

## MITOTANE

Most patients treated with Mitotane 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 Mitotane are insufficiency, nausea and vomiting, lethargy, and dizziness.

### ADVERSE DRUG REACTION MANAGEMENT GUIDE

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|----------------------|-----------------------------------|
| 1. Myelosuppression  | 6. Fever                          |
| 2. Diarrhea          | 7. Lethargy, Fatigue and Weakness |
| 3. Anorexia          | 8. General pain                   |
| 4. Nausea & vomiting | 9. Hypotension                    |
| 5. Rash              | 10. Flushing                      |

#### 1. Myelosuppression

Mitotane 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. **Mitotane 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 Mitotane. 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. Anorexia

Up to 25% of patients will experience a decreased appetite while taking Mitotane.

**Prevention:** Advise patient to:

- Have several small meals a day
- Eat slowly

**Management:**

- Light exercise and fresh air may help
- Drink plenty of fluids
- Eat a high calorie meal plan
- Consider Cyproheptadine to stimulate appetite

### 4. Nausea & vomiting

Nausea and vomiting may occur in up to 25% of patients on Mitotane. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Mitotane 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 Mitotane 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. Rash

Rash is a common adverse effect of Mitotane. 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 Mitotane therapy is begun, and continue throughout treatment.

You should advise your patient to:

- Cleanse with mild soaps or cleaners 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

## 6. Fever

Fever, or increased body temperature, may occur with this drug. While fever is uncomfortable, be careful if the patient is at risk of febrile neutropenia from the drug. Reducing fever can mask the symptoms of emergent infection and cause a delay in management of this potentially life-threatening problem.

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

- Non-pharmacologic approaches, such as a sponge bath with tepid water, or a cool cloth on the forehead, may provide some relief from fever
- Antipyretics- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)

## 7. Lethargy, Fatigue and Weakness

About one in four patients on Mitotane will experience lethargy and somnolence. Some patients will experience asthenia (or general weakness). These symptoms 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

## 8. General pain

Patients on Mitotane may experience pain. 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

## 9. Hypotension

Some patients may experience low blood pressure, either alone or as part of another toxicity. Blood pressure should be monitored to determine if the hypotension is temporary or if it persists. Increasing fluid consumption may help.

If the blood pressure is too low, the patient may experience blackouts or fainting. Loss of consciousness may be a symptom of a more serious underlying condition, perhaps unmasked by the drug therapy, so the patient should seek urgent medical advice. For frequent or extended loss of consciousness, the patient should go to the local Emergency Department (by ambulance or an alternate driver).

## 10. Flushing

Flushing is a reddening of the skin, often accompanied by a feeling of heat. It is caused by local vasodilation. Flushing can be very troublesome for many patients.

**Prevention:** Advise the patient to:

- Keep room temperature lower, if possible
- Dress in layers, so layers can be removed if hot flushes become uncomfortable
- Psychoeducational interventions, as sometimes offered by psychosocial support teams in the cancer centres, may help patients to find ways to improve these symptoms

**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,

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

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011