SORAFENIB

Most patients treated with Sorafenib will experience adverse effects, but the effects will differ from one patient to the next.

Hand-foot skin reactions are very common in patients taking Sorafenib.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Bleeding disorders

Sorafenib may cause easy or unusual bleeding. This may include bleeding from mouth, nose, stomach or gut, rectum, lungs or windpipe, and nail beds. Symptoms may include blood blisters; red or purple pinpoints on skin; bruising; coughing up blood or vomit that looks like coffee grounds; and black, tar-like stools or blood in stools.

2. Myelosuppression

Sorafenib 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. **Sorafenib 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. Avoid crowds or family/friends with active infections, do not eat uncooked vegetables, wash hands often. If the platelet count is low, tell the patient to take care when shaving or performing any activity of daily living when the skin could be cut.

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.

3. Hand-foot skin reaction (HFSR)

About 30-60% of patients taking Sorafenib will develop hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia. HFSR is the most clinically significant, dose-limiting, skin-related side effect of Sorafenib. The typical pattern of localized sensitive lesions with skin thickening, surrounded by redness, differs from classic HFSR, in which symmetrical changes in skin sensation, redness and swelling occurs. Patients may experience extreme tenderness of the hands and feet – enough to affect hand or foot function and disrupt their quality of life. *The look and onset of this reaction is different than capecitabine-induced HFSR*.

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

HFSR usually occurs within the first 2 to 4 weeks of Sorafenib therapy. Tender, scaly sores – with or without blistering – appear on the palms and soles. The edges of thickened skin patches on fingertips, toes, and other pressure or flexure points, such as elbows or knuckles, may be surrounded by a swollen, reddish halo. The hands or feet may tingle or feel sensitive to touch or heat.

After several weeks, thickened, callus-like skin develops over the sores. These areas are usually painful and impair range of motion, function, and weight bearing.

If the patient tells you on the call back phone call that their hands or feet are bothering them, 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: During the first 2–4 weeks of therapy, 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
- 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
  - Skin products in use for HFSR
    - Cetaphil® skin cleansers
    - Aveena® shower gel
    - Udderly Smooth®, Gold Bond®, Aveeno® lotions
    - Norwegian Formula moisturizer and foot cream (Neutrogena®)
    - Bag Balm®
    - Eucerin® cream and Dry Skin Therapy
    - Aquaphor® Healing Ointment
    - Kerasal®
    - Sunblock
    - Lipikar, Lipikar balm, and Xerand
- 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 MKI, 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
- Oral NSAIDS, codeine, pregabalin, for pain
- 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 Sorafenib
- If symptoms worsen after 2 weeks, interruption of Sorafenib treatment may be required.

4. Hypertension

Patients taking Sorafenib are 6X more likely to develop hypertension than those taking other drugs of this class. Patients should be monitored for the onset or worsening of hypertension. If you have a blood pressure monitoring device, consider checking the patient's blood pressure when they visit the pharmacy and report any elevation to the cancer care team. Hypertension is usually mild to moderate and manageable with standard antihypertensive therapy. Management may be done by either the cancer care team of the family physician- BUT *beware of any potential drug interactions as new anti-hypertensive therapy is initiated*.

5. Rash and Other Skin Problems

Rash is a common adverse effect of Sorafenib, occurring in up to 19% of patients. Rash symptoms may occur after 6 weeks of Sorafenib. This rash presents with spots and bumps on the upper chest, back or face that may or may not contain fluid. There is not usually any infection in the raised areas. Generalized skin rashes are usually mild to moderate, tend to decrease over time, and rarely require dose reduction.

Patients taking Sorafenib may develop a red-coloured rash with scaly patches on the face and scalp. This may present 1-2 weeks after treatment begins, and resembles acne, but is caused by inflammation rather than bacteria. Areas on the scalp affected by the rash may experience a loss or distortion of sensation. This rash usually fades or disappears after several weeks, and prescribed therapy is not usually needed.

Sorafenib may cause inflammation of the skin. Skin may become dry or scaly and may shed. Assure your patients that these side effects are reversible with dosage adjustment or when therapy ends.

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 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:

- Topical corticosteroid (e.g., hydrocortisone 2.5%)
- Oral corticosteroids (e.g., prednisone 1 mg/kg daily with or without topical triamcinolone acetonide 0.1% ointment
- Topical clindamycin 1%

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 Sorafenib treatment initiation or any report of early rash symptoms.

6. Pruritus

Pruritus (itchiness) is a common side effect of Sorafenib, and usually occurs because skin has lost its moisture. This is not usually associated with a rash or xerosis (dry skin); however, it may be disruptive to the patient during sleep or while he/she is awake.

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®)
- 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 Pruritus, consider advising patients to:

- Apply more lotion that 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

7. Stomatitis

Stomatitis (mouth sores) is a common side effect of Sorafenib. Integrity of mucous membranes may be affected by Sorafenib 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 Sorafenib 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 Sorafenib 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 and 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!***

8. Diarrhea

Sorafenib commonly causes diarrhea—43% of patients with advanced kidney cancer and 55% of patients with liver cancer 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.

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

9. Joint, bone, or muscle pain

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).

Bone and joint pain may begin in the first month of therapy and commonly subside after a few months. Pain may affect the leg bones, hips, and knees, and may appear in an asymmetrical pattern. Although there are no evidence-based guidelines for prevention or treatment, anecdotal reports and expert experience suggest that some patients' pain could be eased by using mineral supplements.

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

- Calcium and magnesium supplements
- Mild pain medications
- Avoid using quinine or drinking tonic water.

REFERENCES:

Nexavar® Product Monograph, Bayer Inc. Canada, 1 May 2013

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

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

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011