

# THALIDOMIDE

Most patients treated with Thalidomide will experience adverse effects, but the effects will differ from one patient to the next. Symptoms may indicate that the underlying cancer is not under control or has relapses. Cancer patients may also have co-morbid diseases that require treatment and cause symptoms.

The most common adverse effects with Thalidomide are anemia, leukopenia, neutropenia, thrombocytopenia, constipation, somnolence/fatigue, dizziness, peripheral neuropathy, tremor, peripheral edema, and asthenia.

### ADVERSE DRUG REACTION MANAGEMENT GUIDE

1. Myelosuppression
2. Diarrhea
3. Constipation
4. Nausea & Vomiting
5. Xerostomia
6. Pruritis
7. Rash
8. Xerosis (dry skin)
9. Dermatitis
10. Arthralgia, myalgia, back and neck pain
11. General pain
12. Fatigue & weakness
13. Insomnia

#### 1. Myelosuppression

Thalidomide may cause suppression of the blood cell production in the myeloid tissues of the bone marrow. This can result in lowering of white blood cells and platelets. It is important to have a Complete Blood Count (CBC) blood test prior to the start of each cycle of this agent. If any blood cell component is reduced below an acceptable level, the drug may need to be held until the blood cells recover. **Thalidomide must NOT be dispensed** until the CBC test is completed and verified prior to each cycle of the treatment. Verification will be done by an oncology health professional.

**Prevention:** General infection preventative measures should be followed while on this drug, especially if the blood counts are low. Advise patient to:

- Limit contact with people who are sick, have colds, or have been recently vaccinated
- Rest often
- Do not eat uncooked vegetables
- Wash hands often

If the platelet count is low, tell the patient to take. Advise patient to:

- Take care when shaving or performing any activity of daily living where the skin could be cut
- Use a soft toothbrush.
- Tell your doctor before dental work is done.

**Management:** If the patient has a fever or other signs of an infection when the blood counts are low, advise him/her to go directly to the Emergency Department and contact the oncologist when there.

The ER staff needs to be told that the patient is taking this drug, and that it is a form of chemotherapy. Empiric antibiotics will be required.

If the patient has unusual bleeding when the platelet counts are low, advise him/her to go to the Emergency Department, tell the ER staff about this drug, and contact the oncologist when there.

## **2. Diarrhea**

Diarrhea is common in patients treated with Thalidomide. Dietary modifications are not recommended in anticipation of diarrhea, but must be considered if diarrhea occurs.

### **Management:**

For mild diarrhea (less than 4 loose stools per day)

- Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours)

For moderate diarrhea (more than 4 to 6 loose stools per day or night-time diarrhea), tell the patient to be more aggressive with loperamide (e.g., Imodium®) for early-onset diarrhea

- Take 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours
- This dosage is higher than packaging recommendations.

Replace lost fluids: Fluid intake is more important than eating in patients with diarrhea. To replace lost fluid, advise patients to increase fluids by up to 3 to 4 litres per day (unless there is a known contraindication to increased fluid intake). The patient may drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea

Anal care: Recommend to your patient to:

- Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation
- Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste
- Soak in a warm bathtub or sitz bath to relieve discomfort

Dietary changes during diarrhea: Advise your patients to change their diet while diarrhea is a problem:

- Eat and drink small quantities of food often
- Avoid spicy, greasy, or fried foods
- Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve
- Follow a lactose-free diet
- Avoid cabbage, brussel spouts, and broccoli, which may produce stomach gas, bloating and cramps

### 3. Constipation

Constipation is generally understood to be a reduction in bowel movements to fewer than 3 per week, or unsatisfactory (e.g. incomplete) defecation. Reduced bowel function may give the misperception of constipation to patients who expect one or more movements daily. Constipation may be caused by this medication, other medications being taken concurrently (e.g. narcotic analgesics), or by the underlying cancer. Reduced physical activity or dietary changes, possibly related to this medication or the overall cancer treatment, may contribute to constipation. Abdominal pain is often associated with constipation, but if symptoms become severe a medical assessment to examine for fecal impaction or bowel obstruction may be needed.

**Prevention:** Advise patient to:

- Change diet, if possible, to include more fruits, vegetables, and high-fibre foods. If the patient is taking a low-calorie diet, consider increasing calories to improve colonic transit.
- Use of a regular laxative regimen, such as senna or bisacodyl at bedtime
- Consider a bowel routine to maintain regularity, such as attempting bowel movements each morning after breakfast (usually the optimal time for a movement), using the toilet when there is an urge instead of repressing it, placing a footstool in front of the toilet to elevate thighs during movement.
- Consider adding light exercise for patients with mostly sedentary lifestyles
- Weight loss in over-weight patients may help improve bowel function

**Management:**

- If prophylactic stimulant laxative is not effective, try osmotic laxative (e.g. lactulose or PEG)
- Stool softeners have not been shown to be effective
- Drink of fluids
- Biofeedback and relaxation techniques may help some patients with pelvic floor dysfunction. Psychosocial teams in the cancer centres may help with this type of intervention.

### 4. Nausea & Vomiting

Nausea and vomiting may occur in up to 30% of patients on Thalidomide. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Thalidomide tend to have nausea of lesser severity and longer duration, with or without emesis. This can be more distressing to patients' quality of life than acute nausea and vomiting. Often patients will have nausea without the relief that comes from emesis.

**Management:** The following may provide relief from nausea and vomiting:

- Prophylactic antiemetic agents (e.g. dopaminergic agents such as prochlorperazine, or promotility agents such as metoclopramide) given with each dose of Lenalidomide and repeated as needed for nausea control. While there is no evidence to support the use of dimenhydrinate, there is evidence that ginger products (e.g. Gravol® Ginger) may be effective, with fewer adverse effects

- Avoid spicy or greasy foods that may contribute to the feeling of nausea. Bland foods, fresh air, and plenty of clear water may reduce the feelings of nausea

### 5. Xerostomia

Patients may experience xerostomia (dry mouth). This condition is characterized by a dry, tough tongue; cracks in lips and at corners of mouth; pain or burning in mouth or on tongue; sticky, dry mouth; and thick, stringy saliva. This may cause patients to have trouble speaking or swallowing, a constant sore throat, hoarseness, and dry nasal passages that may result in nosebleeds. Xerostomia can cause mouth sores, gum disease, and tooth loss. Oral candidiasis is also associated with xerostomia.

**Prevention:** Advise patients to:

- Check their mouth daily for red, white, or dark patches; sores or sign of tooth decay
- Chew sugarless gum or candies to increase saliva flow
- Avoid mouthwashes or dental products containing alcohol
- Use a cool-mist humidifier (especially at night)
- Sip water throughout the day or suck on ice chips
- Drink 8 cups of water daily; eat soft, moist food; avoid alcohol, caffeinated beverages, and spicy, sugary, or acidic foods
- Avoid smoking

**Management:**

There are several OTC treatments to address xerostomia:

- Artificial saliva (e.g. Biotène®, Moi-Stir®, Mouth Kote®)
- Meticulous oral hygiene
  - Brush teeth 2-4 times daily with a soft bristle toothbrush. Soak toothbrush in warm water to soften bristles.
  - Floss gently once daily to avoid gum injury
  - Salt and baking soda rinses (1/2 tsp of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
  - Use a low-abrasive fluoride toothpaste
  - Avoid products that contain sodium lauryl sulfate, which may worsen canker sores
  - Orajel®, Vaseline®, or glycerine swabs to relieve dryness and cracks on lips and under dentures

Prescribed medications such as fluoride gel (dentist) and pilocarpine (or other drugs that increase saliva production).

### 6. Pruritis

Pruritis (itchiness) may occur when taking Thalidomide, and usually happens because skin has lost its moisture.

**Prevention:** Preventing dry skin is the key to preventing pruritis. Advise your patients to:

- Use mild soaps that are deodorant and fragrance-free (e.g. Dove® or Neutrogena®)
- Apply lotions or bland emollients (Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, Vaseline Intensive Care® Advanced Healing Lotion) often.
- Use liquid shower gels in place of soap.

**Management:** For mild-moderate Pruritis, consider advising patients to:

- Apply more lotion than usual to help eliminate itchiness.
- Use lotions that contain aloe vera or dimethicone Moisturel®
- Use antidandruff shampoo and conditioner
- Use hair products that contain tea tree oil, which contain extra moisturizers and may help with symptoms

## 7. Rash

Rash is a common adverse effect of Thalidomide. Rash symptoms often appear soon after starting treatment. This rash presents with spots and bumps on the forearms, trunk, and sometimes, the face. They are often itchy, but if scratched, may become infected and crusty. Most cases of this generalized skin rash are mild and go away on their own. Rash is more common in women and patients on higher doses, and may worsen after sun exposure.

It is important to recognize rash symptoms early and start symptomatic therapy promptly.

**Prevention:** Prevention should begin when Thalidomide therapy is begun, and continue throughout treatment.

You should advise your patient to:

- Cleanse with mild soaps or cleansers or bath or shower oils to avoid skin dryness
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®
- Remove make-up with a gentle, skin-friendly cleanser (e.g., Neutrogena®, Dove®).
- Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide

**Management:** For mild to moderate skin rash, there are some over-the-counter options you may consider:

- Antihistamine (diphenhydramine)
- Topical steroid (hydrocortisone 0.5%)
- Coal tar preparations

If the rash progresses to moderate to severe, the patient may need prescribed therapy:

- Oral corticosteroids (short course, with or without topical triamcinolone acetonide 0.1% ointment)
- Temporary interruption of therapy until the rash resolves, and then re-challenge at low dose

## 8. Xerosis (dry skin)

Xerosis (dry skin) occurs in up to 20% of patients treated with Thalidomide. Dry, scaly, itchy skin resembling atopic eczema may begin within 3 months after starting therapy; it is persistent and often lasts several months. This dry, scaly skin may appear on the limbs, and torso. It often affects the fingertips, heels, and toes. Painful fissures may develop in these areas, in nail folds, and over finger joints in excessively dry skin. This can make wearing shoes or performing tasks difficult. Dry skin may become increasingly fragile and bruise easily. Xerosis may worsen, becoming chronically red and irritable. Secondary infection with *S. aureus* may occur. General measures to hydrate the skin and choosing the right treatment is critical to alleviating skin dryness. Frequent application of emollients that contain ammonium lactate (e.g., hydrolac or Lac-Hydrin®) or 5% to 10% urea (e.g. Eucerin® 5 or Uremol® 10) may significantly improve dryness. Instruct the patient to avoid occlusive topical creams and lotions, as they may obstruct hair follicles and thus lead to infection.

**Prevention:** Advise patients to:

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness
- Take short showers with warm water
- Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®

**Management:**

- At the first signs of skin dryness; dry skin on face, back, and chest: advise patient to switch to oil-in-water creams.
- For moderate to severe xerosis; dry skin on limbs: Use greasy water-in-oil creams or ointments.
- For eczema, recommend short-term use (1-2 weeks) of weak topical corticosteroid creams. Refer to doctor if it is not controlled by OTC treatment.
- For infection, recommend topical antibiotics. Refer to doctor if it is not controlled by OTC treatment.
- For skin fissures, treatment options include:
  - 50% propylene glycol under a plastic bandage
  - Salicylic acid 10% ointment
  - Colloid dressing

Refer to doctor if it is not controlled by OTC treatment.

## 9. Dermatitis

Dermatitis is a non-specific term for a variety of skin reactions that exhibit erythema, scaling, vesicles and crusts (sometimes also called eczema). Skin changes always include an inflammatory response, with initial erythema (redness) from vasodilation and usually edema from leakage of the engorged

vasculature. Swelling may lead to fluid-filled vesicles in the skin which may ooze or weep when broken and then crust over as they dry. Dermatitis may be worsened by topical allergens or harsh soaps and detergents, humid weather, excessive sweating, dietary allergens, and the itch-scratch cycle.

**Prevention:**

- Avoid use of any topical products that are irritating (e.g. soaps, deodorants).
- Wear breathable, loose-fitting clothing. Natural fabrics are usually less irritating than synthetic fabrics. Always wash new clothes before the first use. Do not use fabric softeners or bleach in washing or drying cycles.

**Management:**

- Use a systemic antihistamine, either an H1 blocker (e.g. diphenhydramine) or a non-sedating antihistamine (e.g. loratidine, cetirizine, desloratidine). Consider adding an H2 blocker antihistamine (e.g. ranitidine, famotidine) for chronic urticaria
- Bathing with colloidal oatmeal preparations (e.g. Aveeno®) and use of unscented moisturizing creams after bathing may help with itchiness and dry skin
- Cooling salves, such as menthol or camphor-containing products (e.g. Gold Bond®) may provide relief. Keep products in the refrigerator for additional cooling effect.
- Topical corticosteroids, beginning with OTC Hydrocortisone 0.5% cream and progressing as needed to more potent prescription corticosteroid creams, are often used
- Acetaminophen may be added to the treatment of urticarial for more painful lesions.

**10. Arthralgia, myalgia, back and neck pain**

Aching joints or muscle and muscle cramps occur in 15-20% of patients taking Thalidomide. Muscle cramps may occur in the hands, feet, calves, or thighs. Cramps have been described as sustained muscular contractions that follow a consistent pattern, frequency, and severity. Muscle cramps may be related to exertion or could happen at night. Patients should avoid using quinine or drinking tonic water (contains quinine).

Joint pain may begin in the first month of therapy and commonly subside after a few months. Pain may affect the leg bones, hips, and knees, and may appear in an asymmetrical pattern. Although there are no evidence-based guidelines for prevention or treatment, anecdotal reports and expert experience suggest that some patients' pain could be eased by using mineral supplements.

**Management:** The following may provide relief from muscle aches or cramps:

- Calcium and magnesium supplements
- Mild pain medications- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
- For bone or joint pain, consider the use of heating pads, ice packs, or topical arthritis creams and liniments
- Mild exercise and/or massage therapy may help reduce bone and joint pain

- Avoid using quinine or drinking tonic water

### **11. General pain**

Patients on Thalidomide may experience other types of pain. About 40% of patients have headaches while on this treatment. Generalized pain maybe a drug side effect or may be related to the cancer.

**Management:** The following may provide relief from headaches and other general pain problems:

- Mild pain may respond to non-pharmacologic approaches, such as rest, distraction, cool cloth on the forehead
- Mild pain medications- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
- Acetaminophen with codeine, either OTC (low dose) or on prescription (higher dose) may be considered for more severe pain.
- If acetaminophen is not sufficient to control pain, consider prescription opioid analgesics for management of more severe pain (possibly due to tumor)
- If there is a neuropathic component to the pain, consider a trial with a tricyclic antidepressant (e.g. low dose amitriptyline or imipramine) or gabapentin

### **12. Fatigue & weakness**

About 80% of patients on Thalidomide will experience fatigue. Fatigue is are not life-threatening but will significantly reduce quality of life.

**Management:** The following may provide relief from fatigue:

- There are no medications that have demonstrated an effect to relieve fatigue
- Mild exercise is very helpful to reduce fatigue, but must be manageable if there is also muscle weakness

### **13. Insomnia**

Insomnia, or the inability to fall asleep and/or stay asleep, may be a symptom of depression, a drug side effect, a reaction to unresolved pain, or a natural reaction to daily stress and worries (e.g. about the cancer). Many drugs can contribute to insomnia problems.

**Prevention:** Advise patients to:

- Avoid alcohol, nicotine (e.g. smoking, nicotine supplements) and caffeine intake, especially in the evening
- Avoid large meals late in the evening
- Use earplugs and/or eye masks if helpful. Turn the clock face away from sight and use the alarm daily.
- Try relaxation exercises
- Maintain a regular pattern of timing for going to bed and rising, 7 days a week. Limit mid-day naps. Do not sleep in on weekends or free days.



- Regular aerobic exercise (e.g. walking) during the day can help stimulate the need for sleep at night. Exercise should be enough to cause sweating, with a duration of 30 to 40 minutes daily. Do not overexert if there are other physical limitations to exercise

**Management:** There are many medications (prescription and OTC) used for insomnia. Try to start with the least potent options and limit use to short periods if possible.

- Common OTC products contain diphenhydramine or doxylamine. These products may help patients to fall asleep.
- Natural health products have limited evidence of effectiveness, but are often used. Products may contain Valerian or Melaton.
- Prescription hypnotics may be considered. Options include benzodiazepines (e.g. lorazepam, flurazepam) and non-benzodiazepines (e.g. zopiclone).

#### **REFERENCES:**

ONTarget Resource Guide, Common Side Effects from Targeted Therapy. The Groupe d'étude en oncologie and The Canadian Association of Pharmacy in Oncology, 2012.

Systemic Therapy Manual for Cancer Treatment, Cancer Care Nova Scotia, 2013

Patient Self-Care. Helping Your Patients Make Therapeutic Choices. Canadian Pharmaceutical Association , 2010

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011