GEFITINIB

Most patients treated with Gefitinib 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 Gefitinib are anorexia, diarrhea, nausea and vomiting, rash, acne, dry skin, pruritis, and asthenia.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

1. **Rash**
2. **Pruritis**
3. **Xerosis (dry skin)**
4. **Alopecia**
5. **Diarrhea**
6. **Nausea & vomiting**
7. **Anorexia**
8. **Conjunctivitis/Keratoconjunctivitis sicca (dry eyes)**
9. **Nosebleeds (Epistaxis**

1. Rash

Rash occurs in more than 50% and up to 100% of patients treated with Gefitinib. Rash may appear 1-3 weeks after beginning treatment. The severity of the rash may be reduced by the early introduction of preventive strategies, including the prescription of oral antibiotics, such as doxycycline. The rash most patients experience is mild to moderate; severe rash is uncommon. This rash has an acne-like appearance (inflammatory papules or pustules), but it has a distinct pathology from acne vulgaris. It may occur on the face, neck, and upper torso. Rash may be accompanied by dry skin, pruritis, or erythema (redness). The rash may wax and wane throughout therapy or peak 2-3 weeks after therapy begins. In most patients, it tends to improve gradually, but spontaneous resolution may occur. The rash usually disappears within a few weeks of discontinuing therapy; however, sometimes residual hyperpigmentation and dry skin remain.

There is no association between the severity of rash and type of skin or history of acne. The rash from Gefitinib occurs due to inflammation, rather than infection. No true comedones are seen. The rash may undergo several stages:

- Swelling, redness, burning sensation
- Formation of small, solid, round papules of less than 5 mm in diameter; may evolve into pustules containing inflammatory material and cellular debris
- Yellowish crusting of drying papules

Prevention: Being proactive is critical to managing rash. Prevention should begin when Gefitinib 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

- Take short showers with warm water
- 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 as soon as possible and may need prescribed therapy:

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

PLUS

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

For severe rashes (generalized, severe itching or tenderness, significant impact on daily living, potential for infection), refer the patient to a doctor as soon as possible. Dose reduction may be recommended. Prescribed medications may include:

- Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution, or pimecrolimus 1% cream PLUS doxycycline/minocycline (100 mg BID PO) PLUS methylprednisolone
- Analgesics for patients with painful rash

Encourage patients who are treated with topical agents to continue using them for 7 days after the rash abates (or as directed by their physician).

2. Pruritis

In patients who are taking Gefitinib, pruritis (itch) is commonly associated with rash or xerosis. Pruritis 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 bland emollients (Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, Vaseline Intensive Care® Advanced Healing Lotion)

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

- Apply more lotion that 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.

3. Xerosis (dry skin)

Xerosis (dry skin) occurs in as many as 35% of patients treated with Gefitinib. Dry, scaly, itchy skin resembling atopic eczema usually begins between 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 EGFRI-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 shores 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.

4. Alopecia

Up to 5% of patients will have hair loss while taking Gefitinib. 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. Diarrhea

Diarrhea is very common in patients treated with Gefitinib, occurring in up to 54% of patients. Dietary modifications are not recommended in anticipation of diarrhea, but must be considered if diarrhea occurs. Diarrhea may begin about 12 days after the start of therapy. It is usually mild and does not worsen with time.

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

6. Nausea & vomiting

Nausea and vomiting may occur in up to 15% of patients on Gefitinib. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Gefitinib 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 Gefitinib 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

7. Anorexia

Between 1 and 10% of patients will experience a decreased appetite while taking Gefitinib.

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

8. Conjunctivitis/Keratoconjunctivitis sicca (dry eyes)

Eye disorders occur in about one-third of patients treated with Gefitinib, which may cause eye and eyelid irritation; oily secretions and crustiness around the eyes; a grittiness, burning or foreign body sensation in the eye; eyelid growth; and some vision fluctuation. The most common eye disorders are conjunctivitis and keratoconjunctivitis sicca (dry eye). Mild to moderate cases of both conditions usually respond to traditional OTC therapies.

Gefitinib-induced conjunctivitis is different from pink eye; redness, itchiness, and swelling of the clear, thin, mucous membrane under the eyelid and covering the sclera (white of the eye) is likely caused by an inflammatory reaction to targeted therapy, rather than a bacterial or viral infection. However, a typical pink eye infection may result from Gefitinib-induced dry eye. Conjunctivitis of infectious origin may resolve on it sown within a week (viral) or respond to topical antibiotic therapy (bacterial).

Refer immediately to eye doctor patients who experience:

- Unrelenting eye pain
- Loss of vision
- Extreme eye redness
- Light sensitivity
- No improvement in eye symptoms after 1 week of OTC therapy

Dry eye

Management: OTC treatment:

- Eye products without preservatives such as lubricating eye drops, gels, gel inserts or ointments and artificial tears, 4-6 times daily
- Warm eye soaks
- Wear close-fitting glasses or sunglasses
- Use a humidifier to moisten indoor air and change furnace air filters often

Prescription corticosteroid eye drops may be prescribed to decrease inflammation.

Conjunctivitis

Management:

- Ophthalmic antibiotic drops or ointments (OTC or prescription)
- Topical steroid eye preparations

9. Nosebleeds (Epistaxis)

Nosebleed, or epistaxis,,is one manifestation of hemorrhage, which may occur rarely in patients receiving Gefitinib. If self-management by the patient is ineffective, the patient may need to visit the doctor for medical intervention (e.g. cauterization using silver nitrate sticks, packing nose with sterile dressing).

Management: OTC treatment:

- Apply direct pressure by pinching the soft fleshy part of the nose; continue for at least 5 minutes (up to 20 minutes) until a clot forms inside the nose and bleeding stops. Tilt the head forward while pinching the nose, to prevent nausea and airway obstruction.

- Try a nasal spray with a vasoconstrictive agent (e.g. oxymetozoline or phenylephrine- usually sold as nasal decongestants)

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

Iressa® Product Monograph, AstraZeneca Canada Inc., 27 September, 2012

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

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011