Management of Thalidomide Toxicity

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Abstract

Thalidomide has re-emerged as a novel antineoplastic agent with immunomodulatory and antiangiogenic activities. In the early sixties, it was withdrawn from the market after its infamous association with congenital abnormalities that left about 10,000 children affected world-wide. With strict regulations and precautions, thalidomide is now approved by the FDA for the treatment of erythema nodosum leprosum. Its role in cancer therapy is promising, with clinical trials in the past 5 years showing significant activity in multiple myeloma. Several trials are ongoing in other malignancies, such as myelodysplastic syndrome, agnogenic myeloid metaplasia, renal cell carcinoma, and prostate cancer. The major toxicities of thalidomide are birth defects, sensorimotor peripheral neuropathy, somnolence, rash, fatigue, and constipation. Less common side effects include deep venous thrombosis, Stevens-Johnson syndrome, elevated liver enzymes, malaise, and peripheral edema. The incidence and severity of adverse events are related to dose and duration of therapy. Doses of the drug of 200 mg/day or less are usually well tolerated. In this review, we will discuss the incidence and management of the side effects of thalidomide and the precautions and interventions needed to minimize the toxicities of this drug.

Thalidomide [Thalomid, α-(N-phthalimido)-glutarimide] is a glutamic acid derivative that was used in the late 1950s as a sedative and as a therapy for pregnancy-related morning sickness. It was available in over 40 countries, including Germany, Canada, and Australia. Its use in the United States during this period was restricted to clinical trials since the Food and Drug Administration (FDA) did not approve the drug, citing lack of safety data [1, 2]. In 1961, the teratogenicity of thalidomide was recognized, and the drug was quickly taken off the market worldwide [3–5]. Over the past 5 years, thalidomide has reemerged as an anticancer agent with anti-angiogenic and immunomodulatory properties.

Although the resurgence of thalidomide into clinical practice occurred only recently, the drug never fully disappeared from clinical use since the 1960s. Shortly after its withdrawal from the market, it was found to be effective in the treatment of erythema nodosum leprosum (ENL) [6]. In the early 1990s it showed promise in the treatment of HIV wasting syndrome, graft-versus-host disease [7], and Behçet’s disease. In 1998, thalidomide was approved by the FDA for the treatment of ENL with certain safety requirements. Prescription of thalidomide in the United States requires participation of physicians, pharmacists, and patients with the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®) program to prevent teratogenicity [8].
Thalidomide is now commonly used in clinical practice “off label” in the treatment of multiple myeloma [9–11]. Its use in myeloma is based on several reports showing significant activity in relapsed and refractory disease [12–15]. More recently, the combination of thalidomide with dexamethasone has shown promise as initial therapy for newly diagnosed myeloma [16, 17]. Currently, two phase III studies are evaluating the combination of thalidomide with dexamethasone versus dexamethasone alone in newly diagnosed myeloma.

Thalidomide has also shown some activity against renal cell carcinoma, Kaposi’s sarcoma, agnogenic myeloid metaplasia, Waldenström’s macroglobulinemia, and myelodysplastic syndrome [18, 19]. However, there are still only limited efficacy data in these conditions compared to myeloma, and its use in these settings is investigational. Studies are ongoing in several other malignant and nonmalignant disorders.

Given the increasing clinical use of thalidomide, it becomes important to study the adverse effects of this agent. Besides teratogenicity, thalidomide has certain unique and frequent toxicities, such as constipation, sedation, fatigue, and neuropathy. This review summarizes the incidence, nature, and management of the adverse effects associated with thalidomide therapy. The frequencies of adverse events described in this paper (Tables 1 and 2) are approximate estimates based on clinical trials in myeloma as well as other malignant and nonmalignant disorders. Further, the recommendations for prevention and treatment of adverse events (Table 3) are just guidelines and are most applicable in the treatment of relapsed refractory myeloma and similar serious malignancies. They need to be adapted according to the clinical condition of the patient and the disease being treated.

**Side Effects of Thalidomide: General Considerations**

Teratogenicity is the most feared adverse effect; however, it is also the most preventable with appropriate precautions. With adequate precaution, education, and the S.T.E.P.S. program [8], the possibility of teratogenicity can be completely avoided. The most common side effects seen in clinical practice include somnolence, fatigue, peripheral neuropathy, constipation, and skin rash. Less common side effects include xerostomia, neutropenia, toxic epidermal necrolysis/Stevens-Johnson syndrome, deep venous thrombosis, hypothyroidism, menstrual irregularities, loss of libido, impotence, hyper- or hypoglycemia, asthenia, tremors, confusion, peripheral edema, elevation of liver enzymes, pruritus, hair loss, and fever.

The incidence of toxicities correlates with the dose of the drug. Patients receiving doses of 200 mg or less seem to tolerate the treatment well with minimal side effects. Conversely, almost all patients taking more than 400 mg/day experience thalidomide-related toxicities. There is a similar correlation with duration of therapy. With long-term thalidomide use (more than 6 months of therapy), peripheral neuropathy and hypothyroidism increase in frequency. In contrast, with time the incidence of constipation and sedation actually decreases, probably related to tolerance and dose modifications. The toxicity also increases when the drug is combined with dexamethasone or other chemotherapy drugs.

Approximately 10% of patients receiving thalidomide for the treatment of multiple myeloma discontinue therapy secondary to intolerance of drug toxicities [20–22].

**Teratogenicity**

Ingestion of thalidomide during the first trimester of pregnancy can cause serious fetal malformations, including absence of the ears; deafness, absence, or hypoplasia of the arms (phocomelia) preferentially affecting the radius and the thumb; defects of the tibia and femur; and cardiac, bowel, uterine, and gallbladder malformations [4, 5]. The critical period
is thought to be around 35–50 days after the last menstrual period. In this period, a single dose of thalidomide can cause serious teratogenicity. The risk of other birth defects outside the critical period is not well defined, and thalidomide is absolutely contraindicated throughout pregnancy.

**Precautions and interventions.** Because of its severe teratogenicity, the use of thalidomide in pregnant women is absolutely contraindicated. It should not be used in women of childbearing age unless there are no other alternatives available. If thalidomide is prescribed, women of childbearing age must abstain from sexual intercourse or use two effective contraceptive methods during treatment. One of these methods must be highly effective, e.g., hormonal contraception, an intrauterine device, tubal ligation, or a partner’s vasectomy. The additional method could include latex condoms, a diaphragm, or cervical cap. Contraception must begin 4 weeks prior to thalidomide therapy and continue 4 weeks after discontinuation of the drug. Women of childbearing age must undergo pregnancy testing 24 hours before therapy is initiated, every week during the first 4 weeks of treatment, then at 4-week intervals in women with regular menstrual cycles or 2-week intervals in women with irregular menstrual cycles. If a patient misses a menstrual cycle, treatment with thalidomide must be stopped immediately, and pregnancy testing and counseling should be performed. In the event of conception, patients must be referred to an obstetrician experienced in the field of reproductive toxicity.

It is not known whether thalidomide is excreted in human milk. Because the drug, like many others, may be excreted in human milk, it is recommended that breast-feeding be discontinued during thalidomide therapy. Men must abstain from sexual intercourse or use a condom while receiving treatment, even if they have had a successful vasectomy. This is because thalidomide may also be present in semen. In addition, male patients should be instructed not to undergo sperm donation while taking thalidomide. As mentioned earlier, in the United States, before therapy is initiated, all patients, physicians, and pharmacists must participate in the S.T.E.P.S. program [8], which explains these risks and precautions.

**Neurological Complications**

Studies in patients with multiple myeloma have shown that neurological complications account for over 80% of the major toxicities of thalidomide [13, 20, 21, 23–28]. They include peripheral neuropathy, somnolence and fatigue, dizziness, tremors, confusion, and incoordination.

**PERIPHERAL NEUROPATHY**

Neuropathy is a common side effect of thalidomide that usually occurs after prolonged administration, though there is no clear correlation with a cumulative dose [21, 24, 25]. The risk seems to occur mainly after 6 months or more of therapy. The National Cancer Institute Common Toxicity Criteria (CTC) grade 1–2 peripheral neuropathy can occur in more than 80% of patients, whereas severe grade 3–4 neuropathy occurs in about 3%–5% of patients receiving thalidomide. Neuropathy usually presents with sensory or motor symptoms, such as numbness, tingling, pain in the hands and feet, or weakness, with or without interference with daily activities. Symptoms may occur even after the termination of therapy. It is usually reversible with dose reductions or cessation of therapy, though it may be irreversible in some patients even after therapy is discontinued.

**Precautions and interventions.** At baseline all patients should be questioned about sensory and motor neuropathy symptoms. Patients are then evaluated regularly for symptoms and signs of early neuropathy during treatment. Electrophysiological testing can be used at baseline and every 6 months thereafter to detect asymptomatic neuropathy, although we do
not feel that this is indicated on a routine basis. The use of concurrent medications that can lead to neuropathy should be avoided if possible.

If neuropathy develops, the general recommendation is to stop therapy completely. However, in settings such as relapsed and/or refractory myeloma, the risks of serious neuropathy need to be balanced with the risks of discontinuing effective therapy for a fatal disease. Therefore, in this setting, rather than discontinuing therapy, we reduce the dose by 50% for CTC grade 1 neuropathy, especially if there are no other alternative therapeutic options. Similarly, if grade 2 neuropathy develops, we withhold therapy until toxicity resolves to baseline or decreases to less than grade 1, and then restart at a 50% dose reduction. If grade 3 or 4 neuropathy develops, thalidomide should be discontinued permanently. We are stricter with dose reductions and discontinuing therapy when treating patients with newly diagnosed myeloma, where alternative therapeutic options are available [29].

Typically, patients who are unable to tolerate doses as low as 50 mg/day may need to discontinue thalidomide. Patients whose symptoms recur after reinstitution of thalidomide or whose neuropathy does not improve to less than grade 1 may need to discontinue thalidomide permanently.

**SOMNOLENCE AND FATIGUE**

Somnolence and fatigue are common side effects of thalidomide [20, 21, 23–26, 28]. Mild sedation can occur in over 75% of patients. Patients may also complain of fatigue, weakness, inability to concentrate, and mood alterations. Serious (grade 3/4) sedation and fatigue can occur in up to 5%–10% of patients.

**Precautions and interventions.** To minimize daytime sedation, the total daily dose of thalidomide may be taken as a single bedtime dose. Physicians should advise their patients about the possible impairment of mental and/or physical abilities. Patients should avoid performing hazardous tasks and the use of concurrent medications or alcohol that may also cause drowsiness. If grade 3 somnolence, such as drowsiness, interferes with the activities of daily living, or if obtundation, stupor, or coma occurs, therapy should be withheld until the toxicity resolves to baseline. The drug may then be restarted at a 50% lower dose.

**OTHER NEUROLOGICAL COMPLICATIONS**

Mild tremors can occur in about 35% of patients, and ataxia can occur in approximately 15% of patients receiving thalidomide therapy. Hearing loss has been reported in about 3% of patients [21, 25]. Seizures have also been reported in the literature; however, it is not clear whether the seizures were related to thalidomide only or were a result of studying a high-risk population (eg, one with recurrent gliomas). Other reported neurological toxicities include agitation, anxiety, nervousness, psychosis, amnesia, insomnia, confusion, depression, euphoria, causalgia, circumoral paresthesia, hyperesthesia, neuralgia, paresthesia, peripheral neuritis, and vasodilation.

**Precautions and interventions.** Physicians should be careful in using thalidomide in patients with preexisting seizure disorders or who have a high risk for seizure activity. These patients should be monitored closely for any epileptic activity. For the other neurological side effects such as tremors and ataxia, the dose should be withheld if needed until the symptoms improve and then resumed at a 50% lower dose.
Gastrointestinal Complications

Gastrointestinal side effects can occur in more than 80% of patients taking thalidomide. The side effects are usually mild in severity.

CONSTIPATION

Constipation is a common side effect of thalidomide and can vary from mild to severe. As many as 80%–90% of patients can develop mild constipation [21, 23, 25, 28, 30]. The constipation is hypothesized to be secondary to the effects of thalidomide on autonomic nerve endings in the gut, as with other neurotoxic agents, such as vincristine. Most patients can be managed easily by the treating physician with simple measures. However, in some cases severe symptoms can occur, leading to obstruction and even toxic megacolon. Such severe constipation usually occurs in patients receiving high doses of thalidomide, especially among those who lead a sedentary lifestyle and are more prone to develop constipation.

Precautions and interventions. All patients should be advised about the occurrence of constipation as a common side effect of thalidomide and be given information about the use of prophylactic measures, such as change of diet and exercise. We recommend routine use of low-dose stool softeners and/or laxatives prophylactically in all patients starting on thalidomide. If constipation occurs, it should be managed according to the degree of severity. In patients with severe constipation requiring manual extraction or an enema, thalidomide should be withheld until the condition resolves. If thalidomide therapy is needed for a serious illness such as myeloma, the drug may be restarted with the addition of prophylactic laxatives and dose reduction.

OTHER GASTROINTESTINAL TOXICITIES

Xerostomia, or dry mouth, occurs in approximately 10% of patients receiving thalidomide, although its etiology is unclear [23–25, 31]. In addition, elevated liver enzymes may occur in some patients. Other gastrointestinal complications include anorexia, vomiting, increased appetite, weight gain, dyspepsia, eructation, flatulence, and intestinal obstruction.

Dermatologic Complications

The development of skin rash is a common side effect of thalidomide [31]. In most instances, the rash is mild and resolves with moisturizing lotions and dose adjustments. Skin rash can occur in the form of a macular or papular eruption, erythema with pruritus, vesicular eruption, or desquamation, usually covering less than 50% of the body surface. Occasionally, more serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, can occur [32]. In a recent report, Hall et al [31] found minor to moderate skin eruptions in over 40% of patients taking thalidomide alone or in combination with dexamethasone for myeloma. These toxicities included morbilliform, seborrheic, maculopapular, or nonspecific dermatitis. Severe skin reactions (exfoliative erythroderma, erythema multiforme, and toxic epidermal necrolysis) that required hospitalization and withdrawal of thalidomide developed in 3 of 50 patients receiving thalidomide and dexamethasone. Other skin manifestations reported in the literature include acne, alopecia, dry skin, eczematous rash, exfoliative dermatitis, ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating, urticaria, and vesiculobullous rash.

Precautions and interventions. If mild grade 1–2 dermatologic side effects occur, thalidomide should be discontinued until the toxicity resolves to baseline or at least to less than grade 1. The drug may then be resumed with a 50% dose reduction. If severe forms of exfoliative, purpuric, or bullous rash occur, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, thalidomide should be discontinued indefinitely. Drugs
known to cause serious skin reactions, such as trimethoprim/sulfamethoxazole or allopurinol, should be avoided in patients receiving thalidomide. We also do not recommend thalidomide doses in excess of 200 mg/day in combination with dexamethasone.

**Thromboembolic Complications**

**DEEP VENOUS THROMBOSIS**

Deep venous thrombosis (DVT) and/or pulmonary embolism (PE) occurs in only about 1%–3% of patients receiving single-agent thalidomide for myeloma [17, 33–37]. It is unclear whether the risk of DVT/PE in these patients is any higher than what can be expected in patients with any serious malignancy [38]. For instance, patients with multiple myeloma are more predisposed to develop DVT/PE due to their malignancy, and also due to immobility secondary to osteolytic lesions and fractures [35]. However, among patients who are receiving concomitant dexamethasone, the incidence increases up to 10%–12% [17, 26]. This is similar to rates observed with vincristine/doxorubicin (Adriamycin)/dexamethasone (VAD) therapy for myeloma. In patients receiving thalidomide and concomitant doxorubicin, the incidence climbs to 25% or higher [34, 39].

*Precautions and interventions.* The risk of thalidomide-induced thrombosis is highest in newly diagnosed patients when the drug is given in combination with dexamethasone, doxorubicin, or other chemotherapeutic drugs. The risk is elevated in the elderly and in patients with an underlying inherited or acquired thrombotic predisposition. The use of routine prophylactic warfarin or low-molecular-weight heparin or aspirin for all patients receiving thalidomide in combination with dexamethasone is being considered. We believe that the risk can be minimized if the dosage of thalidomide is escalated gradually when given in combination with steroids, eg 50 mg/day for 2 weeks, 100 mg/day for 2 weeks, and then 200 mg/day (maximum), as tolerated. Alternatively, studies are needed in newly diagnosed patients to see if the risk can be minimized by starting thalidomide with the second month of therapy (following 1 month of single-agent dexamethasone).

Thalidomide is best avoided in combination with doxorubicin. If this combination is employed, routine full-dose anticoagulation is needed. Similar risk of DVT/PE has been seen with other chemotherapeutic agents in combination with thalidomide, such as docetaxel (Taxotere) and gemcitabine (Gemzar).

If patients develop thrombotic complications, discontinue the thalidomide and treat the coagulopathy. Thalidomide may be restarted as needed once the toxicity resolves and adequate anticoagulation is in place.

**Hematologic Complications**

**NEUTROPENIA**

Thalidomide has been associated with the development of mild neutropenia in 15%–25% of patients. Patients with HIV or patients with neutropenia prior to therapy should be monitored closely [20, 23, 40]. Generally, patients with an absolute neutrophil count (ANC) of less than 750/mm$^3$ should not be started on thalidomide therapy.

*Precautions and interventions.* While patients are receiving thalidomide, they should be monitored via a repeated complete blood count and differential. If a patient develops neutropenia with an ANC between 500–1,000/mm$^3$, consider growth factors (G-CSF) or reduce thalidomide dose by 50%. If the ANC falls below 500/mm$^3$, stop the thalidomide immediately and consider the use of growth factors (G-CSF) until the neutrophil count
recovers (ANC > 500/mm$^3$). Thalidomide may then be restarted at a 50% dose reduction, with or without growth factor support, depending on need.

**OTHER HEMATOLOGIC COMPLICATIONS**

They are rare but include hypochromic anemia, macrocytosis, leukocytosis, thrombocytopenia, eosinophilia, and possible splenomegaly. Causality is unclear.

**Cardiovascular Complications**

Cardiovascular complications include bradycardia, tachycardia, hypertension, hypotension, peripheral vascular insufficiency, and peripheral edema.

**SINUS BRADYCARDIA**

Mild sinus bradycardia can occur in as many as 25% of patients, whereas severe sinus bradycardia is rare and occurs in only 1%–3% of patients receiving thalidomide [20, 22, 23, 26]. The mechanism of thalidomide-induced cardiovascular side effects is still not well understood.

*Precautions and interventions.* Physicians need to be aware of the potential cardiovascular side effects of thalidomide. If significant bradycardia occurs, thalidomide should be discontinued and appropriate management initiated.

**PERIPHERAL EDEMA**

Mild peripheral edema occurs in about 15% of patients, whereas severe edema that limits function and does not respond to therapy, or anasarca, is less common, occurring in up to 3% of patients [9, 20, 21, 23]. Patients who are more prone to fluid retention manifest peripheral edema more commonly, such as patients with systemic amyloidosis, renal insufficiency, or congestive heart failure.

*Precautions and interventions.* In patients with severe edema, thalidomide should be stopped and diuretics prescribed as needed. Thalidomide can be restarted at a 50% dose reduction once the edema resolves or becomes minimal.

**ORTHOSTATIC HYPOTENSION**

Orthostatic hypotension and dizziness have been reported with thalidomide [9, 14, 23]. These reactions may be a manifestation of autonomic neuropathy.

*Precautions and interventions.* Physicians should advise their patients about the symptoms of orthostatic hypotension and teach them adequate precautions, such as sitting upright for a few minutes prior to standing up from a recumbent position. In severe cases, thalidomide should be withheld until the symptoms resolve and then restarted at 50% lower dose.

**Constitutional Complications**

Other possible thalidomide toxicities include constitutional manifestations, such as headache, weakness, weight loss, and fever. Mild forms of these symptoms are common and can occur in up to 60% of patients receiving thalidomide [9, 14]. Severe weakness and fatigue occur in about 3%–5% of patients. Fatigue and weakness were discussed earlier, along with sedation, since these symptoms can be hard to distinguish and are often seen together.

*Precautions and interventions.* If severe side effects occur, thalidomide should be withheld until the toxicity resolves; the drug may then be restarted at a 50% lower dose.
Effect of Thalidomide on Stem-Cell Mobilization

Thalidomide is increasingly used in myeloma patients as first-line therapy prior to autologous stem-cell transplantation. In our studies, thalidomide therapy has not significantly affected the ability to mobilize CD34 cells or reach the target of CD34 collection needed for autologous stem-cell transplantation. However, in our study, all patients were taken off thalidomide at a median of 3.6 weeks (range, 1.9–23.0 weeks) before mobilization [41]. Current large, randomized, prospective studies using thalidomide induction prior to autologous stem-cell mobilization and transplantation will answer this important and relevant question.

Precautions and interventions. Based on the available data, we would recommend that all patients receiving thalidomide discontinue therapy for approximately 2–4 weeks prior to stem-cell mobilization.

Effect of Thalidomide on Engraftment

Another important question is the effect on engraftment of thalidomide therapy prior to autologous stem-cell transplantation [42]. In our study, thalidomide used for a limited time and discontinued approximately 3–4 weeks before attempted mobilization did not affect neutrophil engraftment or time to reach a platelet count of 50,000/µL. The requirement for platelet transfusions was not different in patients who received prior thalidomide compared with patients who did not receive thalidomide [41]. Current prospective phase III clinical trials of thalidomide and dexamethasone compared with dexamethasone alone as induction therapy prior to autologous stem-cell transplantation will answer this question more definitively.

Precautions and interventions. Given our current knowledge, clinicians need to be aware of the lack of good data on engraftment kinetics, especially if thalidomide is used for a long period as first-line therapy before stem-cell mobilization.

Hypersensitivity

Hypersensitivity to thalidomide occurs rarely and may include the development of an erythematous macular rash sometimes associated with fever, tachycardia, and hypotension [43].

Precautions and interventions. If a hypersensitivity reaction occurs, thalidomide should be withheld until the symptoms and signs resolve; therapy may then be resumed at a 50% dose reduction. If the reaction recurs when the drug is restarted, thalidomide should be discontinued. If a severe reaction occurs, thalidomide should be discontinued and not restarted.

Other Side Effects Reported in the Literature

Many other rare toxicities have been reported in the literature. They include opportunistic infections [44], photosensitivity, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, hypothyroidism [45], lung toxicity [46], diabetes, electrolyte abnormalities, hyperglycemia, hyperkalemia, hyperuricemia, hypocalemia [47], hypoproteinemia, impotence, loss of libido, gynecomastia [48], arthritis, bone tenderness, hypertonia, arthralgias, leg cramps, myalgia, myasthenia, cough, epistaxis, voice alteration, amblyopia, dry eyes, eye pain, deafness, tinnitus, decreased creatinine clearance, hematuria, orchitis, proteinuria, and urinary frequency [43]. It is unclear whether the relationship of thalidomide to these toxicities is truly causal or coincidental.
Precautions and interventions. In general, thalidomide should be discontinued once a complication occurs that is related to the drug. It can be re instituted at a 50% dose reduction once the symptoms resolve. In severe or life-threatening complications, thalidomide should be discontinued indefinitely. In all cases, patients should be instructed not to share their medication with anyone else and not to donate blood while taking thalidomide.

Drug Dependence, Abuse, and Overdosage

Thalidomide has not been reported to induce physical or psychological dependence. However, as in the case of other tranquilizers/hypnotics, habituation has been reported to occur with the use of thalidomide. There have been three reported cases of overdose and attempted suicides, with no fatalities. The doses used were up to 14.4 g, and all patients recovered without complications.

Conclusion

Thalidomide has become one of the most significant advances in the treatment of multiple myeloma. In addition, it is being tested in many other hematological and solid malignancies, with promising results. It is also used in many other non-neoplastic conditions. The drug is usually well tolerated and has minimal side effects at doses of 200 mg/day or less. However, with higher doses and in some patients, serious toxicities may occur. Analogs of thalidomide, IMiDs (eg, CC-5013) have the promise of improved efficacy against multiple myeloma and with fewer side effects than thalidomide [49]. These agents are currently being tested in clinical trials. Because of its popularity as a novel neoplastic agent and its seemingly wide applicability, physicians need to be aware of the toxicities of thalidomide and the appropriate interventions to be instituted.

PEER VIEW POINT

Commentary by Seema Singhal, MD, and Jayesh Mehta, MD

Drs. Ghobrial and Rajkumar have provided a detailed review of the potential toxicities of thalidomide and have suggested possible management options. While our approach at Northwestern is broadly similar, based upon our own clinical experience [1–3], we have identified some additional aspects that may be significant and helpful in practice [4, 5]. An important point to note about both the article and our commentary is that most of the recommendations are empiric because there are no formal studies evaluating specific management of the adverse effects of thalidomide.

The management of adverse effects of thalidomide was a much greater concern in the early days of the use of the drug [1], when few other options were available for patients with end-stage myeloma. Indeed, in our early experience with myeloma [1], 1 in 6 patients discontinued thalidomide because of side effects. Today, that proportion is higher—1 in 5 or 1 in 4—because of the availability of bortezomib (Velcade) [6] and clinical trials of other agents [5, 7].

Gradual escalation from a low starting dose may reduce the incidence of some of the adverse effects of thalidomide and allow the patient time to get accustomed to the effects of the drug. However, this may not be an option for patients with rapidly progressive disease [4] who require higher doses and/or combination therapy.

Although thalidomide does not have the side-effect profile of a conventional cytotoxic drug, it still has a broad array of adverse effects. Except in the context of a clinical trial, its use in situations not requiring therapy under usual circumstances (eg, smoldering myeloma) should be avoided. However, if there is no therapeutic alternative and the
disease is responding, the side effects of thalidomide may well be worth its use. Appropriate use of thalidomide, therefore, is dependent upon the situation.

Some of the side effects include:

- **Drowsiness.** While initial drowsiness is very common, tachyphylaxis often occurs with continued administration. It is best to initiate therapy at bedtime, but as daytime somnolence patterns vary considerably, the time of administration may need to be modified. Patients who experience significant daytime drowsiness often benefit from taking thalidomide in the early evening, rather than at bedtime. Patients with dose-dependent somnolence sometimes benefit from taking a lower dose twice daily. Methylphenidate is helpful in some patients, if they have no contraindications to its use.

- **Constipation.** Constipation is virtually a universal problem in patients taking thalidomide. In addition to increasing dietary fiber, it is advisable to start a stool softener or a laxative routinely, and, in fact, the threshold to add a second or even a third agent should be low. Some patients benefit from a regular break in therapy, such as weekend “drug holidays.” With an aggressive approach to its management, constipation should rarely be a reason to discontinue thalidomide.

- **Peripheral neuropathy.** One third to one half of patients taking thalidomide for more than 3 months complain of neuropathic symptoms. Gabapentin (Neurontin), amitriptyline, and a local doxepin cream can help with symptoms. The role of pyridoxine and other vitamins remains unclear, although we recommend them routinely to all patients for prophylaxis.

- **Deep vein thrombosis.** Appropriate precautions (Table 1) ought to minimize the clinical impact of this problem. Dexamethasone, thalidomide, cisplatin, Adriamycin, cyclophosphamide, and etoposide (DT-PACE) is a highly effective salvage regimen in myeloma. It may, therefore, be difficult to avoid the combination of dexamethasone and doxorubicin despite the high risk of thrombosis. We administer low-molecular-weight heparin to these patients. The same recommendation would probably apply to coadministration of thalidomide with gemcitabine (Gemzar) or paclitaxel (Taxol).

- **Skin rash.** We have not seen a problem with concomitant use of trimethoprim-sulfamethoxazole and thalidomide. This is relevant in practice because prophylaxis against *Pneumocystis carinii* may be important in patients receiving high-dose dexamethasone. We have also not noticed a relationship between the thalidomide dose and skin reactions in patients receiving concomitant dexamethasone. In patients with a rash that does not respond to local measures, the addition of low-dose prednisone is often effective and may have a beneficial effect on the underlying disease (myeloma).

- **Hypothyroidism.** This is uncommon but rectifiable when it does occur. Early symptoms may well be overlooked because the fatigue may be attributed to thalidomide. Thyroid function should be checked routinely every 3–6 months in patients receiving thalidomide.

- **Bradycardia and syncope.** Concomitant use of drugs that slow the heart rate (such as beta blockers) should be avoided. A minority of myeloma patients with responsive disease and no therapeutic alternatives who developed these problems have had pacemakers implanted to be able to continue thalidomide.

Seema Singhal, MD
Jayesh Mehta, MD
REFERENCES


PEER VIEW POINT
Commentary by Christian Meierhofer, MD

In 1998 thalidomide was approved by the FDA for the first time in the United States. It has been more than 35 years since the teratogenic properties of thalidomide were suspected independently by two physicians, McBride and Lenz, in 1961, with the drug subsequently being withdrawn from the market [1, 2]. The approval of thalidomide is still restricted to the treatment of erythema nodosum in leprosy and linked with special safety conditions. The safe use of thalidomide must be ensured, and the prevention of teratogenic side effects should be guaranteed via Celgene Corporation’s S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety) program.

Since the withdrawal and reintroduction of the drug, increasing knowledge has been gained about thalidomide’s activity itself and about drug approval in general. After its withdrawal, careful molecular and clinical investigations continued that widened our understanding of thalidomide’s activity, and improved methodology and greater knowledge about immunology, inflammation, and angiogenesis helped to interpret the features of thalidomide. The molecular activity of thalidomide comprises a wide range of mechanisms—alteration of the cytokine-release profile, alteration of tumor necrosis factor-alpha (TNF-α) levels, gene-regulatory effects, and transcriptional control of inflammation. Thalidomide also proved to have immunomodulatory and anti-angiogenic properties [3, 4].

PROMISING APPLICATIONS

The continuing study of thalidomide revealed its benefit in erythema nodosum of leprosy, and since then several new clinical applications have been postulated. Beneficial effects...
have been reported in dermatology for the treatment of systemic lupus erythematosus, sarcoidosis, and Behçet disease; in gastroenterologic disorders, such as inflammatory bowel disease; in immunology for graft-versus-host reaction; and also in infectious diseases, neurology, and rheumatology. Thalidomide’s beneficial effects in oncologic and hematologic disorders have been shown in the past decade [3, 4]. Thalidomide’s activity against advanced myeloma, with a durable response in some patients with refractory multiple myeloma after high-dose chemotherapy, was shown in a phase II study by Singhal et al [5]. Now the focus of interest is shifting to thalidomide’s adverse affects and their prevention.

SIDE EFFECTS
Ghobrial and Rajkumar present an excellent overview of the common and not so common problems that thalidomide can cause, with suggested management strategies and recommendations for dose modification. The first severe adverse effect of thalidomide was reported in 1960, when neuropathogenicity after prolonged use of the drug was recognized. Thalidomide was first synthesized in 1954 and now almost half a century later we have gained a lot of experience about possible adverse effects and their frequency [3, 4]. Peripheral neuropathy is a common side effect of thalidomide and often calls for the cessation of therapy when the symptoms are severe.

A second serious side effect is deep venous thrombosis, which has been reported in the past few years. The reported rate of thromboembolism in thalidomide therapy varies in the literature from 0% to 43%. Limited data from a phase II study showed a thromboembolic event rate of 43% for renal cell cancer patients treated with thalidomide and chemotherapy, compared with a rate of 3% for patients with similar clinical characteristics who were treated with chemotherapy alone [6]. The incidence rate seems to depend on the underlying disease and concomitant application of glucocorticoids or multiagent chemotherapy.

Keratinocyte death in toxic epidermal necrolysis was reported to be a result of apoptosis secondary to elevated TNF-α levels. A randomized, double-blind, placebo-controlled trial showed that thalidomide was not effective in halting necrolysis and treatment with the drug was associated with increased levels of TNF-α and increased mortality [7, 8]. In September 2000, Rajkumar and coworkers published a report of a case of life-threatening toxic epidermal necrolysis in the presence of thalidomide therapy for refractory myeloma [9]. Thus, thalidomide should be discontinued indefinitely when severe dermatological disorders, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, occur. Some side effects were beneficial in certain circumstances; for instance, weight gain made thalidomide attractive for HIV therapy and tumor wasting syndrome.

There is no doubt that thalidomide has a broad range of serious side effects, and careful risk/benefit assessments need to be done when considering its use. The patient’s general condition and co-morbidities also need to be carefully considered. However, most of the common side effects need only symptomatic therapy, with or without thalidomide dose adjustment.

Accurate dosing regimens and guidelines for the handling of adverse reactions are necessary for thalidomide if its use is to expand. Understandably, there is a great lobby of innocent victims affected years ago by the teratogenic properties of thalidomide that opposes the reintroduction of thalidomide into the market. The safety conditions must guarantee that such a pharmacological catastrophe will be prevented in the future.

FUTURE PROSPECTS
New enantiomers and analogs may improve the tolerability of thalidomide. Thalidomide and its co-stimulatory IMiD analogs, in particular CC-4047 and CC-5013 (Celgene
Corp.), are currently being assessed in patients with advanced myeloma and some solid tumors, with promising effects [10]. However, despite the promising effects of thalidomide on a broad range of serious diseases, further, very careful research on the pharmacologic and pharmacodynamic properties of thalidomide is necessary.

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REFERENCES


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References


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### Table 1

Common Toxicities of Thalidomide

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>ORGAN SYSTEM INVOLVED</th>
<th>APPROXIMATE FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Neurologic</td>
<td>Mild: 85% Severe: 3%–5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Neurologic</td>
<td>Mild: 75% Severe: 5%–10%</td>
</tr>
<tr>
<td>Constipation</td>
<td>Gastrointestinal</td>
<td>Mild: 80%–90% Severe: 5%</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Gastrointestinal</td>
<td>10%</td>
</tr>
<tr>
<td>Skin rash</td>
<td>Dermatologic</td>
<td>Mild: 45%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Hematologic</td>
<td>15%–25%</td>
</tr>
<tr>
<td>Weakness</td>
<td>Constitutional</td>
<td>Mild: 60% Severe: 5%–5%</td>
</tr>
</tbody>
</table>
### Table 2

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>ORGAN SYSTEM INVOLVED</th>
<th>APPROXIMATE FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic epidermal necrolysis/Stevens-Johnson syndrome</td>
<td>Dermatologic</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>Hematologic</td>
<td>1%–3% (with single-agent therapy)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Cardiovascular</td>
<td>Mild: 25% Severe: 3%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Cardiovascular</td>
<td>Mild: 15% Anasarca: 3%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Cardiovascular</td>
<td>Rare</td>
</tr>
<tr>
<td>Tremors</td>
<td>Neurologic</td>
<td>35%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Neurologic</td>
<td>15%</td>
</tr>
<tr>
<td>Seizures</td>
<td>Neurologic</td>
<td>Rare</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Neurologic</td>
<td>3%</td>
</tr>
<tr>
<td>Confusion</td>
<td>Neurologic</td>
<td>Rare</td>
</tr>
<tr>
<td>Impotence</td>
<td>Neurologic</td>
<td>Rare</td>
</tr>
<tr>
<td>Elevation of liver enzymes</td>
<td>Gastrointestinal</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Endocrine</td>
<td>Rare</td>
</tr>
<tr>
<td>Menstrual irregularities</td>
<td>Endocrine</td>
<td>Rare</td>
</tr>
<tr>
<td>Hyperglycemia or hypoglycemia</td>
<td>Endocrine</td>
<td>Rare</td>
</tr>
<tr>
<td>Headache</td>
<td>Constitutional</td>
<td>Mild: 10%</td>
</tr>
</tbody>
</table>
### Table 3
Prevention and Management of Thalidomide Complications

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>PRECAUTIONS AND INTERVENTIONS</th>
</tr>
</thead>
</table>
| Prevention of birth defects | • Pregnancy is contraindicated  
• All female patients of childbearing potential must use two effective contraceptive methods at the same time  
• All male patients must abstain from sex or use a latex condom, even if they have had a vasectomy  
• Both physicians and patients must participate in S.T.E.P.S. program d |
| Peripheral neuropathy     | • Grade 1 severity: reduce thalidomide dosage by 50%  
• Grade 2 severity: withhold thalidomide until toxicity resolves to baseline or decreases to below grade 1 and then restart at a 50% lower dose  
• Grade 3 or 4 severity: discontinue thalidomide permanently |
| Somnolence                | • Instruct patients to take their total daily dose at bedtime  
• Patients should avoid performing hazardous tasks  
• Advise patients to avoid the use of concurrent medications that may cause drowsiness  
• If obtundation, stupor, or coma occurs, withhold thalidomide until toxicity resolves to baseline, then restart the drug at a 50% lower dose |
| Constipation              | • Advise patients about prophylactic measures, such as change of diet and exercise  
• Prescribe a low-dose stool softener and/or laxative  
• In cases of obstipation requiring manual extraction or an enema, or in cases of obstruction and toxic megacolon, withhold thalidomide until condition resolves, then restart thalidomide therapy with the addition of prophylactic laxatives and/or a 50% dose reduction |
| Skin rash                 | • Mild to moderate skin rash: withhold thalidomide until toxicity resolves to baseline or decreases to below grade 1, and then restart treatment with a 50% lower dose  
• Stevens-Johnson syndrome: discontinue thalidomide indefinitely |
| Neutropenia               | • Absolute neutrophil count (ANC) = 500–1,000/mm³: consider a granulocyte colony-stimulating factor or reduce thalidomide dose by 50%  
• ANC < 500/mm³: withhold thalidomide until ANC > 500/mm³ and then restart it at a 50% lower dose |
| Orthostatic hypotension   | • Advise patient to sit upright for a few minutes prior to standing up from a recumbent position |
| All other toxicities      | • Withhold thalidomide until toxicity resolves to baseline or to a mild form, then restart therapy at a 50% lower dose  
• For all severe and life-threatening complications, discontinue thalidomide indefinitely |

d S.T.E.P.S. = System for Thalidomide Education and Prescribing Safety
Table 1
Prophylaxis Against Deep Vein Thrombosis in Patients Receiving Thalidomide

<table>
<thead>
<tr>
<th>PRIOR HISTORY OF DEEP VEIN THROMBOSIS</th>
<th>LOW-RISK (THALIDOMIDE ALONE)</th>
<th>MODERATE-RISK (THALIDOMIDE WITH OTHER AGENTS)</th>
<th>HIGH-RISK (THALIDOMIDE WITH DOXORUBICIN, PACLITAXEL, AND GEMCITABINE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Low-dose warfarin</td>
<td>Warfarin to maintain INR around 2–2.5</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>No</td>
<td>None</td>
<td>Low-dose warfarin</td>
<td>Low-molecular-weight heparin</td>
</tr>
</tbody>
</table>