Managing a Side-Effect

Prevention and management of thalidomide toxicity

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Abstract

Thalidomide is a drug whose efficacy has been reported in numerous conditions which can be attributable to its various mechanism of actions. Hence it would be prudent to know its side effects and its subsequent management so as to use it effectively. The current article reviews side effects of thalidomide and discusses methods of prevention and management of thalidomide toxicity.

Keywords: Management, side effect, thalidomide

Introduction

Thalidomide is one of the important drugs in a dermatologist’s armamentarium whose efficacy has been reported in numerous conditions, which can be attributed to its various mechanisms of actions. These include the immunomodulatory, anti-inflammatory, antiangiogenic, and sedative and hypnotic actions which play an integral role in treatment of conditions such as erythema nodosum leprosum, prurigo nodularis, actinic prurigo, discoid lupus erythematosus, aphthous stomatitis, Behçet’s syndrome, pyoderma gangrenosum, sarcoid, livedoid vasculitis, histiocytosis, graft-versus-host disease, HIV-related mouth and throat ulcers and Kaposi’s sarcoma, and multiple myeloma.[1]

Thalidomide is a synthetic glutamic acid derivative that consists of a chiral center and two amide rings and is a racemic mixture of the (+)(R)-thalidomide and (−)(S)-thalidomide. It was initially used for the treatment of epilepsy in 1957. However, it was found that it did not help much in seizure control but instead caused effective sedation and nausea control. In the year 1962, the phocomelia tragedy highlighted the fact that (+)(R)-thalidomide was an effective sedative, whereas the (−)(S)-thalidomide was a potent teratogen. Thalidomide is a pregnancy category X drug, which needs to be avoided in lactation as well in children <12 years of age.

General side effects of thalidomide

The most dreaded side effect is teratogenicity, whereas the most common side effects seen in clinical practice are somnolence, fatigue, peripheral neuropathy, constipation, and skin rash.

The less common ones 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 seems to correlate with the dose of the drug. Those receiving doses of 200 mg or less seem to tolerate the treatment well with minimal side effects. Conversely, almost all who are taking more than 400 mg/day experience some thalidomide-related toxicity. There is a similar correlation with the duration of therapy. With long-term use (more than 6 months of therapy), occurrence of peripheral neuropathy and hypothyroidism increases in frequency. However, contrarily, the incidence of constipation and sedation decreases with time due to tolerance and dose adjustments. The drug toxicity also increases when it is combined with dexamethasone or other chemotherapeutic agents.[2-4]

Teratogenicity

One of the dreadful and well-known side effect, for which this drug came into limelight was for phocomelia or seal limbs in newborns whose mothers had been treated with thalidomide.
in the 1960s era for nausea. 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.\[1,6\]

Major human fetal abnormalities include skeletal deformities such as amelia or absence of legs and/or arms, absence of bones, phocomelia or short legs and/or arms, and bone hypoplasia; external ear deformities (anotia, microtia or micro pinnna, and small or absent auditory canals); facial palsy; ocular abnormalities (e.g., anophthalmos and microphthalmos); congenital heart defects; renal and urinary tract malformations; genital malformations; and gastrointestinal tract malformations. Mortality rate in neonates with thalidomide-induced abnormalities is about 40%.\[1,5\]

**Precautions and intervention**

It is contraindicated in pregnancy and is to be used in females of childbearing potential only when alternative therapies are contraindicated.\[1,6\]

Before initiation of therapy, females must certify that they are not pregnant or not of childbearing potential (i.e., hysterectomy and postmenopausal [no menses for ≥24 consecutive months]).\[1,6\] Pregnancy must be prevented by the simultaneous use of two forms of reliable contraception for ≥4 weeks before, throughout, and for 4 weeks after completion of therapy. It is advocated to use a highly effective birth control method (intrauterine device or oral/injectable or implanted hormonal contraceptives/tubal ligation/have a vasectomized partner along with effective barrier methods such as latex condom, diaphragm, or cervical cap).\[1,6\]

Mandatory contraception is not required for females who have undergone hysterectomy, are postmenopausal, and have had no menses for ≥24 consecutive months.

Sexually mature males must completely avoid unprotected sexual contact with women of childbearing potential (i.e., use latex condom throughout and for ≥4 weeks after thalidomide therapy) because thalidomide distributes into semen. In addition, male patients should be instructed not to undergo sperm donation while taking thalidomide. Sperm donation while taking thalidomide should be made available only through restricted distribution program. The System for Thalidomide Education and Prescribing Safety (STEPS) is designed to help ensure that fetal exposure does not occur.\[1,6\] This limits the access to thalidomide to prescribing clinicians, pharmacies, and patients who are registered in program and mandates compliance with registration, education, and safety requirements. It facilitates pregnancy testing and counseling in accordance with STEPS program along with prescribing and dispensing ≤28-day supply of drug. For the drug refill, a new prescription is mandatory, and another authorization from STEPS program is required.\[1,6\] Pregnancy should be excluded by negative pregnancy test ≤24 h before treatment initiation. Repeat the pregnancy tests once weekly during the 1st month, then monthly or every 2 weeks in women with regular or irregular menstrual cycles, respectively, till treatment therapy.

Patient or parent/legal guardian must provide a written acknowledgment of understanding of these warnings and need for mandatory contraceptive measures.\[1,6\]

**Constipation and Other Gastrointestinal Side Effects**

Constipation is a common side effect which varies from mild to severe. Up to 80%–90% of patients can develop mild constipation.\[1,7–10\] This is hypothesized to be secondary to the effects of thalidomide on autonomic nerve endings in the gut. In some cases who are receiving high dose of thalidomide, severe symptoms can lead to obstruction and even toxic megacolon.

**Precautions and interventions**

All patients should be advised regarding the occurrence of constipation and the use of prophylactic measures such as change of diet and exercise. The incidence of constipation reduces over a period of time due to tachyphylaxis. In addition to increasing dietary fiber, it is advisable to start a stool softerner or a laxative routinely. Some patients benefit from a regular break in therapy such as weekend “drug holidays.” 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, the drug may be restarted with the addition of prophylactic laxatives and dose reduction.\[2\]

Less common gastrointestinal side effects are xerostomia which occurs in approximately 10% of patients receiving thalidomide.\[1,7–10\] In addition, sometimes, elevated liver enzymes may occur. Others include anorexia, vomiting, increased appetite, weight gain, dyspepsia, eructation, flatulence, and intestinal obstruction.

**Neurological Symptoms**

Studies in patients with multiple myeloma have shown that neurological complications account for over 80% of the major toxicities of thalidomide.\[1,7–9\] This include peripheral neuropathy, somnolence and fatigue, dizziness, tremors, confusion, and incoordination.

**Peripheral neuropathy**

Neuropathy is a common side effect that occurs after prolonged administration though there is no clear correlation with a cumulative dose.\[1,8\] The risk seems more likely after 6 months or more of therapy. According to National Cancer Institute Common Toxicity Criteria 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. It usually presents with proximal sensory or motor symptoms such as numbness, tingling, pain in the hands and feet, or weakness, with or without interference with daily activities. It is usually reversible with dose reduction or cessation of therapy though it may be irreversible in some even after discontinuation of therapy. Differentiation of neuropathologic symptoms caused by thalidomide and changes caused by underlying disease such as in leprosy with type 2 lepra reaction may be difficult at times.[1,11,12]

**Prevention and interventions**

Hence, primary evaluation of the patients for preexisting signs and symptoms of peripheral neuropathy such as numbness, tingling, pain, or a burning sensation in the hands and feet should be done, and counseling and questioning the patients regularly during therapy to look for its signs and symptoms (i.e., monthly for first 3 months of thalidomide treatment and periodically 6 monthly thereafter).[11,13]

It is advocated to do a baseline electrophysiologic testing consisting of sensory nerve action potential amplitude measurement and then onward every 6 months to detect asymptomatic neuropathy.[1]

If manifestations of peripheral neuropathy develop, ideally to discontinue therapy immediately to minimize further damage.[1]

If drug administration is a must, then reduce the dose by 50% for Grade 1 neuropathy. If Grade 2 neuropathy is developed, therapy is withheld 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.[14]

Cautious use with concomitant drugs known to be associated with peripheral neuropathy is advocated such as dapsone, stavudine, didanosine, and isoniazid. Gabapentin and amitriptyline can partly help to alleviate the symptoms. The role of pyridoxine and other vitamins remains unclear but can be recommended to patients to prevent neuropathy.[2]

**Sedation and drowsiness**

Drowsiness, somnolence, and fatigue are common side effects of thalidomide.[1,4,7,15] 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 ≤400 mg daily preferably at bedtime ≥1 h after evening meal[1] or, alternatively, in divided doses with water ≥1 h after meals. The patients should be advised about the possible impairment of mental and/or physical abilities and the need to avoid performing hazardous tasks and avoidance of concurrent medications such as barbiturates, chlorpromazine, or alcohol that may cause aggravation of symptoms. If Grade 3 somnolence, such as drowsiness, interferes with the activities of daily living, or if obtundation, stupor, or coma occurs, then withhold treatment until it resolves to baseline. The drug may then be restarted at a 50% lower dose.[2]

**Tremors, ataxia, and seizures**

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.[3,9] 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 (e.g. one with recurrent gliomas). Other reported neurological toxicities include agitation, anxiety, nervousness, psychosis, amnesia, insomnia, confusion, depression, euphoria, causalgia, circumoral paresthesia, hyperesthesia, neuralgia, and paresthesia.

**Precautions and interventions**

Use cautiously in patients with preexisting seizure disorders or who have a high risk for seizure activity with close monitoring 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.

**Venous Thromboembolism**

There are reports of increased risk of venous thromboembolism (e.g., deep vein thrombosis and pulmonary embolism) in patients with multiple myeloma on monotherapy with thalidomide (1%–3%) and especially when used in combination with chemotherapy, which includes dexamethasone, the incidence increases up to 10%–12%.[16,17]

This has also been reported in occasional cases of erythema nodosum leprosum. Individual risk factors for thromboembolic events include advanced age, previous history of thromboembolism, an indwelling central venous catheter, comorbid conditions (e.g., infections, diabetes, cardiac disease, obesity), current or recent immobilization, recent surgery and inherited thrombophilic abnormalities, cancer, and cancer therapy itself.

**Precautions and intervention**

In those patients with known risk factors, concomitant use of thalidomide with oral contraceptives and steroids needs careful patient monitoring. Monitoring for signs and symptoms of thromboembolism such as shortness of breath, chest pain, and arm or leg swelling is required and decision regarding thromboprophylaxis needs to be taken on careful assessment of patient’s risk factors.

International Myeloma Working Group recommends aspirin for thalidomide-treated multiple myeloma patients with ≤1 individual and/or myeloma-related risk factor and a low molecular weight heparin (LMWH) for those with ≥2 such
risk factors. Thromboprophylaxis with an LMWH can be considered in patients receiving thalidomide with high-dose dexamethasone, doxorubicin, or multiple antineoplastic agents, independent of additional risk factors. Full-dose warfarin (international normalized ratio 2–3) can be used as an alternative to LMWH.

The risk can also be minimized if the dosage of thalidomide is escalated gradually when given in combination with steroids, for example, 50 mg/day for 2 weeks, 100 mg/day for 2 weeks, and then 200 mg/day (maximum), as tolerated. 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 Effects

Mild neutropenia can occur in 15%–25% of patients. Patients with HIV or patients with neutropenia before therapy should be closely monitored. Do not initiate therapy in patients with an absolute neutrophil count (ANC) of <750/mm³.

#### Precautions and Interventions

Patient on therapy with thalidomide should be monitored by routinely doing complete and differential blood counts. If neutropenia develops with an ANC between 500 and 1000/mm³, consider using growth factors (granulocyte colony-stimulating factor [G-CSF]) or reduction in thalidomide dose by 50%. If the ANC falls below 500/mm³, thalidomide should be stopped immediately and growth factors (G-CSF) need to be used until the neutrophil count recovers (ANC >500/mm³). Thalidomide may be then restarted at a 50% dose reduction, with or without growth factor support, depending on the necessity.

### Sensitivity Reactions

Hypersensitivity reactions such as erythematous macular rash associated with fever, tachycardia, and hypotension have been reported.

#### Precautions and Interventions

Discontinue the drug if signs and symptoms of hypersensitivity are severe. If therapy is resumed and reaction recurs, then permanent discontinuation of the drug is advocated. Do not resume therapy if rash is exfoliative, purpuric, or bullous, or if Stevens–Johnson syndrome or toxic epidermal necrolysis is suspected.

### Cardiovascular Side Effects

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

#### Sinus Bradycardia

Mild sinus bradycardia can occur in up to 25% of patients. Severe sinus bradycardia is rare and occurs in only 1%–3% of patients receiving thalidomide. 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 is seen about 15% of patients, whereas severe edema that limits function is less common, occurring in up to 3%. Patients with systemic amyloidosis, renal insufficiency, or congestive heart failure are more prone.

#### 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 may be a manifestation of autonomic neuropathy.

#### Precautions and Interventions

The patients should be advised about the symptoms of orthostatic hypotension and taught adequate precautions such as sitting upright for a few minutes before standing up from a recumbent position. In severe cases, thalidomide should be withheld until the symptoms resolve and then restarted at 50% lower dose.

### Conclusion

Due to the wide spectrum of use and multimodal actions of thalidomide, it has gained popularity in recent times. Hence, the physicians need to be aware of the toxicities of thalidomide and the appropriate interventions to be instituted. Risk management plan for commonly occurring or dreaded side effects should be kept ready and should be followed by physicians so that side effects can be minimized and drug can be effectively used for thalidomide-responsive dermatoses.

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### Conflicts of Interest

There are no conflicts of interest.

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