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Positive Quality Intervention: Olaparib (Lynparza®) Clinical Management

Description: Olaparib is a poly ADP-ribose polymerase (PARP) enzyme inhibitor and is FDA approved as a targeted therapy for *BRCA*-mutated breast cancer, ovarian, pancreatic cancer, as well as prostate cancer. This PQI will highlight its place in therapy in these disease states, safety profiles, and clinical pearls regarding dose adjustment.

Background: *Breast Cancer* - About 5-10% of breast cancers can be associated with gene mutations inherited from a parent, most common mutations in the *BRCA*1 and *BRCA*2 genes.[12]

Lifetime Risk of Developing Breast Cancer		
Mutation	Women	Men
BRCA1	Up to 72%	6.8%
BRCA2	69%	Less frequent cause

Ovarian Cancer - Currently, ovarian cancer is primarily treated with surgery and systemic chemotherapy. About 25% of ovarian cancer cases are related to a BRCA mutation (15% germline and 7% somatic).[14,15]

Pancreatic Cancer - Up to 7% of patients with pancreatic cancer have a g*BRCA* mutation.[16,17]

Prostate Cancer - Olaparib is approved for patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer in combination with gonadotropin-releasing hormone analog or prior bilateral orchiectomy (full indication list in supplemental information).

PQI Process:

- Verify the dose is correct
  - Typical starting dose for all FDA-approved indications: 300 mg orally twice daily
    - Available as 100 mg and 150 mg tablets
    - See Supplemental Information Section for current FDA-approved indications
  - The dose of olaparib must be adjusted to 200 mg twice daily for renal dysfunction when creatinine clearance is ≤ 50 mL/minute; olaparib has not been studied in patients with creatinine clearance ≤ 30 mL/minute
- Dose adjustments for adverse reactions
  - Consider holding treatment or dose reductions if patients experience adverse reactions

Dose reduction	Recommended Dose	How to Supply
1st dose reduction	250 mg BID	One 150 mg tablet + one 100 mg tablet BID
2nd dose reduction	200 mg BID	Two 100 mg tablets BID

- Drug interactions
  - Avoid concomitant use with moderate and/or strong CYP3A4 inhibitors
    - If a strong CYP3A4 inhibitor must be used concomitantly, the olaparib dose should be reduced to 100 mg twice daily
    - If a moderate CYP3A4 inhibitor must be used concomitantly, the olaparib dose should be reduced to 150 mg twice daily
  - Avoid concomitant strong CYP3A inducers; if a moderate CYP3A inducer must be used, there is the potential for reduced efficacy of olaparib
- Laboratory monitoring

- Complete blood counts should be performed at baseline and monthly thereafter
- Renal function should be verified at baseline and periodically thereafter
- Taking other anticancer agents may cause a potentiation/prolongation of myelosuppression

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet
- Counsel patient on side effect profile (see supplemental information and Olaparib (Lynparza®) Adverse Event Management PQI)
- Instruct patient to avoid grapefruit, grapefruit juice, Seville oranges, and/or Seville orange juice
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. U.S. Breast Cancer Statistics. Breastcancer.org. Last updated Feb 13,2019.
2. Pal T et al. *Cancer*. 2005;104(12):2807-2816.
3. Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma.
5. SEER Cancer Stat Fact Sheets: Pancreatic Cancer. National Cancer Institute. https://seer.cancer.gov/statfacts /html/pancreas.html. Accessed March 20, 2020.
6. Lynparza® (olaparib) [package insert].

Supplemental Information:

Current FDA-approved indications: Starting dose is 300 mg twice daily for all indications

Indication	Efficacy	Safety
Ovarian cancer		
First-line maintenance treatment for deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to first-line platinum-based chemotherapy (SOLO-1)	mPFS results: olaparib 56 months vs placebo 13.8 months 5-Year PFS: olaparib 48% vs placebo 21%	Most common AEs with olaparib: nausea, vomiting, fatigue, anemia, diarrhea Serious AEs occurred in 21% of olaparib patients vs 12% of placebo patients, most commonly anemia
In combination with bevacizumab for maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either deleterious or suspected deleterious *BRCA* mutation and/or genomic instability PAOLA-1 trial	Reduced the risk of disease progression or death by 67% (equal to HR of 0.33) and improved progression-free survival to a median of 37.2 months vs 17.7 months with bevacizumab alone Higher Risk: mPFS olaparib 36.0 vs. 16.0 bevacizumab Lower Risk: mPFS olaparib Not Reached vs. 22.1 bevacizumab	Adverse reactions (Grade 1-4) occurring in ≥10% of patients treated with olaparib/bevacizumab in PAOLA-1 compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), and leukopenia (18%), diarrhea (18%), neutropenia (18%), urinary tract infection (15%), and headache (14%)
Maintenance treatment for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to platinum-based chemotherapy – 2 randomized trails completed[10] SOLO-2 trial Study 19	SOLO-2: PFS: olaparib 19.1 months vs placebo 5.5 months OS: olaparib 51.7 months vs placebo 38.8 months Study 19: PFS: olaparib 8.4 months vs placebo 4.8 months; OS: olaparib 29.8 months vs placebo 27.8 months	SOLO-2: Most common Grade 1/2 AEs in both groups: nausea, fatigue, vomiting, abdominal pain, and diarrhea Most common ≥ Grade 3 AE: anemia Study 19: Most common AEs of all grads in olaparib arm included nausea (71%), fatigue (63%), vomiting (35%), diarrhea (28%), anemia (23%), constipation (22%), respiratory tract infection (22%), decreased appetite (21%), and headache (21%)
Deleterious or suspected deleterious gBRCAm advanced ovarian cancer after ≥3 prior lines of chemotherapy	Single arm trial PFS results: ORR: 34%; Median DoR: 7.9 months	Serious AEs reported in 30% of patients, most frequently anemia, abdominal pain

Breast Cancer		
Deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer after treatment with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting (OlympiAD trial)	PFS: olaparib 7 months vs chemotherapy 4.2 months	Rate of ≥ Grade 3 AEs olaparib (36.6%) vs chemotherapy (50.5%) AEs that occurred more frequently with olaparib: anemia, nausea, vomiting, fatigue, headache, and cough
Pancreatic Cancer		
Maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen (POLO trial)	PFS results: olaparib vs. placebo: median 7.4 months vs. 3.8 months ORR: 23% in olaparib arm (12% in placebo arm) OS: olaparib 19.3 months vs placebo 17.1 months	Most common AE at grades 3-4 for olaparib: anemia (11%) All grades AE >30% for olaparib: Fatigue (60%), nausea (45%), abdominal pain (34%) All grade diarrhea occurred at a rate of 29%
Prostate Cancer		
Treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone (PROfound trial) Treatment of adult patients in combination with abiraterone and prednisone (or prednisolone) for adult patients with deleterious or suspected deleterious BRCAm mCRPC (PROpel trial)	Reduced risk of disease progression or death by 66% (HR 0.34) Radiographic PFS median of 7.4 months vs. 3.6 months with enzalutamide or abiraterone in men with *BRCA1/2* or *ATM* gene-mutated mCRPC OS: olaparib 19.1 months vs placebo 14.7 months	PROfound: Most common AE (Grade 1-4) occurring in ≥10% in the olaparib arm were anemia (46%), nausea (41%), fatigue including asthenia (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%) and dyspnea (10%) Venous thromboembolic events, including pulmonary embolism occurred in 7% of patients with mCRPC who received olaparib plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT PROpel: Most common AE (≥10%) in patients receiving olaparib plus abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%). Seventy-two patients (18%) required at least one blood transfusion and 46 (12%) required multiple transfusions.

PFS: progression free survival; AEs: adverse events; ORR: objective response rates; DoR: duration of response

Based on current ASCO Guidelines:

- Women diagnosed with epithelial ovarian cancer
    - Offer germline genetic testing for BRCA1/2 and other ovarian cancer susceptibility genes at time of diagnoses
    - Perform somatic tumor testing for BRCA1/2 and other likely pathogenic variants in women who are negative for a germline mutation
    - First/second-degree blood relatives with a known germline susceptible gene mutation/variant should be offered individualized genetic risk evaluation/counseling and genetic testing
- Olaparib was previously available as both a tablet and a capsule, and the two dosage forms had different bioavailability therefore are not interchangeable on a milligram-per-milligram basis
    - Capsules were discontinued August 2018; only the tablets are currently available in the United States