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Positive Quality Intervention: Sacituzumab govitecan-hziy (Trodelvy®): Prophylaxis and Management of Adverse Events

Description: The purpose of this PQI is to provide information on the management of common adverse events of sacituzumab govitecan-hziy including diarrhea and neutropenia, as well as prophylaxis of nausea and vomiting.

Background: Sacituzumab govitecan-hziy is an antibody drug conjugate (ADC) that consists of an anti-Trop-2 humanized monoclonal antibody, hRS7 IgGk, coupled to the topoisomerase I inhibitor SN38 via a hydrolysable linker. It binds to Trop-2, a surface protein overexpressed in most epithelial cancer cells. Once internalized, SN38 is released intracellularly leading to cell death.[1]
Sacituzumab govitecan-hziy is indicated in patients with:

- Unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- Unresectable locally advanced or metastatic hormone receptor (HR)positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine based therapy and at least two additional systemic therapies in the metastatic setting.

In a pooled safety population of 1063 patients treated with sacituzumab govitecan, decreased neutrophil count (75%), diarrhea (64%), nausea (64%), and vomiting (35%) were common adverse reactions. Proactive management of neutropenia, diarrhea, and nausea/vomiting can prevent early discontinuation of treatment.[1]

PQI Process:

- Ensure proper dose of 10 mg/kg once weekly on Days 1 and 8 of continuous 21-day treatment cycles
- Patients with UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia; and may be at increased risk for other adverse reactions[4]
    - This genetic test is not commonly performed prior to administration and is not required
- Sacituzumab has box warnings for severe, life-threatening, or fatal neutropenia and severe diarrhea
- Neutropenia Prevention and Management[2-4]
    - Neutropenia is the most common cause of dose-interruption or dose-delay alongside leukopenia and anemia
        - The median time to first onset of neutropenia (including febrile neutropenia [FN]) was 16 days
    - Primary prophylaxis with G-CSF is recommended starting in the first cycle of treatment in all patients at increased risk of FN, including older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities.[1]
        - Patient risk factors for FN per ASCO® guidelines[4]: age > 65 years, advanced disease, previous chemotherapy or radiation therapy, preexisting neutropenia or bone marrow involvement with tumor, current infection, open wounds or recent surgery, poor performance status/nutritional status, poor renal function, liver dysfunction, cardiovascular disease, multiple comorbid conditions, HIV infection

- Obtain a CBC with Diff on Days 1 and 8 of each cycle
- ANC cut-offs for treatment: Day 1 $\geq$ 1500/mm^3 & Day 8 $\geq$ 1000/mm^3
- Ensure proper timing between cycles; if Day 8 is delayed for any reason, ensure a minimum of 14 days between Day 8 and the next cycle's Day 1
  - Monitor CBC before each dose
- Ongoing discussions with disease state experts have evaluated alternative approaches to preventing neutropenia to keep patients on-track and meeting treatment parameters, such as administering daily filgrastim between day 1 and day 8, in addition to post-day 8 pegfilgrastim, as well as defining patient risk-factors for empiric dose-reductions or omission of the day 8 dose[3]

- Diarrhea Prevention and Management[5]
  - Box warning: Severe diarrhea may occur
  - Evaluate for infectious cause at onset of diarrhea and provide treatment with antibiotics if clinically indicated
  - Loperamide (OTC)
    - Recommended for mild/moderate AND severe/persistent diarrhea
    - Take 2 tablets (4 mg) by mouth initially at onset of diarrhea, followed by 2 mg every 4 hours for mild/moderate diarrhea or every 2 hours for severe/persistent diarrhea or 4 mg every 4 hours overnight for severe/persistent diarrhea
      - Max 16 mg/day
    - Discontinue 12 hours after diarrhea resolves
    - If diarrhea is not resolved after 24 hours, the patient should contact their healthcare provider
    - May schedule loperamide around the clock before adding another agent
  - Additional anti-diarrheals to consider: diphenoxylate/atropine or octreotide
  - Diphenoxylate/atropine (Rx)
    - Take 2 tablets (5 mg) by mouth 3-4 times daily (max 8 tablets/day)
    - May alternate with loperamide to achieve around the clock coverage
  - Octreotide:
    - Inject 100-150 mcg subcutaneously three times daily
  - If patient exhibits excessive cholinergic response (similar to irinotecan - abdominal cramping, diarrhea, salivation, etc.), they may receive pre-medications such as atropine with subsequent treatments
  - Bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration
  - Discontinuation of lactose-containing foods and drinks and alcohol
- Nausea and Vomiting (CINV) Prevention and Management[6]
  - Sacituzumab-govitecan is considered highly emetogenic per NCCN Antiemesis guidelines
  - The preferred method for acute and delayed emesis prevention includes a four-drug regimen of: a second-generation atypical antipsychotic, a neurokinin-1 receptor antagonist (NK1 RA), a selective serotonin receptor antagonist (5-HT3), and a corticosteroid
  - Example antiemesis regimen (for complete list of regimens refer to NCCN Antiemesis guidelines):
    - Day 1: olanzapine 5-10 mg orally + fosaprepitant 150 mg IV + ondansetron 16-24 mg orally or 8-16 mg IV + dexamethasone 12 mg orally or IV; one time prior to sacituzumab dose
    - Days 2-4: olanzapine 5-10 mg orally + dexamethasone 8 mg orally or IV once daily

Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet and Supplemental Diarrhea Sheet
- Provide and counsel patient on take-home medications, including anti-emetics and loperamide
- Ensure patient has a working thermometer at home prior to starting
    - Instruct patients to call their provider (or on-call provider) at first sign of fever (≥100.4°F/38°C)
- Explain median timeline to neutropenia is as early as 7-10 days
- Explain sacituzumab govitecan-hziy associated diarrhea may happen during the infusion or days to weeks after starting
    - Instruct patients to call their provider for diarrhea non-responsive to antidiarrheals or black/bloody stools
    - Encourage patients to take loperamide at the onset of a loose, watery stool and every two hours until resolution of diarrhea
    - Provide OTC loperamide education handouts
    - Bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration
    - Discontinuation of lactose-containing foods and drinks and alcohol

Table 1. Dosage Reduction Levels

Dose Level	**Dosage and Schedule**
Recommended starting dose	10 mg/kg once weekly on Days 1 and 8 of 21-day treatment cycles
First dose reduction	Reduce to 7.5 mg/kg
Second dose reduction	Reduce to 5 mg/kg
Requirement for further dose reduction	Permanently discontinue treatment

Table 2. Dose Modifications for Adverse Reactions

Adverse reactions	Severity	Dose Modification
Neutropenia	Grade 3-4 neutropenia (Absolute Neutrophil Count [ANC] <1000/mm3) or febrile neutropenia	• Withhold TRODELVY until ANC ≥1500/mm3 for Day 1 dose or ANC ≥1000/mm3 for Day 8 Dose • Administer G-CSF during treatment as clinically indicated. • Reduce one dose level for each occurrence of febrile neutropenia or prolonged Grade 3-4 neutropenia, or discontinue according to Table 1.
Nausea/Vomiting/ Diarrhea	Grade 3-4 nausea, vomiting or diarrhea that is not controlled with antiemetics or anti-diarrheal agents	• Withhold TRODELVY until resolved to ≤ Grade 1 • Reduce one dose level with each occurrence, or discontinue according to Table 1.
Other Toxicities	Other Grade 3-4 toxicities of any duration despite optimal medical management	• Withhold TRODELVY until resolved to ≤ Grade 1 • Reduce one dose level with each occurrence or discontinue according to Table 1.

References:

1. Sacituzumab govitecan-hziy package insert. Revised 2/2023. Accessed March 9th, 2023.
2. Gilead MI: Trodelvy® (sacituzumab govitecan-hziy -hziy) Neutropenia and Growth Factor Support (Pooled Safety) (askgileadmedical.com).
3. Staff, Targeted Oncology. "Part 2: Managing Sacituzumab-Associated Neutropenia in TNBC." Targeted Oncology, 2 Mar. 2022, www.targetedonc.com/view/part-2-managing-sacituzumab-associated-neutropenia-in-tnbc.Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Practice Guideline Update. Vol 33, Issue 28, 2015.
4. T homas J. Smith et al., Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. JCO 33, 3199-3212(2015). DOI:10.1200/JCO.2015.62.3488
5. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004 Jul 15;22(14):2919-26.
6. Ettinger, MD/Chair D, Berger, PharmD, BCOP/Vice Chair M. NCCN Guidelines Version 1.2024 Antiemesis. Nccn.org. Published 2024.