An Update on Ovarian Cancer with a Focus on PARP Inhibitors

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Disclosure
• I have no professional/financial disclosures regarding this presentation.

Objectives
• Review the pathophysiology of ovarian cancer
• Summarize current treatment recommendations for ovarian cancer
• Explore new treatment options for recurrent ovarian cancer, with a focus on PARP inhibitors
• Discuss future directions for treatment of ovarian cancer

Ovarian Cancer
Background
Anatomy/Pathophysiology
Staging
Treatment Overview

Epidemiology
• 22,440 estimated new cases in 2017
• 14,080 estimated deaths in 2017
• Median age at diagnosis 63 y/o
• Highest prevalence in Caucasian females

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cases by Stage</th>
<th>5-year Relative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>15%</td>
<td>92.5%</td>
</tr>
<tr>
<td>Regional</td>
<td>20%</td>
<td>73%</td>
</tr>
<tr>
<td>Distant</td>
<td>60%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6%</td>
<td>25.1%</td>
</tr>
</tbody>
</table>


Anatomy/Pathophysiology
• Most commonly epithelial ovarian cancer (EOC)
  ▫ High-grade serous carcinoma
• Less common histologic subtypes
  ▫ Endometrioid/low-grade serous carcinomas
  ▫ Clear cell carcinomas
  ▫ Mucinous carcinomas
  ▫ Carcinosarcoma
• Malignant sex cord-stromal tumors
• Malignant germ cell tumors
• Fallopian tube cancer and primary peritoneal cancer are less common but present in a similar fashion
• Common sites of metastases: liver, lung, peritoneum

The MD Anderson Manual of Medical Oncology, 3e.
Histologic Subtypes

- High-grade serous carcinomas: 70-80% of all ovarian cancers
  - Molecular features: p53 mutation, BRCA1 dysfunction, FGFR2 amplification (25-40%)
  - Includes transitional cell carcinoma and undifferentiated carcinoma
- Low-grade serous carcinoma: 5-8% of all ovarian cancers (6-10% of serous)
  - Molecular features: mutations in K-RAS (20-40%) and/or BRAF (5%)
- Endometrioid adenocarcinoma (high or low grade): 10% of all ovarian tumors
  - Molecular features: mutations in p53, PIK3CA, CTNNB1, PTEN; BRCA1 dysfunction
- Clear Cell Carcinoma: 5-10% of all ovarian cancers
  - Molecular features: PTEN mutation/loss of heterozygosity, PIK3CA mutation
- Mucinous: 3% of all ovarian cancers
  - Molecular features: mutations in K-RAS, p53

Staging

<table>
<thead>
<tr>
<th>Stage (T N M)</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IC</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II A</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II B</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II C</td>
<td>T2c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III A</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III B</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III C</td>
<td>T3c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T N M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary adjuvant treatment: Depends on stage (IA, IB, IC, II A, II B, II C, III A, III B, III C, IV). The treatment includes chemotherapy, radiation, or surgery based on the stage and presence of metastases.

Primary adjuvant treatment for stage IA, IB, IC, II A, II B, II C:
- No adjuvant therapy recommended.

Primary adjuvant treatment for stage III A, III B, III C, IV:
- Treatment options include chemotherapy, hormone therapy, or targeted therapy. The choice of treatment depends on the specific subtype of the cancer and the patient's overall health.

Clinical work up and primary treatment:
- Preoperative evaluation: Imaging studies (CT scan, MRI), blood tests, and physical examination.
- Treatment options based on the stage and type of the cancer.
- Postoperative treatment: Depends on the stage and presence of metastases.

Consolidation/recurrent disease treatment:
- Targeted therapy: Immunotherapy, targeted drugs, or hormonal therapy.

References:
### What is PARP?
- Poly (ADP-ribose) polymerase (PARP) enzymes
- Family of 18 proteins which repair single-stranded DNA damage via:
  - Base-excision repair
  - Inhibition of the non-homologous end-joining DNA repair pathway (a method of double-strand break repair)
- Inhibition of the PARP1 and PARP2 enzymes results in the accumulation of double-stranded breaks, which are typically repaired by the homologous recombination double-stranded DNA repair pathway.

### Why PARP Inhibitors?
- **BRCA1** and **BRCA2** enzymes repair double-stranded DNA breaks via homologous recombination:
  - A germline or somatic mutation in one **BRCA1/2** allele can be compensated for by the remaining wild-type allele.
  - Loss of the remaining wild-type allele, known as loss of heterozygosity (LOH), renders the homologous recombination pathway ineffective.
- Tumor cells which have LOH are therefore most susceptible to PARP inhibition, as they have no mechanism to repair double-stranded breaks.

### Olaparib (Lynparza®)
- Granted accelerated approval on December 19, 2014
- Initial indication:
  - Olaparib capsules as monotherapy for patients with deleterious or suspected deleterious germline **BRCA** mutated recurrent ovarian cancer who were previously treated with ≥3 prior lines of chemotherapy.
  - Approved with BRACAnalysis CDx, a diagnostic test which detects **BRCA** mutations.

### Olaparib for Recurrent Disease
- Multicenter, single arm, phase II trial:
  - Enrolled patients with a **gBRCA1/2** mutation and recurrent ovarian, breast, pancreatic, or prostate cancer
  - 298 patients enrolled → 193 patients with ovarian cancer resistant to prior platinum-based therapy or unsuitable for further platinum chemotherapy.
  - Tumor response rate:
    - 31.1% in patients with ovarian cancer (95% CI, 24.6-38.1)
    - Did not differ based on **BRCA1** vs **BRCA2** mutation.
Olaparib for Recurrent Disease


Maintenance Olaparib

- Olaparib tablets granted regular approval on August 17, 2017
- Indication:
  - Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy
  - Monotherapy for patients with deleterious or suspected deleterious germline BRCA mutated recurrent ovarian cancer who were previously treated with three or more prior lines of chemotherapy
- As the tablets also received approval for the initial indication of recurrent disease, the capsules will be phased out and will only be available through Lynparza Specialty Pharmacy Network

Olaparib

Dosage Form
- Capsule Tablet
- Dosage: 50 mg (to be phased out) 100, 150 mg

Indication/Dosing
- Recurrence: 400 mg PO BID
- Maintenance: 300 mg PO BID

Administration
- With or without food

Emetic Risk
- Moderate

Dose Reductions:
- Concomitant Therapy
  - CYP3A4 inhibitors: moderate (200 mg BID) or strong (150 mg BID)
- Dose Reductions: Renal
  - CrCl 31‐50 mL/min: 300 mg BID

Toxicity
- 1st reduction: 200 mg BID
- 2nd reduction: 100 mg BID

Storage
- Room temperature

Rucaparib (Rubraca®)

- Granted accelerated approval on December 19, 2016
- Indication:
  - Treatment of patients with deleterious BRCA mutation (germinal and/or somatic) associated advanced ovarian cancer who have been treated with ≥2 prior lines of chemotherapy
- Approved with FoundationFocus CDX®: a next-generation sequencing diagnostic that detects alterations in the BRCA1/2 genes
ARIEL2 Part 1

- 2-part, phase II, open-label trial
- Rucaparib in patients with recurrent, platinum-sensitive, high-grade ovarian carcinoma with or without a BRCA mutation
  - 3 subgroups: deleterious germline/somatic BRCA mutant, BRCA wild-type + LOH high, or BRCA wild-type + LOH low
- 206 patients received rucaparib 600 mg BID for continuous 28 day cycles

Median PFS:
- BRCA mutant: 12.8 months (95% CI 9.0-14.7, p<0.0001 compared to LOH low)
- LOH high: 5.7 months (95% CI 5.3-7.6, p=0.011 compared to LOH low)
- LOH low: 5.2 months (95% CI 3.6-5.5)

Rucaparib

- Dosage form
  - 200, 250, 300 mg tablets
- Dosing
  - Recurrent: 600 mg PO BID with or without food
  - Moderate emetic risk!
- Dose reductions
  - 1st dose reduction: 500 mg BID
  - 2nd dose reduction: 400 mg BID
  - 3rd dose reduction: 300 mg BID
- Substrate of BRCP, P-glycoprotein, CYP1A2 (minor), CYP2D6 (minor), CYP3A4 (minor)
- Store at room temperature

Niraparib (Zejula®)

- Granted regular approval on March 27, 2017
- Indication:
  - Maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy

ENGOT-OV16/NOVA

- Randomized, double-blind, phase III trial
- Niraparib for patients with platinum-sensitive recurrent ovarian cancer in complete or partial response following platinum-based therapy
  - 2 cohorts: gBRCA mutation (homologous recombination deficiency [HRD] or non-HRD) and no gBRCA mutation
  - 553 patients randomized 2:1 to niraparib 300 mg daily vs placebo


Rubraca™ (rucaparib) [prescribing information].
Niraparib

- Dosage form
  - 100 mg capsule
- Dosing
  - Maintenance: 300 mg PO daily with or without food
  - Low emetic risk
- Dose adjustments
  - No renal or hepatic dose reductions required
  - Toxicity (hematologic or non-hematologic)
    - First dose reduction: 200 mg daily
    - Second dose reduction: 100 mg daily
    - Discontinue if <100 mg daily is required
- Substrate of BCRP, P-glycoprotein; inhibits BCRP
- Store at room temperature
Summary

<table>
<thead>
<tr>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage Form</td>
<td>50 mg capsule 100, 150 mg tablet</td>
<td>200, 250, 300 mg tablet</td>
</tr>
<tr>
<td>Indication</td>
<td>Recurrent ovarian Maintenance for ovarian, fallopian tube, or primary peritoneal</td>
<td>Recurrent ovarian Maintenance for ovarian, fallopian tube, or primary peritoneal</td>
</tr>
<tr>
<td>Dosing</td>
<td>Recurrence: 400 mg BID Maintenance: 300 mg BID</td>
<td>Recurrence: 400 mg BID Maintenance: 300 mg QD</td>
</tr>
<tr>
<td>Administration</td>
<td>With or without food</td>
<td>With or without food</td>
</tr>
<tr>
<td>Emetic Risk</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Dose Reductions</td>
<td>CYP3A4 inhibitor CrCl ≤ 50 ml/min</td>
<td>No renal/hepatic adj toxicity</td>
</tr>
<tr>
<td>Storage</td>
<td>Room temperature</td>
<td>Room temperature</td>
</tr>
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</table>

Future Directions

Current PARP Inhibitors

New PARP Inhibitors

Future Directions: Current PARP Inhibitors

- **Rucaparib**
  - ARIEL3: maintenance therapy for platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer
  - ARIEL4: phase III study of rucaparib vs. chemotherapy for relapsed, BRCA mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
  - Ovarian cancer (+ anti-PDL1)

- **Niraparib**
  - Ovarian cancer (+ anti-PD1)
  - Recurrent ovarian cancer

Future Directions: New PARP Inhibitors

- **Talazoparib**
  - Ovarian cancer after prior PARP exposure
  - Ovarian cancer recurrence

- **Veliparib**
  - Ovarian cancer (+ topotecan)
  - Ovarian cancer (+ carboplatin/paclitaxel)
  - Ovarian cancer (+ liposomal doxorubicin/carboplatin/bevacizumab)
  - Ovarian cancer maintenance
  - Ovarian cancer recurrence

Conclusions

- Ovarian cancer remains a malignancy with a poor prognosis, particularly if diagnosed at a later stage
- PARP inhibition represents a novel treatment strategy for ovarian cancer, both in the recurrent and maintenance setting
- Further research into use of PARP inhibitors may change the landscape of treatment of ovarian cancer, and allow for potentially more treatment options

Reminder...

WOMEN'S CANCER ISN'T ALWAYS PINK

THIS SEPTEMBER, SPREAD AWARENESS FOR OVARIAN CANCER.
An Update on Ovarian Cancer with a Focus on PARP Inhibitors

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