

LETROZOLE

Most patients treated with Letrozole 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 Letrozole are hot flashes, arthralgia, flushing, asthenia, edema, arthralgia, headache, and dizziness, hypercholesterolemia, sweating increased, bone pain, and musculoskeletal pain.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Diarrhea

Diarrhea is common in patients treated with Letrozole. 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

2. Constipation

Constipation is generally understood to be a reduction in bowel movements to fewer than 3 per week, or unsatisfactory (e.g. incomplete) defecation. Reduced bowel function may give the misperception of constipation to patients who expect one or more movements daily. Constipation may be caused by this medication, other medications being taken concurrently (e.g. narcotic analgesics), or by the underlying cancer. Reduced physical activity or dietary changes, possibly related to this medication or the overall cancer treatment, may contribute to constipation. Abdominal pain is often associated with constipation, but if symptoms become severe a medical assessment to examine for fecal impaction or bowel obstruction may be needed.

Prevention: Advise patient to:

- Change diet, if possible, to include more fruits, vegetables, and high-fibre foods. If the patient is taking a low-calorie diet, consider increasing calories to improve colonic transit.
- Use of a regular laxative regimen, such as senna or bisacodyl at bedtime
- Consider a bowel routine to maintain regularity, such as attempting bowel movements each morning after breakfast (usually the optimal time for a movement), using the toilet when there is an urge instead of repressing it, placing a footstool in front of the toilet to elevate thighs during movement.
- Consider adding light exercise for patients with mostly sedentary lifestyles
- Weight loss in over-weight patients may help improve bowel function

Management:

- If prophylactic stimulant laxative is not effective, try osmotic laxative (e.g. lactulose or PEG)
- Stool softeners have not been shown to be effective
- Drink of fluids

Biofeedback and relaxation techniques may help some patients with pelvic floor dysfunction.

Psychosocial teams in the cancer centres may help with this type of intervention.

3. Nausea & vomiting

Nausea and vomiting may occur in up to 20% of patients on Letrozole. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Letrozole 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 Letrozole 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

4. Dyspepsia

Dyspepsia, or acidic stomach, may be a temporary or chronic problem for some patients. It generally presents as upper abdominal pain, postprandial fullness or early satiety. Dyspepsia occurs in 25% of people, so it may be hard to tell if it is caused by the drug. It may or may not lead to peptic ulcers, but is not usually accompanied by heartburn. Management is often symptomatic and as needed.

Prevention: Advise patients to:

- Avoid foods that cause stomach upset (e.g. spicy foods)
- Avoid lying down after meals
- Reduce alcohol and/or caffeine intake
- Eat smaller meals more frequently
- Reduce stress from daily life

Management:

There are several OTC and prescription treatments to address dyspepsia:

- Antacids (aluminum hydroxide, calcium carbonate, magnesium salts, combinations with or without simethicone for gas)
- Histamine type 2 receptor antagonists (e.g. ranitidine, famotidine)

Proton pump inhibitors (e.g. omeprazole, esomeprazole, pantoprazole, lansoprazole)

5. Insomnia

Insomnia, or the inability to fall asleep and/or stay asleep, may be a symptom of depression, a drug side effect, a reaction to unresolved pain, or a natural reaction to daily stress and worries (e.g. about the cancer). Many drugs can contribute to insomnia problems.

Prevention: Advise patients to:

- Avoid alcohol, nicotine (e.g. smoking, nicotine supplements) and caffeine intake, especially in the evening
- Avoid large meals late in the evening
- Use earplugs and/or eye masks if helpful. Turn the clock face away from sight and use the alarm daily.
- Try relaxation exercises
- Maintain a regular pattern of timing for going to bed and rising, 7 days a week. Limit mid-day naps. Do not sleep in on weekends or free days.
- Regular aerobic exercise (e.g. walking) during the day can help stimulate the need for sleep at night. Exercise should be enough to cause sweating, with a duration of 30 to 40 minutes daily. Do not overexert if there are other physical limitations to exercise

Management: There are many medications (prescription and OTC) used for insomnia. Try to start with the least potent options and limit use to short periods if possible.

- Common OTC products contain diphenhydramine or doxylamine. These products may help patients to fall asleep.
- Natural health products have limited evidence of effectiveness, but are often used. Products may contain Valerian or Melaton.
- Prescription hypnotics may be considered. Options include benzodiazepines (e.g. lorazepam, flurazepam) and non-benzodiazepines (e.g. zopiclone).

6. Depression & Anxiety

Depression is a mood disorder, which may include features such as diminished interest or pleasure in life, significant gain or loss of weight, sleep disturbances, agitation, fatigue, feelings of worthlessness or guilt, or reduced ability to concentrate. While depression is common in the general population, the incidence is higher in cancer patients. Several drugs can contribute to the severity of depression. Duration of symptoms may vary between patients.

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

- Psychotherapeutic approaches are often used, including cognitive behavioral therapy and interpersonal therapy. These generally require a referral to a therapist, psychologist or psychiatrist.

Antidepressant drugs- There are several antidepressant agents in use for this disorder. There are a number of classes of agents used. Pay particular attention to potential drug-drug interactions, to help determine if certain antidepressants should be avoided.

7. Hot flashes

Hot flashes (or hot flushes) can be very troublesome for many patients. Waves of heat sensation may occur without warning, similar to the hot flashes from female menopause.

Prevention: Advise the patient to:

- Keep room temperature lower, if possible

- Dress in layers, so layers can be removed if hot flushes become uncomfortable
- Natural health products may be tried, such as black cohosh, phytoestrogen supplements, evening primrose oil, dong quai, or ginseng. Evidence of benefit is lacking for most of these products. Watch for potential drug-drug interactions with the herbal product before advising use.
- Accupuncture has been tried for relief of hot flushes, but there is no evidence of effectiveness
- Psychoeducational interventions, as sometimes offered by psychosocial support teams in the cancer centres, may help patients to find ways to improve these symptoms

Management:

Try systemic treatment with clonidine, venlafaxine, paroxetine or gabapentin (prescription); evidence of benefit is minimal, and drug side effects may limit use for some patients.

8. Hyperhidrosis

Hyperhidrosis, or excessive sweating, can reduce quality of life for some patients. Sweating may be manageable for some patients by lifestyle options.

Prevention: Advise the patient to:

- Use strong antiperspirants (higher concentration of aluminum, e.g. DrySol 20% aluminum chloride)
- Bathe or shower with soap and water once or more daily
- Wear clothing from natural fibres- not synthetics fibres
- If scented products cause irritation, use unscented deodorant, soap and skin care products

Management:

- Systemic anticholinergics, e.g. oxybutinin, glycopyrrolate or propantheline bromide (prescription)

9. Pruritis

Pruritis (itchiness) may occur when taking Letrozole, and usually happens because skin has lost its moisture.

Prevention: Preventing dry skin is the key to preventing pruritis. 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 Pruritis, consider advising patients to:

- Apply more lotion than 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

10. Rash

Rash is a common adverse effect of Letrozole. 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 Letrozole therapy is begun, and continue throughout treatment.

You should advise your patient to:

- 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:

- 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

11. Fatigue & Weakness

About one in eight patients on Letrozole will experience fatigue and fewer than one in ten 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. Arthralgia, bone pain, back pain, muscle pain

Aching bones, back, or joints occur in 10-35% of patients taking Letrozole. 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- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
- For bone or 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 bone and joint pain
- Avoid using quinine or drinking tonic water.

13. Pain problems

Patients on Letrozole may experience other types of pain. About 20% 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

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

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

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011