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

Description: Sacituzumab govitecan-hziy is an antibody drug conjugate (ADC) that is indicated in triple negative as well as hormone receptor positive, HER2 negative [HR(+) HER2(-)] breast cancer.[1-3] The purpose of this PQI is to provide information on the management of common adverse events including diarrhea and neutropenia, as well as prophylaxis of nausea and vomiting.

Background: Sacituzumab govitecan-hziy is an ADC that consists of an anti-Trop-2 humanized monoclonal antibody, hRS7 IgGk, coupled to the topoisomerase I inhibitor SN38 via a hydrolyzable linker. Sacituzumab govitecan-hziy binds to Trop-2, a surface protein overexpressed in most epithelial cancer cells. Once internalized by the cancer cell, a cytotoxic payload (SN38) is released intracellularly leading to cell death. In addition, the hydrolyzable linker enables SN38 to be released into the tumor microenvironment resulting in death of adjacent tumor cells.[4] The most common side effects leading to dose reduction or discontinuation of sacituzumab govitecan-hziy are neutropenia (63% all grade, 49% grade 3-4), diarrhea (59% all grade; 10% grade 3-4) and nausea/vomiting (57% all grade, 3% grade 3-4).[4]. Proactive management of neutropenia, nausea/vomiting, and diarrhea can prevent early discontinuation of treatment.

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, FN, 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
- Neutropenia Prevention and Management[5-7]
    - Neutropenia (boxed warning) 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) was 16 days
    - Potential options for G-CSF secondary neutropenia prophylaxis include:
        - Pegfilgrastim OBI on Day 8 or pegfilgrastim injection on Day 9 of cycle
    - 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.[6]

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Table 1.

Patient Risk Factors for Febrile Neutropenia[7]
Age > 65 years
Advanced disease
Previous chemotherapy or radiation therapy
Preexisting neutropenia or bone marrow involvement with tumor
Infection
Open wounds or recent surgery
Poor performance status or poor nutritional status
Poor renal function
Liver dysfunction, most notably elevated bilirubin
Cardiovascular disease
Multiple comorbid conditions
HIV infection

Table 2. Dose Adjustment for Neutropenia

Neutropenia Grade	**Occurrence**	**Dose Modification**
Grade 4 Neutropenia ≥ 7 days OR Grade 3-4 febrile neutropenia OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2-3 weeks for recovery to Grade ≤ 1	First	25% dose-reduction Administer G-CSF
	Second	50% dose-reduction Administer G-CSF
	Third	Discontinue treatment Administer G-CSF
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to Grade < 1	First	Discontinue treatment Administer G-CSF

- Diarrhea Prevention and Management[10]
  - Boxed 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
        - May not be conducive for patients unable to self-inject or are averse to needles
    - 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

- Prevention and Management of Chemotherapy-Induced Nausea and Vomiting (CINV)[8]
    - 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, 3, 4: olanzapine 5-10 mg orally + dexamethasone 8 mg orally or IV; both once daily

Table 3. Ancillary Dose Adjustment Table

Nonhematologic toxicity:	**Occurrence**	**Dose Modification**
Grade 4 non-hematologic toxicity of any duration OR Any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with anti-emetics and anti-diarrheal agents OR Other Grade 3-4 non hematologic toxicity persisting > 48 hours despite optimal medical management OR At time of scheduled treatment, grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2-3 weeks for recovery to Grade $\leq$ 1	First	25% dose-reduction
	Second	50% dose-reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover within 3 weeks to Grade $\leq$ 1	First	Discontinue treatment

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Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet and Supplemental Diarrhea Sheet
- Provide upfront 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 at first sign of diarrhea 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
- Diet Recommendations
    - Bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration
    - Discontinuation of lactose-containing foods and drinks and alcohol

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