

VEMURAFENIB

Most patients treated with Vemurafenib 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 Vemurafenib are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Rash

Rash is a common adverse effect of Vemurafenib, occurring in about 37% of patients. It is not uncommon for patients to develop a moderately severe rash. Preventive therapy is recommended to reduce the incidence of grade 3 to 4 skin rashes in Vemurafenib-treated patients. Avoid exposure to sunlight and wear sunscreen that contains UVA filters (titanium dioxide) and has an SPF of 30 or greater. Early recognition of symptoms and a prompt start to therapy are the mainstays of treating this rash. Mild to moderate symptoms may be managed while the patient continues therapy. Refer any patient who develops a severe rash to their doctor.

Prevention: General skin care should be coordinated with HFSR prevention (above). Prevention should begin when Sorafenib therapy is begun, and continue throughout treatment.

You should advise your patient:

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness
- Moisturize 2-3 times a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or 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 broad-spectrum sunscreen (SPF 30 or higher) that contains zinc oxide or titanium dioxide

2. Pruritis

Pruritus (itchiness) is a common side effect of Vemurafenib. Nearly 1 in 4 patients will develop this adverse effect, which usually occurs because skin has lost its moisture. This is usually associated with a rash and may be disruptive to the patient during sleep or while he/she is awake. Preventive therapy is the key to reducing the incidence and severity of pruritis.

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

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

Management: For mild to moderate Pruritus, advise patients to:

- Apply more lotion than usual to help reduce or 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

For moderate to severe pruritus, antihistamines may provide some relief. Refer patients experiencing intense, widespread itching to their doctors.

3. Photosensitivity reaction

Sunlight can cause sunburn reactions in up to one-third of patients treated with Vemurafenib. Up to 12% of patients develop a moderately severe sunburn reaction. Prevention is recommended to avoid these reactions.

Prevention: When patients begin therapy, advise them to AVOID sun exposure and:

- Use a broad-spectrum sunscreen (with an SPF of 30 or higher that protects against UVA rays and contains UVA filters) all day long, inside and outside. Wear protective clothing, including a hat, to cover the head, face, arms, legs, hands, and feet.
- Remind patients that UV rays go through glass (house, car windows, etc.).

4. Hair loss

Between 35 and 45% of patients will have hair loss while taking Vemurafenib. 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

5. Xerosis (dry skin)

Xerosis (dry skin) occurs in as many as 35% of patients treated with Vemurafenib. Dry, scaly, itchy skin resembling atopic eczema usually begins anywhere from 1 week to 3 months after starting therapy; it is persistent and often lasts several months. This dry, scaly skin may appear on the limbs, torso, and areas of EGFR-induced rash. 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.

6. Diarrhea

Vemurafenib commonly causes diarrhea—about 28% of experience diarrhea. 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.

If mild to moderate diarrhea persists for 48 hours, despite dietary modification and loperamide, a second-line agent may be needed; advise the patient to seek medical attention.

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 liters 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

7. 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.

8. Nausea & vomiting

Nausea and vomiting may occur in up to 30% of patients on Vemurafenib. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Vemurafenib 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 Dasatinib 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

9. Dysgeusia (distorted taste)

Dysgeusia is an altered or distorted taste sensation, sometimes associated with cancer treatments and other drugs. It is hard to determine exact etiology, since taste is related to sense of smell and other stimuli. Change of taste sensation, or loss of taste, can impact quality of life for some patients, making certain foods taste unpleasant or metallic. Often patients lose their taste for meats, if these foodstuffs become excessively bitter or unpleasant. Patients may lose their appetite and lose weight over time. Unpleasant sensations may become conditioned responses, leading to lifelong avoidance of certain foods after dysgeusia is resolved.

Prevention: Advise patients to:

- Avoid eating 'favorite' foods when the dysgeusia is expected

- Choose bland, less flavorful, less odorful foods when dysgeusia is troublesome.
- Eat smaller meals more frequently

Management:

There are several OTC and prescription treatments to address dysgeusia:

- Consider zinc supplementation (25-100 mg PO daily)- zinc deficiency may cause dysgeusia, and may be resultant from cancer treatments.
- If saliva production is lessened during dysgeusia, consider artificial saliva products, or systemic pilocarpine (prescription)
- Consider alpha lipoic acid (ALA) as a natural health product. ALA is available in meats and yeast products, as well as a supplement forms, and has been shown to improve taste sensation for several patients in one study.

10. Fatigue

About 40-55% of patients on Vemurafenib will experience fatigue and one in five will have 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

11. General pain (headache)

Patients on Vemurafenib may experience other types of pain. Some 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. 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)

13. 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

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