

EVEROLIMUS

Most patients treated with Everolimus 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 Everolimus are stomatitis, infections, asthenia, fatigue, cough, and diarrhea.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Myelosuppression

Everolimus 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. **Everolimus 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.

Counseling tips:

Reinforcement is important. Make a note to yourself (or book a time for a follow up call) to repeat these suggestions 2-3 weeks after the Everolimus treatment initiation or any report of early rash symptoms.

2. Rash

Rash is a common adverse effect of Everolimus, occurring in 30% of patients. This rash presents as spots or small raised bumps with or without fluid that appear on the chest, upper back, and sometimes, the face. Most cases are mild to moderate in severity. Some experts recommend the use of oral antihistamines for symptoms, such as itching and pruritis.

Prevention: Being proactive is critical to managing rash. Prevention should begin when Everolimus 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 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 skin rashes (localized, few symptoms, no impact on daily activities, no sign of infection), there are some over-the-counter options you may consider:

- Topical corticosteroids (hydrocortisone 0.5%)
- Mild soap and cleansers
- Moisturizers twice daily

Prescribed medications may include: topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream, or clindamycin 1% cream or topical solution.

If the rash progresses to moderate (generalized, mild symptoms such as itching or tenderness, minimal impact on daily activities), the patient should be referred to his/her doctor and may need prescribed therapy:

- Topical corticosteroid (e.g., hydrocortisone 2.5%, clindamycin 1% cream or topical solution, or pimecrolimus 1% cream)

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- Doxycycline (100 mg BID PO) or minocycline (100 mg BID PO)

3. Pruritis

Pruritus (itchiness) is a common side effect of Everolimus. Up to 1 in 5 patients will develop this adverse effect, which usually occurs because skin has lost its moisture. Pruritis may be mild or localized, widespread or intense, or worsen to the point where it interferes with daily activities.

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.

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 pruritis, antihistamines may provide some relief. Refer patients experiencing intense, widespread itching to their doctors.

4. Xerosis

Xerosis (dry skin) occurs in as many as 35% of patients treated with Everolimus. 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.

5. Hand-foot skin reaction

Hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia, is an uncommon side effect of Everolimus. HFSR is a potentially dose-limiting, skin-related side effect if not managed and prevented at an early stage.

If the patient tells you on the call back phone call he/she is bothered by pain in the hands or feet, you might want to **have the patient drop by the pharmacy** for you to have a look and determine if any prevention or management is required.

Prevention: Prevention of traumatic activity and rest are crucial. Urge your patients to:

- Have a manicure or pedicure to remove thickened skin or calluses; follow with moisturizing cream
- Use a moisturizing cream (e.g. Udderly Smooth®, Bag Balm®)
- Wear loose-fitting, soft shoes or slippers, foam absorbing soles, gel inserts to cushion pressure points, cotton socks
- Cushion callused areas with soft or padded shoes
- Reduce exposure of hands and feet to hot water (showers, dishwashing, etc.)
- Avoid excessive friction to hands or feet when performing tasks
- Avoid vigorous exercise or activities that place undue stress on the hands and feet
- Wear thick cotton gloves or socks to protect hands and feet and keep them dry
- Report any signs or symptoms immediately to ensure early-stage treatment

Counseling tips:

Tell your patient about prevention of HFSR early in the treatment. If the patient is not prepared for detailed counselling on the day the prescription is picked up, plan a follow up call in a couple of days.

Management: For *Mild* HFSR, there are several management strategies you may consider:

- Avoid hot water; cool water or cold compresses may ease symptoms
- Diligently apply moisturizers to keep palms and soles soft and pliable to prevent cracks or breaks in skin integrity- Use moisturizing creams twice daily; also use aloe vera lotion as needed and use 20% to 40% urea cream or 6% salicylic acid on callused areas
- Soak feet in magnesium sulfate (Epsom salts) to soften calluses and reduce pressure pain
- Use low to moderate dose pain killers
- Advise patients to consult their doctor about reducing their dosage of Everolimus, if symptoms of HFSR worsen after being treated for 2 weeks

For *Moderate to Severe* HFSR, the patient will likely need prescribed therapy, such as:

- Topical corticosteroid (e.g., clobetasol 0.05% ointment)
- 2% lidocaine topical ointment
- For thick, tender sores after acute rash with/without blisters resolves: 40% urea cream; or Tazarotene 0.1% cream; or Fluorouracil 5% cream
- Dose modification of the Everolimus

6. Stomatitis

Stomatitis (mouth sores) is a common side effect of Everolimus. Integrity of mucous membranes may be affected by Everolimus 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 Everolimus 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 Everolimus 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-alchoic)
- 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. Nausea & vomiting

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

8. Diarrhea

Diarrhea is very common in patients treated with Everolimus, occurring 27-30% of patients. 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

9. 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).

10. Dysgeusia

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.

11. Fatigue & weakness

About one third of patients on Everolimus 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

12. General pain (arms, legs, chest, back, abdomen, headache)

Patients on Everolimus 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.

Counseling tips:

Reinforcement is important. Make a note to yourself (or book a time for a follow up call) to repeat these suggestions 2-3 weeks after the Everolimus treatment initiation or any report of early rash symptoms.

- 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

13. Pain in joints

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

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,