

# HYDROXYUREA

Most patients treated with Hydroxyurea 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 Hydroxyurea are myelosuppression and hyperuricemia.

### ADVERSE DRUG REACTION MANAGEMENT GUIDE

1. Myelosuppression
2. Diarrhea
3. Constipation
4. Nausea & vomiting
5. Stomatitis
6. Anorexia
7. Rash (maculopapular rash)

#### 1. Myelosuppression

Hydroxyurea 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. **Hydroxyurea 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 common in patients treated with Hydroxyurea. 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

### **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 Hydroxyurea treatment initiation or any report of diarrhea

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. 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.

#### **4. Nausea & vomiting**

Nausea and vomiting may occur in some patients on Hydroxyurea. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Hydroxyurea 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 Hydroxyurea 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<sup>®</sup> 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. Stomatitis

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

## 6. Anorexia

Some patients will experience a decreased appetite while taking Hydroxyurea.

**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. Rash (maculopapular rash)

Rash is a common adverse effect of Hydroxyurea. 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 Hydroxyurea 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

#### 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

Hydrea® Product Monograph, Bristol-Myers Squibb Canada, 18 January 2008

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

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011

#### 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 Hydroxyurea treatment initiation or any report of early rash