

PROCARBAZINE

Most patients treated with Procarbazine 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 Procarbazine are myelosuppression, nausea and vomiting and peripheral neuropathy.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

- | | |
|----------------------|---------------------------------------|
| 1. Myelosuppression | 10. Pruritis |
| 2. Diarrhea | 11. Rash |
| 3. Constipation | 12. Hives |
| 4. Anorexia | 13. Dermatitis |
| 5. Nausea & vomiting | 14. Alopecia |
| 6. Stomatitis | 15. Arthralgia |
| 7. Xerostomia | 16. Myalgia |
| 8. Insomnia | 17. General pain (including headache) |
| 9. Lethargy | |

1. Myelosuppression

Procarbazine 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. **Procarbazine 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 Procarbazine. 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. Anorexia

Some patients will experience a decreased appetite while taking Procarbazine.

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

5. Nausea & vomiting

Nausea and vomiting may occur in 50% of patients on Procarbazine. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Procarbazine 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 Procarbazine 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. Graval[®] 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

6. Stomatitis

Stomatitis (mouth sores) is a common side effect of Procarbazine. Integrity of mucous membranes may be affected by Procarbazine treatment, leading to the swelling and reddening of membranes lining the mouth. Mouth sores or cankers may develop. Patients may complain of changes on the inner cheeks or mouth surfaces, even when mouth sores are not present or only a mild redness is evident. Patients may experience:

- Mouth pain
- Difficulty chewing
- Painful swallowing (dysphagia)

This side effect may lead to Procarbazine dosage reductions. It is important to maintain good oral health during treatment. Aggressive prevention may reduce incidence and severity of stomatitis. Treatment during stomatitis event(s) can relieve symptoms (including oral pain, oral bleeding, dental complications, soft tissue infection and dietary restrictions) and restore oral health, often within 7 to 14 days.

Prevention and Management: Good oral care is the key to prevention of stomatitis. If possible, the patient should work with their dentist (and oncologist) to correct any pre-existing dental problems before starting Procarbazine treatment. Careful and thorough oral hygiene is important, and particularly irritating foods (e.g. very spicy foods, rough textures, alcohol-containing foods or liquids) should be avoided.

Management may be achieved in many patients without prescribed therapies. Most important is meticulous oral hygiene:

- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles

- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash (non-alcoholic)
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®).

If the patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips, contact the cancer care team at once and tell the patient to contact the oncology nurse or oncologist for immediate advice or a visit.

Topical preparations in widespread use for chemotherapy-induced stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. Although there is no significant evidence of the effectiveness or tolerability of these combinations, there may be a degree of symptom management (e.g. oral pain, improved ability to maintain a proper diet). Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of stomatitis resolution from chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, and salt-and-baking soda rinses. Hydrogen peroxide may worsen mouth ulcers. In addition, mouthwash preparations containing *antifungals* (i.e. nystatin), broad-spectrum *antibiotics*, or *corticosteroids* have shown no benefit and possibly further worsening of stomatitis- **these combinations are not recommended!**

7. 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).

8. 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).

9. **Lethargy**

Some patients on Procarbazine will experience fatigue and lethargy. 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

10. **Pruritis**

Pruritis (itchiness) may occur when taking Procarbazine, 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

11. **Rash**

Rash is a common adverse effect of Procarbazine. 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 Procarbazine 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

12. Hives

Urticaria, or hives, is a common complication from many types of drugs. Hives are itchy, red, raised wheals of various sizes and shapes. They generally last for less than 24 hours and can be very irritating to patients (who tend to scratch the hives and cause broken skin and bleeding). New lesions may continue to erupt during drug therapy. Dry skin can exacerbate hives.

Prevention: Advise patients to:

- Avoid over bathing, bathing in very hot water, use of harsh soaps and bubble baths. Consider showering with tepid water or adding 4 tablespoons of baking soda to bath water.
- Use tap water compresses to relieve affected skin.

Management: In addition to management of dry skin, the patient may try one or more option below:

- 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.

13. 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.

14. Alopecia

Some patients will have hair loss while taking Procarbazine. Most patients will lose a minimal amount of hair on the oral form of this agent.

Prevention:

- Although there is no way to prevent hair loss, you may advise the patient that hair will usually regrow, once the treatments are over. The replacement hair may have a different colour or consistency.

Management:

If hair loss bothers the patient, a wig, hat, cap, scarf or hair piece may be worn

15. Arthralgia

Aching joints or arthritic pain is a common co-morbidity in cancer patients and can be initiated or exacerbated by some medications.

Prevention:

- Some light exercise (e.g. walking, jogging) and regular physical activity will help reduce pain and discomfort, even if it is painful to start some activities.

Management:

- Acetaminophen on a regular basis may help to manage pain. Try the controlled-release product, 1 or 2 tablets every 8 hours. Be careful not to take too much Acetaminophen (i.e. limit Acetaminophen from other sources, such as PRN dosing or Acetaminophen-containing narcotic analgesics)
- Do NOT use systemic non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
- For 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 joint pain
- If the arthralgia persists, see a physician, and tell them about all medications, including the cancer treatment drugs

16. Myalgia

Aching muscles and muscle cramps can be very disruptive, lowering patient quality of life. 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).

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

- 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)
- Use of a muscle relaxant may be considered (e.g. cyclobenzaprine- prescription, or acetaminophen/methocarbamol combinations-OTC)

17. General pain (including headache)

Patients on Procarbazine may experience other types of pain. About 40% of patients have headaches while on this treatment. Generalized pain may be 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

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