PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

Tew et al.
Introduction

- The introduction of poly(ADP-ribose) polymerase inhibitors (PARPis) has led to major change in the approaches to epithelial ovarian, tubal or primary peritoneal cancer (EOC) management across the treatment life cycle.

- Recent studies have confirmed that the efficacy of PARPis is enhanced not only in g/sBRCA EOC but also in cancers in which homologous recombination deficiency (HRD) is caused by other underlying etiologies.

- The applications of PARPis in the management of EOC are complex and all approvals to date are predicated on the absence of prior exposure to PARPis.

- The purpose of this guideline is to provide clinicians, other health care practitioners, patients, and caregivers with recommendations regarding the role of PARPis in the management of EOC based on the best available evidence.
ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:

www.asco.org/guideline-methodology
Clinical Questions

1. Should PARPi therapy for EOC be repeated over the course of treatment?

2. In which patients with newly diagnosed EOC are PARPis recommended?
   a. What are the histologic types of EOC for which PARPis are recommended?
   b. What are the biomarker subsets for which PARPis are recommended?

3. Is PARPi monotherapy recommended for recurrent EOC? If so,
   a. In which settings (eg, second-line maintenance or treatment of recurrent disease)?
   b. At what dose and duration?

4. Are there settings where PARPis in combination with chemotherapy or other targeted therapy are recommended?

5. How should clinicians manage the specific toxicities of the various PARPis?
Target Population and Audience

**Target Population**
Patients diagnosed with epithelial ovarian, tubal, or primary peritoneal cancer (EOC) who have not previously received a poly (ADP-ribose) polymerase inhibitor (PARPi).

**Target Audience**
Medical, radiation, and surgical oncologists; gynecologic oncologists; gynecologists; advanced practice and other health professionals; women with ovarian cancer, and their families.
Summary of Recommendations

CLINICAL QUESTION 1
Should PARPi therapy for EOC be repeated over the course of treatment?

Recommendation 1.0
Repeating PARPi therapy in the treatment of EOC is not recommended at this time. Consideration should be made as to the best time in the life cycle of an individual patient’s EOC in which to use PARPi; clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)
Summary of Recommendations

CLINICAL QUESTION 2
In which patients with newly diagnosed EOC are PARPis recommended?
- What are the histologic types of EOC for which PARPis are recommended?
- What are the biomarker subsets for which PARPis are recommended?

Recommendation 2.0
PARPis are not recommended for use in initial treatment of early stage (stage I-II) EOC because there is insufficient evidence to support use in this population (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).
Summary of Recommendations

**Recommendation 2.1**

Women with newly diagnosed stage III-IV EOC that is in complete or partial response to first-line platinum-based chemotherapy should be offered PARPi maintenance therapy with olaparib (for those with germline or somatic pathogenic or likely pathogenic variants in BRCA1 or BRCA2 genes) or niraparib (all women) in high-grade serous (HGS) or endometrioid ovarian cancer.

- PARPi maintenance therapy should consist of olaparib (300 mg orally every 12 hours for 2 years) or niraparib (200-300 mg orally daily for 3 years). Longer duration could be considered in selected individuals. (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Summary of Recommendations

**Recommendation 2.2**

The addition of olaparib to bevacizumab maintenance may be offered to patients who have stage III-IV HGS or endometrioid ovarian cancer and germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes and/or genomic instability, as determined by Myriad myChoiceCDx, and who have had a partial or complete response to chemotherapy plus bevacizumab combination (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

**Recommendation 2.3.**

Inclusion of the PARPi veliparib with combination chemotherapy followed by veliparib maintenance therapy cannot be recommended at this time. There are no data that this approach is superior, equal, or less toxic than a switch maintenance (Type: evidence based, benefits/harm ratio unknown; Evidence quality: intermediate; Strength of recommendation: strong).

*Note.* As of this writing, veliparib is not commercially available.
Summary of Recommendations

CLINICAL QUESTION 3
Is PARPi monotherapy recommended for recurrent EOC? If so,
- In which settings (eg, second-line maintenance or treatment of recurrent disease)?
- At what dose and duration?

Recommendation 3.0
PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of BRCA mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care.

- Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily. (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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Summary of Recommendations

**Recommendation 3.1**

Treatment with a PARPi should be offered to patients with recurrent EOC who have not already received a PARPi and have a germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes.

- Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

**Recommendation 3.2**

Treatment with a PARPi monotherapy should be offered to patients with recurrent EOC who have not already received a PARPi and whose tumor demonstrates genomic instability, as determined by Myriad myChoice CDx, and has not recurred within 6 months of platinum-based therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Summary of Recommendations

**Recommendation 3.3**

PARPis are not recommended for treatment of BRCA wild-type or platinum-resistant recurrent EOC (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Summary of Recommendations

CLINICAL QUESTION 4

Are there settings where PARPis in combination with chemotherapy or other targeted therapy are recommended?

Recommendation 4.0

PARPi are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)
Summary of Recommendations

CLINICAL QUESTION 5

How should clinicians manage the specific toxicities of the various PARPis?

Recommendation 5.0 Anemia

a. Patients requiring a blood transfusion for symptom relief and/or hemoglobin level < 8 g/dL should be monitored. PARPi dose should be reduced with evidence of repeated anemia to avoid multiple transfusions.

b. Patients with progressive anemia may be offered growth factor per ASCO guidelines and physician and patient comfort.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
Summary of Recommendations

**Recommendation 5.1 Neutropenia**

a. Growth factor is not indicated for use in patients receiving daily PARPi.

b. Neutropenia (grade 4 lasting at least 5-7 days or associated with fever) should result in dose hold until recovery of infection and granulocyte count, followed by dose reduction. Growth factor support may be used in this setting to support patient safety during the drug hold.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
Summary of Recommendations

**Recommendation 5.2 Platelets**

a. Thrombocytopenia is most common with niraparib. Niraparib dosing guidelines should be used to lower starting dose (200 mg) based on weight and platelet count.

b. Discontinue PARPi for persistent thrombocytopenia or significant bleeding despite dose reduction.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
Summary of Recommendations

**Recommendation 5.3 Persistent cytopenia**

a. Evaluation for treatment-related myelodysplastic syndrome/acute myeloid leukemia should be initiated in patients with persistent cytopenia that occurs despite drug hold.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

**Recommendation 5.4 Nausea**

a. Many patients will have tachyphylaxis of nausea symptoms over the first cycle of therapy.

b. Persistent nausea requiring daily antiemetic intervention, causing a reduction in performance status, and/or resulting in > 5% weight loss should result in dose reduction.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).
Patient and Clinician Communication

▪ Women with advanced ovarian cancer considering treatment or maintenance with a PARPi do so during a time of rapidly emerging new data and complex regulatory approvals.

▪ Shared decision-making is essential, and patients should be informed that the evidence-based options for treatment (or maintenance), as well as the potential benefits and risks communicated by the physician, are based on knowledge that continues to evolve.

▪ It is essential that providers thoroughly explain the potential impact on quality of life during the initial 30-to 60-day adjustment period and provide a plan for aggressive management of adverse events during this phase and beyond.

▪ Patients should also be informed that a potential dose reduction may be reasonable to manage adverse effects.

▪ Connection with other patients who have already navigated adjustment to PARPis, through local or on-line support networks, may increase tolerability and adherence.
Health Disparities

- A recent, large, population-based study of multigene testing in patients with breast or ovarian cancer observed racial disparities in genetic testing.\(^1\)
  - While approximately 34% of White women were tested, only about 22% of Black women and 24% of Hispanic women received testing.
  - Furthermore, racial/ethnic differences in pathogenic variants observed in patients with ovarian cancer include \textit{BRCA1}, which is reported to be 1% in individuals of African descent, 7% in Whites and 16% in Hispanics.\(^1\)

- Patients with cancer who are members of racial/ethnic minorities also suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.\(^2-5\)

- Awareness of these disparities in access to care should be considered in the context of this guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.
Cost Implications

- PARPis are costlier than other available therapies, 18.8, 6.9, and 2.2-2.7 times costlier than paclitaxel, pembrolizumab, and bevacizumab, respectively.

- Patients’ out-of-pocket costs may vary depending on insurance coverage. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies.

- While most insurance carriers will provide some coverage for PARPis, the patient’s copayment can remain prohibitive, nonetheless. Medicare, which is used by many patients with ovarian cancer, given that the disease largely affects older women, does cover most PARPis. The amount of coverage and the size of copay, however, vary from state to state.

- When discussing financial issues and concerns, patients should be made aware of any financial counseling services.

- Discussion of cost can be an important part of shared decision-making.
Discussion

- A major limitation of these guidelines is their focus on women who are PARPi naïve.
- The physician and patient need to consider the full lifetime of the patient and disease and weigh the data benefits and risks, especially given the lack of an OS benefit to date.
- A critical unmet need is to understand the opportunities and where the benefits may be for re-exposure to a PARPi after an initial good response and in combinations after a progression outcome.
- Preclinical development is moving rapidly and some clinical trials have begun.
- Reuse of a PARPi should only be considered in such a trial situation until data develop to guide evidence-based clinical care.
- Future clinical trials that examine PARPi timing within the treatment life cycle and optimal duration of treatment could help establish the best risk-benefit balance practice pattern for PARPi use in the management of EOC.
Additional Resources

More information, including a supplement, slide sets, and clinical tools and resources, is available at

asco.org/gynecologic-cancer-guidelines

Patient information is available at www.cancer.net
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