



Positive Quality Intervention: Management of Abemaciclib Associated Diarrhea

Description of PQI: Abemaciclib is an FDA approved Cyclin Dependent Kinase (CDK) 4 and 6 Inhibitor approved for use in hormone receptor (HR) positive and human epidermal growth factor 2 (HER2) negative metastatic breast cancer. Abemaciclib works downstream of the estrogen receptor to halt the progression from the G1 phase to S phase that is a critical step in the replication of cancerous cells.¹⁻³ Abemaciclib has been studied across multiple lines of therapy for metastatic breast cancer and is FDA-approved in combination with an aromatase inhibitor, fulvestrant, and as a single agent. In addition, these studies have shown a lower risk of neutropenia but an increased risk of diarrhea compared to other approved CDK 4&6 inhibitors.^{1,2,3}

Background: It is imperative that health care professionals understand how to manage agent specific diarrhea to reduce: risk of discontinuing effective therapy, drastic changes in hydration status, and overall quality of life. Although the mechanism of abemaciclib-induced diarrhea is not fully understood, management of diet along with drug therapy remains the standard of care in patients with abemaciclib-associated diarrhea. In clinical trials, abemaciclib associated diarrhea most frequently occurred in the first cycle of treatment, with a median onset between 6 and 8 days. Diarrhea was often managed in the clinical trials using anti-diarrheal agents sparing the need for dosage reductions or interruptions in the majority of the population.^{1,2,3}

PQI process:

Upon receipt of abemaciclib prescription:

- Screen for appropriate antidiarrheal medication:
 - Loperamide
 - Diphenoxylate/atropine
 - Tincture of opium
- If no antidiarrheal agent present on medication list, encourage patient to pick up over-the-counter loperamide and keep well stocked while taking abemaciclib
- Counsel patient on compliance and anti-diarrheal specific administration and side effects
- Follow-up with patient by phone after the first week of therapy
 - If loperamide alone does not control diarrhea, contact prescriber for diphenoxylate/atropine (or other antidiarrheal agent)
 - If severe diarrhea (≥ 7 stools per day), may require inpatient admission for fluid and electrolyte administration

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Diet Recommendations^{4,5,6}:

- Avoid greasy, spicy, or fried food
- Avoid milk, caffeine, alcohol, and high fiber vegetables
- Eat small frequent meals
- B.R.A.T Diet (Bananas, Rice, Apple Sauce, Toast)
- Drink three or more liters of clear fluid per day (water, clear liquids, soup, sports drinks)

Abemaciclib Dose Modifications

CTCAE Grade of diarrhea	Abemaciclib dose modification
Grade 1	No dose modification required
Grade 2	If toxicity dose not resolve within 24 hours to \leq Grade 1, suspend dose until resolution. No dose reduction required
Grade 2 that persists or recurs after resuming the same dose	Suspend dose until toxicity resolves to \leq Grade 1. Resume at next lower dose
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to \leq Grade 1. Resume at next lower dose

Drug Therapy Recommendations^{4,5,6}:

- **Loperamide (over-the-counter)**
 - Take two caplets (4 mg) followed by one caplet (2 mg) every four hours until diarrhea-free for 12 hours
 - Stop loperamide after no sign of diarrhea for 12 hours
 - Do not exceed 8 caplets (16 mg) per day
 - If diarrhea does not improve during the first 24 hours of taking loperamide, the patient should contact their health care provider.
 - May take up to 12 caplets per day for chemotherapy-induced diarrhea under medical supervision
 - May schedule loperamide around the clock before adding another agent

- **Diphenoxylate/Atropine (Prescription Only)**
 - Take 2 tablets (5 mg) three to four times daily (Max of 8 tablets per day)
 - May alternate with loperamide to achieve around the clock coverage
 - Common side effects: dry skin and mucous membranes, tachycardia, urinary retention, hyperthermia
 - Although uncommon, respiratory depression can occur due to the diphenoxylate component

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- **Tincture of Opium (Prescription Only)**
 - Deodorized tincture of opium 10 mg/mL of morphine
 - Take 0.6 mL (6 mg) in water every 3 to 4 hours
 - Common side effects: CNS depression, drowsiness, urinary retention, constipation, nausea, headache
 - Although uncommon, respiratory depression can occur

Patient Centered Activities:

- Patient Compliance
 - Encourage patients to take loperamide at the onset of a loose, watery stool and every two hours until resolution of diarrhea
 - This medication only needs to be taken as needed for loose, watery stools
- Patient Education
 - Explain abemaciclib associated diarrhea's median time to onset in the trials was from 6 to 8 days
 - Drink 6-8 (~3 liters) large glasses (water, clear liquids, soup, sports drinks)
 - Instruct patient to call their provider at the first sign of diarrhea
 - If diarrhea hasn't improved within 24 hours, your doctor may want to reduce the abemaciclib dose

References:

1. Dickler MN, Tolaney SM, Rugo HS et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res* 2017; 23(17): 5218-5224.
2. Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017; 35:2875-2884.
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4. National Comprehensive Cancer Network. Palliative Care (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf. Accessed May 16, 2018.
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6. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Practice* 2007; 13:181-198.

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