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Positive Quality Intervention: Olaparib (Lynparza®) Adverse Event Management

Description: This PQI will review the management of select adverse events associated with olaparib (Lynparza®).

Background: Olaparib is an oral inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. To date, Olaparib monotherapy is approved for maintenance treatment in advanced ovarian cancer with germline (g*BRCA*m) or somatic *BRCA* mutation, treatment of HER2-negative breast cancers with a g*BRCA* mutation, maintenance treatment of g*BRCA*m metastatic pancreatic cancer, metastatic castration-resistant prostate cancer with germline or somatic homologous recombination repair gene mutations, and in combination with bevacizumab for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency positive status defined by either a deleterious or suspected deleterious BRCA mutation, and /or genomic instability. The adverse effects observed in patients taking olaparib are associated with the PARP enzyme targets. PARP1 has been linked with circadian metabolic activities while PARP2 has been implicated to play a role in the regulation of red blood cell production. The most common side effects of olaparib are nausea, anemia, and fatigue. Other toxicities include, but are not limited to, constipation/diarrhea, neutropenia, dyspepsia, dysgeusia, pneumonitis, increased serum creatinine, and venous thromboembolic events (VTEs). Nausea is considered a class toxicity of all PARP inhibitors. Olaparib is categorized as moderate-high emetogenic risk per NCCN guidelines.[1] Nausea occurs in the first 3-5 days and usually resolves in 1-2 months. In the olaparib trials, nausea occurred in greater than 70% of patients with Grade 3 toxicity in 1-3% of patients.[2,3] Although less severe, diarrhea/constipation has also been reported in an estimated one-third of patients treated with a PARP inhibitor.[4] Anemia is a common adverse event associated with all PARP inhibitors. With olaparib, peak onset ranged from 1-2 months with a median duration of up to 3 months. Grade 3/4 anemia was seen in up to 21% of patients.[2,3] Other myelosuppressive toxicities, such as neutropenia, occur in an estimated 20% of patients. Febrile neutropenia is rare and occurs in ≤ 1%. Studies have reported the incidence of dyspepsia and dysgeusia to be approximately 20%. Respiratory toxicities occur in 10%-20% of patients with pneumonitis occurring in < 1% of patients on olaparib treatment. Increases in serum creatinine have reported in 10%-12% of patients; it is important to note that this is not indicative of acute kidney injury.[5] Fatigue developed in greater than 60% of patients with a median duration of 3-6 months.[2,3] In the PROfound trial, VTEs, including pulmonary embolism, were seen in 7% of patients treated with olaparib for metastatic castration-resistant prostate cancer.[4] VTE was a new safety signal identified from this trial. Lastly, consider additional or overlapping toxicities with olaparib combination therapy. Patients administering olaparib in combination with bevacizumab experienced nausea, fatigue, anemia, lymphopenia, vomiting, diarrhea, neutropenia, leukopenia, urinary tract infection, and headache.[4,8] In this PQI, we will review the management of adverse events associated with olaparib including gastrointestinal toxicities, anemia, neutropenia, fatigue, dyspepsia, dysgeusia, pneumonitis, and VTEs.

PQI Process:[4,5,6,7,8]

- Nausea Management
  - Assess patient specific risk factors for developing CINV (including patient's ability to tolerate previous regimens)
  - Consider prescribing a 5HT-3 RA and breakthrough antiemetics
  - Avoid greasy and spicy foods and encourage eating small meals throughout the day

    - If nausea occurs despite appropriate antiemetic treatment, hold olaparib until symptoms resolve within a couple of days; dose adjustments may be necessary if nausea persists for a longer period of time
- Diarrhea Management
    - Evaluate baseline bowel movement frequency
    - Rule out infectious causes such as Clostridium difficile
    - Review and evaluate medication list and diet as contributing factors
    - Once infectious etiology has been ruled out, initiate an anti-diarrheal such as loperamide
    - Depending on severity of diarrhea, hold olaparib until symptoms resolve
    - Review laboratory and physical information such as weight, BUN/SCr, electrolytes, and CBC with differential
    - Consider intravenous hydration and electrolyte replacement as appropriate
- Constipation Management
    - Evaluate baseline bowel movement frequency prior to initiating therapy
    - Counsel patient on proper hydration and fiber intake
    - Review medication list as 5HT-3 RAs and iron supplements could be contributing factors
    - Depending on severity, may require a fast-acting laxative such as magnesium citrate or lactulose
    - Consider initiating a stimulant laxative such as senna or bisacodyl daily to prevent future episodes
- Anemia Management
    - Evaluate baseline hemoglobin which may be low due to previous cancer treatments
    - Iron, B12, and folate deficiencies should be identified and treated prior to olaparib initiation
    - Counsel on the possibility of blood transfusions, dose interruptions, and dose reductions during olaparib treatment
    - For Grade 3/4 anemia (Hg < 8 g/dL), dose reduce to 250 mg PO BID
- Neutropenia Management
    - Evaluate baseline absolute neutrophil count (ANC)
    - Assess if neutropenia or febrile neutropenia episodes occurred with previous cancer treatments
    - Review counseling points on neutropenic precautions (checking temperature, washing hands, avoiding sick individuals, etc.)
    - Dose holds and reductions might be necessary
    - Growth factor support is not recommended
- Fatigue Prevention and Management
    - Evaluate for baseline depression, hypothyroidism, anemia, and pain
    - Review all concurrent medications to rule out drugs that can contribute to fatigue
    - Consider dietary modifications, improved sleep hygiene, increased exercise, psychosocial intervention and psychostimulants [6]
    - Resume previous dose if fatigue resolves in ≤4 weeks
        - If symptoms persist or are severe, dose reduce to 250 mg PO BID
- Dyspepsia & Dysgeusia
    - Educate patients on the possibility of pain associated with digestion
        - Discuss avoiding acidic foods and beverages
    - Reinforce comprehensive oral hygiene (salt and soda mouthwashes, etc.)
    - Encourage to eat foods and drink beverages that the patient prefers (or considers tasty)
- Pneumonitis Management
    - Assess if other comorbid conditions (asthma, COPD, etc.) are controlled prior to initiation
    - Hold treatment for new onset cough, fever, wheezing, or shortness of breath and initiate diagnostic work-up
    - Evaluate CT scan for confirmation of pneumonitis

        - Initiate antibiotics and steroid treatment
- Creatinine Elevation Management
    - For moderate renal impairment (CrCl 31-50 mL/min), reduce dosage to 200 mg PO twice daily
    - Review medications and other co-morbid disease states as contributing factors
    - Consider renal scan
- VTE Management – metastatic castration-resistant prostate cancer
    - Review past medical history for VTEs to ensure patients are on appropriate therapy
    - Ensure hospitalized patients are on VTE prophylaxis or treatment
    - Counsel patients to report new onset pain or swelling in extremities, shortness of breath, chest pain, tachypnea, or tachycardia

Patient Centered Activities:

- Provide Oral Chemotherapy Education Sheet
- Ensure appropriate antiemetics are prescribed upon initiation of olaparib treatment
- Discuss the possible need for over-the-counter anti-diarrheal agents, laxatives, dyspepsia agents, and sunscreen
- Monitor CBC with differential at baseline and monthly thereafter
    - If prolonged hematological toxicity, evaluate weekly until recovery
- Prepare patient for the possibility of blood transfusions, dose interruptions, and dose reductions
- Review concurrent medications to ensure these are not contributing to fatigue, diarrhea, dyspepsia, constipation, or renal impairment

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