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Thalidomide: current therapeutic uses and management of its toxicities

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Thalidomide: Current Therapeutic Uses and Management of Its Toxicities

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Thalidomide (Thalomid®, Celgene Corporation, Warren, NJ) first was introduced as a sedative in Europe and Canada more than 40 years ago. In the early 1960s, phocomelia (i.e., absence of limbs) in newborn babies was linked to thalidomide and led to its immediate withdrawal from the market (Annas & Elias, 1999). From the late 1990s to the present, thalidomide slowly has regained popularity because of its significant therapeutic value in relapsed multiple myeloma (Alexanian & Weber, 2000; Barlogie, Tricot, & Anaissie, 2001; Dimopoulos et al., 2001; Hus et al., 2001; Kyle & Rajkumar, 2001; Singhal et al., 1999).

Because of its antitumor activity in multiple myeloma, thalidomide received an orphan drug status (i.e., classified as a product that treats a rare disease affecting fewer than 200,000 Americans) from the U.S. Food and Drug Administration (FDA) in October 1998. Currently, thalidomide is approved by the FDA only for the treatment of erythema nodosum leprosum. A new study is under way to investigate the response rate of previously untreated patients with multiple myeloma using thalidomide alone versus thalidomide and dexamethasone (Rajkumar, Vesole, & Greipp, 2002). The drug also has been investigated as a single agent or in combination with other drugs in numerous cancers, including myelodysplastic syndromes and chronic myeloproliferative disorders (Thomas, 2000), Waldenström's macroglobulinemia (Coleman & Leonard, 2000), renal cell carcinoma (Eisen et al., 2000), hepatocellular carcinoma (Patt et al., 2000), advanced

Thalidomide currently is used to treat relapsed and refractory multiple myeloma. The drug also is being actively investigated in patients newly diagnosed with multiple myeloma. The therapeutic applications of thalidomide are expected to grow as clinical trials document its activity in treating other neoplastic disorders and diseases. Healthcare providers need to be well informed of its toxicities and able to identify their signs and symptoms immediately. They must have adequate knowledge about thalidomide administration and provide comprehensive patient education regarding thalidomide and its toxicities to ensure patient safety and compliance.

Key Words: angiogenesis inhibitors, teratogens, thalidomide, constipation, fatigue

breast cancer (Baidas et al., 2000; Eisen et al.), colon cancer (Govindarajan et al., 2000), prostate cancer (Figg et al., 1999), Kaposi's sarcoma (Fife, Howard, Gracie, Phillips, & Bower, 1998; Little et al., 2000), and gliomas (Fine et al., 2000). Thalidomide also has been found to be useful in the treatment of cachexia from AIDS, aphthous ulcers from Behcet's disease (Rajkumar & Witzig, 2000), and established chronic graft-versus-host disease (Browne et al., 2000; van de Poel, Pasman, & Schouten, 2001). Because of thalidomide's extensive use either in clinical trials or FDA-approved therapeutic indications, nurses and other healthcare providers need to be well informed of its therapeutic applications and limitations. Immediate identification of the signs and symptoms of its toxicities is crucial to avoid complications that could lead to irreversible serious conditions. Thorough patient education regarding the appropriate use of thalidomide is critical to patients' safety and compliance.

Mechanism of Action

The exact mechanism of the antineoplastic action of thalidomide is unclear. Researchers believe that angiogenesis inhibition, immunomodulation, and cytokine modulation, individually or in combination, likely underlie the drug's antitumor activity (see Figure 1) (Haslett, Corral, Albert, & Kaplan, 1998; McHugh et al., 1995; Moreira, Friedlander, Shif, Kaplan, & Zagzag, 1999; Moreira et al., 1993; Rowland et al., 2001; Singhal et al., 1999). In multiple myeloma, aside from its antiangiogenic properties (D'Amato, Lentzsch, Anderson, & Rogers, 2001; Kenyon, Browne, & D'Amato, 1997), thalidomide has several other properties that contribute to its activity, such as immunomodulation (including stimulation of cytotoxic T cell proliferation and induction of interferon- γ and interleukin- [IL-] 2 secretion) (Haslett et al.), modulation of cell surface adhesion molecule expression (Geitz, Handt, & Zwingenberger, 1996), direct inhibition of myeloma cell growth and survival via free radical mediated oxidative DNA damage (Parman, 1999), and cytokine modulation, which includes inhibition of production of IL-6, IL-1 beta, IL-10, and tumor necrosis factor alpha (Moreira et al., 1993).

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- Inhibition of angiogenesis
- Alteration of adhesion molecule expression
- Selective inhibition of tumor necrosis factor alpha production
- Induction of T helper cell type 2 cytokine production
- Inhibition of interleukin- (IL-) 6, IL-10, and IL-12 production
- Increase in the synthesis of IL-2 by mononuclear cells
- Stimulation of T lymphocytes

FIGURE 1. EXAMPLES OF POTENTIAL MECHANISMS OF ACTION OF THALIDOMIDE IN CANCER

Note. Based on information from Singhal & Mehta, 2001.

In humans, the oral bioavailability of thalidomide is high (Eriksson, Bjorkman, & Hoglund, 2001). Thalidomide appears to be well absorbed, with peak concentration achieved at approximately four hours. The drug is distributed easily throughout the body and undergoes rapid hydrolytic cleavage resulting in more than 20 metabolites that readily are excreted in the urine. The effects of renal or hepatic dysfunction on the clearance of thalidomide are not known (Stirling, 2000).

Toxicities and Their Management

Teratogenicity

Thalidomide is known to cause severe birth defects when taken by pregnant women. To avoid this serious event, Celgene Corporation, the American manufacturer of thalidomide, has developed a program called STEPS (System for Thalidomide Education and Prescribing Safety) for controlling and monitoring access to thalidomide. This process ensures that all prescribers, pharmacists, and patients are educated on precautions to avoid the teratogenic effects of the drug. Before the start of thalidomide treatment, female patients are instructed to avoid pregnancy and male patients are instructed not to impregnate their partners by using two reliable methods of birth control at all times. Female patients of childbearing potential are required to have pregnancy tests every month if their menses are regular or every two weeks if their menses are irregular. Men taking thalidomide or partners of patients taking thalidomide must use latex condoms (including those who have had vasectomies) every time they have sexual contact because thalidomide is found in semen. If pregnancy is suspected while patients are on thalido-

mid therapy, patients must contact their physician immediately. In the event that the drug is discontinued because of poor response or poor tolerance, two reliable methods of birth control must be continued for an additional four weeks after the last day of treatment. Also, all patients on thalidomide must not donate blood during therapy and for four weeks after its discontinuation (Nirenberg, 2001; Zeldis, Williams, Thomas, & Elsayed, 1999).

Constipation, Somnolence, Fatigue, and Skin Rash

Constipation, somnolence, and fatigue were the most common side effects observed in phase II clinical trials of thalidomide (Alexanian & Weber, 2000; Bertolini et al., 2001; Blade et al., 2001; Hus et al., 2001; Tosi, Ronconi, & Zamagni, 2000). Skin rash also was observed but manifested in fewer than 25% of the patients (Blade et al.; Hus et al.; Tosi et al.). In general, these side effects are tolerable and nursing measures can be instituted before their occurrence (Goldman, 2001) (see Figure 2). Patients with constipation should be encouraged to drink adequate amounts of fluid, increase dietary fiber, exercise regularly, maintain a good bowel regimen, and use a stool softener or laxative if needed (Lynch, 2002). Somnolence may be troublesome in some patients who live an active life. The use of sedatives and tranquilizers may compound sedation or somnolence and should be minimized or avoided if possible (Singhal & Mehta, 2001). Also, thalidomide is best taken at bedtime to benefit from its sedative effect. Fatigue is a complex, multifactorial disorder that develops over time and often leads to physical, mental, and psychological deficits among patients with cancer (Portenoy & Itri, 1999). Fatigue must be actively assessed and managed according to clinical practice guidelines (National Comprehensive Cancer Network, 2001). Patients need to be encouraged to perform mild to moderate exercises and continue their regular day-to-day activities as permitted by their physi-

cians to promote a sense of well-being and minimize fatigue. Underlying anemia also needs to be addressed through supportive therapies such as growth factor injections if appropriate, especially among patients post-chemotherapy (Bender, Kramer, & Miaskowski, 2002). When skin rashes (e.g., erythematous, maculopapular, itchy lesions) develop, nurses should instruct patients to apply topical corticosteroids; if no relief results, decreasing the thalidomide dose may alleviate the symptoms. If not, stopping thalidomide and restarting it at a lower dose may resolve the problem (Singhal & Mehta). The dosage of thalidomide may need to be altered depending on the side effects (Kyle & Rajkumar, 2001). These symptoms also must be reported to physicians or advanced practice nurses as soon as possible.

Deep Vein Thrombosis

Deep vein thrombosis (DVT) during the use of thalidomide has been noted in several studies (Flageul et al., 2000; Zangari et al., 2001). Therapeutic anticoagulation must be maintained while patients are receiving thalidomide. Partial thromboplastin time and international normalized ratio (INR) must be checked at regular intervals depending on patients' other medical conditions. Because of variations in laboratory normal range, INR is the preferred test and should be maintained in the range of 1.2–1.5 in patients with uncomplicated conditions. In patients with prior history of DVT, either prophylactic warfarin therapy (Singhal & Mehta, 2001) or the use of low molecular weight heparin may be more beneficial to patients. Patients who are placed on coumadin related to thalidomide treatment need to be monitored carefully for any signs or symptoms of bleeding, especially when their platelet counts are low or if they have clotting disorders. Concomitant use of aspirin and coumadin during thalidomide therapy may be unavoidable in patients with coexisting cardiovascular disease. In this situation, therapeutic coagulation should be maintained carefully and monitored closely.

MOST COMMON (50% of patients or more)	FAIRLY COMMON (25%–50% of patients)	LEAST COMMON (Less than 25% of patients)
Constipation Fatigue Somnolence	Peripheral neuropathy Skin toxicity —	Deep vein thrombosis Bradycardia —

FIGURE 2. SUMMARY OF TOXICITIES RELATED TO THALIDOMIDE

Note. Based on information from Alexanian & Weber, 2000; Blade et al., 2001; Horowitz & Stirling, 1999; Hus et al., 2001; Rajkumar et al., 2000.

Peripheral Neuropathy

Thalidomide-induced peripheral neuropathy does not correlate with the duration of treatment or the dose (Molloy et al., 2001; Ochonisky, Verroust, Bastuji-Garin, Gherardi, & Revus, 1994), and one study found that women and elderly patients are at greater risk (Ochonisky et al.). The toxicity consists of symmetric paresthesias usually beginning in the toes and extending to the feet and legs. This type of neuropathy is axonal and may improve with cessation of thalidomide treatment although symptoms may persist (Kyle & Rajkumar, 2001). Neurologic assessment should be performed and, in some cases, baseline electromyography may be obtained prior to therapy; however, only half of the patients will have objective changes in nerve conduction studies. Pyridoxine (vitamin B₆) at 200 mg per day has been found to be helpful in reducing neuro-

pathic symptoms in a number of patients and may be given prior to start of treatment at 50–100 mg per day to help in preventing peripheral neuropathy (Singhal & Mehta, 2001). Patients may be referred to neurologists depending on the severity or grade of nerve toxicity and how it affects patients' quality of life.

Bradycardia

Bradycardia of unknown etiology occurs in approximately 5%–6% of patients treated with thalidomide (Hus et al., 2001; Singhal & Mehta, 2001). Patients must be monitored carefully, and if their heart rates fall below 50 beats per minute, thalidomide must be stopped immediately and further investigation must be initiated, such as an electrocardiogram or two-dimensional echocardiogram, to assess conduction or circulation

problems. Patients also should be advised about the potential bradycardia associated with concomitant use of beta blockers. Whenever possible, cardiologists should evaluate patients' cardiovascular status while on thalidomide and beta blockers. If thalidomide use is unavoidable despite serious bradycardia, pacemaker implantation may need to be considered (see Table 1).

Other Toxicities

One study has shown that a causal relationship exists between the use of thalidomide and Stevens-Johnson Syndrome (SJS) (Clark, Edom, Larson, & Lindsey, 2001). Also, life-threatening toxic epidermal necrolysis (TEN) has been reported in patients newly diagnosed with multiple myeloma who are treated with thalidomide and dexamethasone (Rajkumar, Gertz, & Witzig, 2000). The same condition

TABLE 1. SUGGESTED APPROACH TO MANAGING SPECIFIC ADVERSE EFFECTS OF THALIDOMIDE THERAPY

ADVERSE EVENT	TYPE/SEVERITY	MANAGEMENT	COMMENTS
Bradycardia	Mild: decrease in resting heart rate by 10–20 per min; rate > 60	Watch carefully, counsel patients to monitor pulse daily, and continue thalidomide.	Avoid concomitant beta blocker usage.
	Moderate: rate 50–60	As above and check echocardiogram (ECG); continue thalidomide if no hypotension or syncopal episodes exist and ECG is normal; stop thalidomide if symptoms exist or ECG is abnormal.	As above
	Severe: rate < 50	Stop thalidomide immediately and check ECG; evaluation for sick sinus syndrome or autonomic neuropathy may be necessary.	Consider pacemaker implantation if thalidomide is considered unavoidable.
Skin rash	Erythematous, maculopapular, itchy lesions	Apply local corticosteroid cream; if relief does not occur, decrease dose gradually or stop the drug and restart at lower dose.	
	Erythema multiforme (Stevens-Johnson Syndrome)	Discontinue thalidomide; repeat administration of the drug is absolutely contraindicated.	
Peripheral neuropathy	Mild symptoms	Increase pyridoxine dose to 200 mg daily; additional vitamins B ₁ , B ₁₂ , and folate may be helpful in some patients; continue thalidomide.	Baseline nerve conduction studies may be useful in patients with preexisting neuropathic symptoms.
	Moderate symptoms	As above; continue thalidomide if symptoms are intermittent; stop thalidomide if symptoms continue.	As above; thalidomide may be restarted if symptoms abate.
	Severe symptoms	As above; stop thalidomide and conduct nerve conduction studies to evaluate extent of neuropathic changes.	As above; thalidomide may be restarted at a lower dose if symptoms abate and therapy is considered unavoidable.
Thrombosis	Deep vein thrombosis	Therapeutic anticoagulation	Consider prophylactic warfarin or low molecular weight heparin in patients with prior history of deep vein thrombosis.
Constipation	Mild to severe	Instruct patients to drink adequate amounts of fluid, increase dietary fiber, exercise regularly, maintain good bowel regimen, and take stool softeners.	May use laxative if needed, but regular use should be discouraged.
Fatigue or somnolence	Mild to severe	Assess fatigue comprehensively and rule out other potential causes; perform mild to moderate exercises, minimize use of sedatives and tranquilizer, and take thalidomide at bedtime.	Daily activities should be encouraged.

Note. From "Thalidomide in Cancer: Potential Uses and Limitations," by S. Singhal and J. Mehta, 2001, *Biodrugs*, 15, 169. Copyright 2001 by Adis International. Reprinted with permission.

also occurred in one patient who was receiving thalidomide for glioblastoma (Horowitz & Stirling, 1999). An increased incidence of adverse reaction involving allergic mechanisms has been reported among patients with HIV infection (Bayard, Berger, & Jacobson, 1992). In SJS and TEN cases, earlier withdrawal of the drug was associated with better survival. Management of these patients must be undertaken in specialized intensive care or burn units. The main principles of symptomatic treatment are the same as for major burns, including warming of the environment, correction of electrolyte imbalances, high caloric intake, and prevention of sepsis (Roujeau, 1999).

Conclusion

Thalidomide is a useful agent in a variety of malignant and nonmalignant (e.g., leprosy) conditions. Several studies are under way to better understand the mechanism of action of this novel drug and its potential uses. Like any other drug, thalidomide is associated with toxicities and limitations. Because of its proven therapeutic use in multiple myeloma and other malignancies, the drug's use is expected to continue to grow in the future. Nurses and other healthcare providers must hone their skills in identifying signs and symptoms of its toxicities and initiate appropriate measures immediately and effectively. Improving patients' tolerance to thalidomide must be included in the overall goals of care to maximize the therapeutic benefits of this drug.

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U.S. Food and Drug Administration: Thalidomide: Important Patient Information
www.fda.gov/cder/news/thalidomide.htm

Cancer Bacup: Understanding Thalidomide
www.cancerbacup.org.uk/info/thalidomide.htm

National Cancer Institute: Thalidomide Continues Its Comeback Against Multiple Myeloma
www.cancer.gov/clinicaltrials/results/thalidomide-comeback0500

Links can be found using ONS Online at www.ons.org.

Rapid Recap

Thalidomide: Current Therapeutic Uses and Management of Its Toxicities

- Thalidomide has documented therapeutic activity in treating relapsed and refractory multiple myeloma.
- Thalidomide is highly teratogenic and the STEPS (System for Thalidomide Education and Prescribing Safety) program is used to educate healthcare providers and patients about how to avoid potential teratogenic effects of the drug.
- Commonly observed side effects associated with thalidomide include constipation, somnolence, fatigue, and skin rash.
- A less commonly observed side effect is deep vein thrombosis. Therapeutic anticoagulation must be maintained while patients receive thalidomide.