PARP Inhibitors: Their Role Across Tumor Types

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Learning Objectives

• Describe approved and emerging PARP inhibitors and approaches
• Outline appropriate interventions to prevent or manage the side effects of PARP inhibitors
• Identify key components for counseling patient about treatment expectations, adverse events, and symptoms management
<table>
<thead>
<tr>
<th>FDA approved PARP inhibitors</th>
<th>Ovarian, fallopian tube or peritoneal cancer</th>
<th>Metastatic Breast Cancer</th>
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</thead>
<tbody>
<tr>
<td>olaparib: frontline(BRCAm) and recurrent setting (regardless of BRCA status)</td>
<td>olaparib: BRCAm, previously treated with chemo, HR+, prior ET</td>
<td>talazoparib: BRCAm locally advanced or metastatic, HER2 neg breast cancer</td>
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<td>rucaparib: recurrent setting BRCAm</td>
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<td>niraparib: recurrent setting, regardless of BRCA status</td>
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<tr>
<td>Metastatic prostate cancer</td>
<td><strong>olaparib</strong>: Phase III PROFOUND trial</td>
<td><strong>rucaparib</strong>: Phase III TRITON3 study</td>
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| Metastatic Pancreatic cancer | **iniparib**: case report of a complete response in a BRCA2+ case | **veliparib**: Phase IB trial of cisplatin, gemcitabine and veliparib BRCA or PALB2 + | }

UpToDate, Investigational approaches for the treatment of advanced prostate cancer, Chemotherapy for the treatment of pancreatic cancer
PARP Inhibitor Mechanism of Action

- *BRCA1* and *BRCA2* genes play a role in DNA repair – homologous recombination
- Individuals with a *BRCA1* or *BRCA2* mutation lose the remaining wild type allele resulting in loss of ability to repair DNA, which can drive carcinogenesis

Adapted from Tong C, et al. *Front Oncol.* 2018;8:227.
Patient case history

- 69 year old woman with strong family history of ovarian/colon cancer, germline and somatic testing negative for BRCA mutation
- Robotic BSO January 2016, risk reduction surgery. Path + for high grade serous adenocarcinoma of the fallopian tube
- May 2016: 6 cycles carbo AUC 5, paclitaxel 175mg/m2
- CA–125 = 9.29
- Observation
Case continued

• July 2018 : CA-125=32.1. CT shows some nodular tissue thickening – peritoneum, sigmoid colon -- Tamoxifen

• September 2018 – CA-125 up to 90. Further progression seen on CT

• October 2018: 3 cycles of carboplatin/liposomal doxorubicin. PPE with liposomal doxorubicin ,cycle 4 carbo alone. CT 1/19 with response. CA-125 down to 24.8
FDA approved PARP inhibitors for patients with advanced ovarian cancer in the recurrent setting

- **olaparib** - treatment of recurrent ovarian, fallopian and peritoneal cancer in patients with germline BRCA mutations after 3 prior lines of chemo or post-platinum maintenance therapy for platinum sensitive recurrences regardless of BRCA status. 300 mg tablets BID

- **rucaparib** – treatment of recurrent BRCA mutated ovarian, fallopian and peritoneal cancer (germline or somatic) after 2 lines of chemo. 600 mg tablets BID

- **niraparib** – treatment of recurrent platinum sensitive ovarian, fallopian and peritoneal cancer **regardless of BRCA status** within 8 weeks of last platinum dose. 300 mg capsules QD
FDA approval of olaparib in frontline maintenance setting for advanced ovarian cancer

- December 2018 – **olaparib** approved for BRCA mutation positive advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (germline, somatic or suspected) with a complete or partial response to platinum in the frontline maintenance setting.

- Based on SOLO-1 trial results – median PFS in the olaparib arm not yet reached (after 41 months of follow up) compared to 14 months in the placebo arm.

- Groundbreaking change in the management of advanced BRCA+ ovarian cancer

Back to our case

• niraparib 200 mg QD initiated January 2019 (DR due to baseline thrombocytopenia after platinum chemo)

• Held 2\textsuperscript{nd} cycle for thrombocytopenia. Restarted at 100 mg per day

• Tolerating well with the exception of platelets, first scan April with response
Side effect management

• niraparib: most common SE are thrombocytopenia, anemia, neutropenia, nausea/vomiting and fatigue. Rare SE include diarrhea, constipation, headache, nasopharyngitis and cough

• Dose reductions are common for myelosuppression. Hold until counts recover then re-initiate at a lower dose

• Take at the same time each day with or without food. In the event of a missed dose, skip and resume the next day.
Case 2

44 year old female diagnosed in 2014 with a right sided T3N1 ER/PR+, HER2 negative breast cancer. + FH of breast cancer. **Myriad germline testing + BRCA2 mutation.**

- Neoadjuvant AC x 4 followed by ddTaxol x 4, Bilateral mastectomies, ALND with ypT2ypN1 disease, declined XRT
- Tamoxifen 2015-2017 when she presented with back pain and was found to have diffuse bony mets on PET scan. Bone biopsy + metastatic carcinoma, breast origin, ER/PR +, HER2 negative
- First line letrozole/palbociclib/denosumab – started 6/17, progression in bone and liver noted on PET scan Jan 2018
FDA approved PARP inhibitors for BRCAm patients with metastatic breast cancer

- **olaparib** - Indicated in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

- **talazoparib** - Indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer.

Phase 3 Clinical Studies

**olaparib–OlympiAD**
- Randomized, open-label, phase 3 trial
- Patients: metastatic BC, +gBRCA1/2, HER2-; 302 randomized
- Olaparib 300 mg twice daily vs standard single-agent therapy (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles)
- Primary endpoint: progression-free survival

**talazoparib–EMBRACA**
- Randomized, open-label, phase 3 trial
- Patients: advanced BC, +gBRCA1/2; 431 randomized
- Talazoparib 1mg/day vs standard single-agent therapy (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles)
- Primary endpoint: progression-free survival

Back to our case

- PARP inhibitor appropriate next step as she is BRCA2+, has received chemo and has progressed on first line endocrine therapy
- Patient started on olaparib 300mg BID
- Well tolerated with the exception of nausea
- Anti-emetic 30 minutes prior to each dose was helpful
Patient case—Treatment Response @ 3 Months

Prior to PARP Inhibitor Therapy

3 months on PARP Inhibitor Therapy
Side effect management with olaparib

• Nausea and vomiting are the most common side effects. Small frequent meals, bland diet and prophylactic anti-emetics have been helpful. Fatigue is also common.

• Less common are myelosuppression, headache, and constipation. Pneumonitis has occurred rarely.
## PARP Inhibitor common side effects

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<td>Nausea/vomiting (most common), fatigue, anemia, increased creatinine, rash, less often neutropenia or thrombocytopenia.</td>
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<td>Thrombocytopenia, anemia (most common), nausea/vomiting, fatigue, increased blood pressure and/or heart rate, increased AST/ALT</td>
<td>Nausea/vomiting, anemia, fatigue, constipation, diarrhea, dysgeusia, thrombocytopenia, rash, increased creatinine, AST or ALT</td>
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<td>Pneumonitis has been reported</td>
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*All PARP inhibitors have shown potential for fetal harm; men and women should be counseled to use effective contraception during and for 3 -6 months after administration

**Slight risk of MDS with all PARP inhibitors
## PARP Inhibitor monitoring and considerations

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<td>CBC and BMP</td>
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<td>CBC weekly for the first month, then monthly thereafter.</td>
<td>CBC and CMP monthly Can increase photosensitivity, discuss sun protection</td>
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<td>Often requires prophylactic anti-emetic</td>
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<td>Monitor hepatic function, blood pressure and HR monthly</td>
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- Often requires prophylactic anti-emetic administration
- Can increase photosensitivity, discuss sun protection
## Patient and family counseling

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<td>Take twice per day with or without food.</td>
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<td>Avoid grapefruit, grapefruit juice and Seville oranges.</td>
<td>Avoid concomitant use with P-gp inhibitors (amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil.</td>
<td>No major drug interactions</td>
<td>Avoid concomitant use of CYP1A2, CYP3A, CYP2C9 and CyP2DC19 substrates. Particular caution with warfarin</td>
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<td>Avoid concomitant use of CYP3A inhibitors (antifungals, clarithromycin, verapamil, diltiazem, St. John’s wart, phenytoin)</td>
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<td>Patients advised to take qhs to avoid nausea. Increases in BP and HR common.</td>
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Do not crush, chew or divide tablets. Do not dissolve or open capsules. If a dose is missed take at the next scheduled time.
Management of nausea and vomiting

- Small frequent meals
- Bland diet
- Prophylactic anti-emetic: NCCN recommends that a 5-HT3 receptor antagonist 30 minutes prior to oral PARP-inhibitor dose. Alternatives could include olanzapine, lorazepam, dronabinol, metoclopramide, prochlorperazine or dexamethasone

Davis, CC. *Oncology Journal*, 33 (2): 58-61
Management of fatigue

- Rule out other causes (anemia, prior treatment with chemotherapy, thyroid dysfunction, insomnia or depression)
- Discuss exercise (PT referral), mind body techniques, counseling and massage
- Sleep hygiene
Key points for patients and family

- Clinical trials have shown that PARP Inhibitors are better tolerated than chemo for BRCA mutation positive patients and have a longer PFS than traditional chemo.
- Side effects are generally mild and can be managed with supportive medications or dose reductions.
- Will require monthly monitoring with blood work, physical exam.
References


Olaparib prescribing information: https://www.azpicentral.com/lynparza_tb/lynparza_tb.pdf#page=1

Rucaparib prescribing information: https://clovisoncology.com/media/1094/rubraca-prescribing-info.pdf

Niraparib prescribing information: https://www.zejula.com/prescribing-information


Walczak JR, Pili R, Carducci MA et al. Investigational approaches for the treatment of advanced prostate cancer, UpToDate.

Ryan DP. Chemotherapy for the treatment of pancreatic cancer. UpToDate


