

TEMOZOLOMIDE

Most patients treated with Temozolomide 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 Temozolomide are nausea and vomiting, constipation, stomatitis, headache, and fatigue.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

- | | |
|----------------------|-----------------------------|
| 1. Myelosuppression | 7. Xerosis |
| 2. Stomatitis | 8. Alopecia |
| 3. Diarrhea | 9. Fatigue |
| 4. Nausea & vomiting | 10. General pain (headache) |
| 5. Constipation | 11. Arthralgia, myalgia |
| 6. Pruritis | |

1. Myelosuppression

Temozolomide 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. **Temozolomide 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.

2. Stomatitis

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

3. Diarrhea

Diarrhea is very common in patients treated with Temozolomide. 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

4. Nausea & vomiting

Nausea and vomiting may occur in up to 60% of patients on Temozolomide. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Temozolomide 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 Temozolomide 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

5. 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.

6. Pruritis

In patients who are taking Temozolomide, pruritis (itch) may or may not be 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 pruritis, advise patients to:

- Apply more lotion than 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.

7. Xerosis

Xerosis (dry skin) occurs in about 5% of patients treated with Temozolomide. Dry, scaly, itchy skin resembling atopic eczema may begin within 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 EGFR-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 shoes 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.

8. Alopecia

Only 4% of patients taking Temozolomide alone, but over 70% of patients on concurrent chemotherapy and radiation therapy, will have hair loss. 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

9. Fatigue

Almost three quarters of patients on Temozolomide will experience fatigue. This is 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

10. General pain (headache)

Patients on Temozolomide may experience other types of pain. About 30% 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

11. Arthralgia, myalgia

Aching joints or muscle and muscle cramps occur in some patients taking Temozolomide. 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.

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