

CAPECITABINE

Most patients treated with Capecitabine 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 Capecitabine.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Myelosuppression

Capecitabine 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. **Capecitabine 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. Hand-foot skin reaction (HFSR)

Hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia, is a common side effect of Capecitabine. It may occur as soon as 11 days or as late as a year after beginning treatment. HFSR is a potentially dose-limiting, skin-related side effect of Capecitabine. In the early stages, skin on the hands and feet may become red and lightly swollen and may cause the patient to experience a prickly feeling or numbness. If Capecitabine is not stopped, the syndrome may escalate to painful swelling and redness that interferes with the use of hands and/or feet. HFSR can increase to moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. At this point, Capecitabine dosing must be interrupted until HFSR resolves, and restarted at a lower dose.

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 (e.g. Udderly Smooth®, Bag Balm®)
- Take vitamin B6 150-200 mg daily (e.g. 100 mg BID with Capecitabine tablets)
- 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
 - Aveeno® shower gel
 - Udderly Smooth®, Gold Bond®, Aveeno® lotions

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.

- 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 Capecitabine, 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 Capecitabine
- If symptoms worsen after 2 weeks, interruption of Capecitabine treatment interruption may be required

3. Stomatitis

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

4. Diarrhea

Diarrhea is very common in patients treated with Capecitabine. 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

5. Nausea and Vomiting

Nausea and vomiting may occur in up to 45% of patients on Capecitabine. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Capecitabine 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 Capecitabine 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

6. Loss of appetite (Anorexia)

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

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

7. Taste disorder (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.

8. Bleeding problems

Patients may experience excessive or unusual bleeding or bruising. This may be accompanied by red pinpoint on the skin or black, tar-like bowel movements or blood in stools. If bleeding or bruising is unusual and will not stop, refer the patient to the Emergency Department.

Prevention: Advise the patient to:

- Use sharp objects with care
- Use a soft toothbrush
- Be careful when shaving
- Consult physician before any dental work is done

9. Dermatitis

Dermatitis is a non-specific term for a variety of skin reactions that exhibit erythema, scaling, vesicles and crusts (sometimes also called eczema). Skin changes always include an inflammatory response, with initial erythema (redness) from vasodilation and usually edema from leakage of the engorged vasculature. Swelling may lead to fluid-filled vesicles in the skin which may ooze or weep when broken and then crust over as they dry. Dermatitis may be worsened by topical allergens or harsh soaps and detergents, humid weather, excessive sweating, dietary allergens, and the itch-scratch cycle.

Prevention:

- Avoid use of any topical products that are irritating (e.g. soaps, deodorants).
- Wear breathable, loose-fitting clothing. Natural fabrics are usually less irritating than synthetic fabrics. Always wash new clothes before the first use. Do not use fabric softeners or bleach in washing or drying cycles.

Management:

- Use a systemic antihistamine, either an H1 blocker (e.g. diphenhydramine) or a non-sedating antihistamine (e.g. loratidine, cetirizine, desloratidine). Consider adding an H2 blocker antihistamine (e.g. ranitidine, famotidine) for chronic urticaria
- Bathing with colloidal oatmeal preparations (e.g. Aveeno®) and use of unscented moisturizing creams after bathing may help with itchiness and dry skin
- Cooling salves, such as menthol or camphor-containing products (e.g. Gold Bond®) may provide relief. Keep products in the refrigerator for additional cooling effect.
- Topical corticosteroids, beginning with OTC Hydrocortisone 0.5% cream and progressing as needed to more potent prescription corticosteroid creams, are often used
- Acetaminophen may be added to the treatment of urticarial for more painful lesions.

10. Hair Loss (Alopecia)

Between 5 and 40% of patients will have hair loss while taking Capecitabine. 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

11. Fatigue and Weakness

Some patients on Capecitabine will experience fatigue and/or 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. Myalgia (Muscle pain)

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 (Joint pain)

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

14. Pain problems

Patients on Capecitabine may experience other types of pain. About 5-10% 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

15. Fever

Fever, or increased body temperature, may occur with this drug. While fever is uncomfortable, be careful if the patient is at risk of febrile neutropenia from the drug. Reducing fever can mask the symptoms of emergent infection and cause a delay in management of this potentially life-threatening problem.

Management: The following may provide relief from headaches and other general pain problems:

- Non-pharmacologic approaches, such as a sponge bath with tepid water, or a cool cloth on the forehead, may provide some relief from fever
- Antipyretics- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)

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