reduce night sweats by blocking the production of TNF-α. In a small series, night sweats were reduced in 4 of 7 patients with advanced malignancy who took 100 mg/d at bedtime.46

**Uremic pruritus.** Proinflammatory cytokines such as TNF-α and IL-6 have been shown to be elevated in patients with pruritus caused by renal disease. Silva et al compared oral thalidomide 100 mg/d at bedtime with placebo. This blinded crossover study had a 7-day washout period between treatment arms. Pruritus was scored by a numeric rating scale from 0 to 3. A 50% decrease in the pruritus score constituted a response. For the 18 patients who finished the study, there was a statistically significant reduction in pruritus scores in the thalidomide arm versus the placebo arm (P < .05).

**Schedule of Administration**

Physicians who prescribe thalidomide must first register with System for Thalidomide Education and Prescribing Safety (STEPS), a proprietary educational and restrictive distribution program that is included as part of the manufacturer’s prescribing information (http://www.thalomid.com/steps_program.aspx).48 The STEPS program was developed because of the toxicity associated with fetal exposure to Thalomid (thalidomide) and to minimize the chance of fetal exposure to it.48 Thalidomide is best administered at bedtime because patients may be sensitive to its sedative effects and because taking it at night can help elderly patients weather the sometimes prolonged sedative effects. The initial dose is 50 mg/d orally. Thalidomide should be discontinued or the dose should be reduced in patients who experience severe adverse effects (eg, constipation, oversedation, or peripheral neuropathy). Dose increments can be made every 2 weeks in patients receiving therapy for multiple myeloma. After adverse effects resolve, thalidomide may be restarted at a lower dose or at the previous dose per the prescribing physician’s clinical judgment.

**Pharmacoeconomics**

Thalidomide is not an inexpensive drug, with an average cost per capsule of about US$2.00. The average wholesale prices for thalidomide are as follows:

- Thalidomide 50 mg—US$117.51
- Thalidomide 100 mg—US$190.74
Thalidomide 150 mg—US$203.95
Thalidomide 200 mg—US$217.17

Conclusion
After decades of disuse because of teratogenic effects discovered after its approval as a sedative and antiemetic, thalidomide has been reevaluated as a therapeutic agent. Its ability to antagonize the effects of cytokines and to stimulate cell-mediated immunity has led to its use as a chemotherapy agent. Although thalidomide has subsequently had therapeutic impact on the treatment of multiple myeloma and myeloproliferative disorders, it has had little impact on the management of solid tumors. Its effect on cytokines has led to its evaluation for use in patients with the cytokine-based disorders commonly seen in palliative care. The findings of placebo-controlled randomized studies suggest that thalidomide may be efficacious as an agent for the palliation of symptoms in patients with anorexia-cachexia, HIV wasting, and aphthous ulceration (also in HIV patients). Offsetting the potential benefit of thalidomide in palliative care are its adverse effects, although these are less severe with lower doses. Other drugs related to thalidomide (ie, the IMiDs [immunomodulatory drugs]) might eventually provide improved efficacy with less severe adverse effects, but these agents require extensive testing, particularly in the palliative care setting.

Declaration of Conflicting Interest
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The authors received no financial support for the research and/or authorship of this article.

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