

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

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.

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

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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