

PAZOPANIB

Most patients treated with Pazopanib 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 Pazopanib are diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Myelosuppression

Pazopanib 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. **Pazopanib 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 very common in patients treated with Pazopanib, over 50% in patients treated for kidney cancer. 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. Nausea & vomiting

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

4. Loss of appetite

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

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. 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.

6. 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).

7. Fatigue & weakness

About 20% of patients on Pazopanib will experience fatigue and about 15% 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

8. General pain (headache)

Patients on Pazopanib may experience other types of pain. About 10% 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.
- 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. Hair & skin colour changes

Pazopanib may cause skin or hair colour changes, particularly a yellowing or complete loss of colour. These changes may occur after the first week of treatment. Assure your patients that these side effects are reversible with dosage adjustment or when therapy ends.

10. 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 Pazopanib. 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

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 Dasatinib, 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 Dasatinib

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.

11. Rash

Rash is a common adverse effect of Pazopanib, occurring 20% of patients. 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 Pazopanib therapy is begun, and continue throughout treatment.

You should advise your patient to:

- Cleanse with mild soaps or hypoallergenic 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
- 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. Alopecia

Some patients will have hair loss while taking Pazopanib. 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

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