“PARP”-ular Targeted Therapy in Advanced Ovarian Cancer Treatment

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August 7th, 2018
Objectives

• Describe the effect of the BRCA gene mutation on ovarian cancer prognosis and treatment options

• Define the patient that would benefit from the addition of bevacizumab to their treatment regimen for ovarian cancer

• Identify which PARP-inhibitor may be the best option for a patient’s ovarian cancer treatment
Ovarian Cancer Epidemiology

- 2.5% of all malignancies among females
- 1 in 70 women will develop ovarian cancer in their lifetime
- Fifth highest cause of cancer-related death in women
- 75% of women present with advanced disease
  - Due to absence of specific symptoms and lack of effective early detection strategies

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>92.3%</td>
</tr>
<tr>
<td>Stage II</td>
<td>74.5%</td>
</tr>
<tr>
<td>Stage III</td>
<td>42.0%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>29.2%</td>
</tr>
</tbody>
</table>
Presentation of Ovarian Cancer

- Median age at diagnosis is 63 years old
- Early stage has no obvious symptoms
  - Screening efficacy has not been proven
- Advanced disease
  - Abdomen swelling (ascites)
  - Non-specific: Back pain, abdominal distension, pelvic pain, altered bowel habits, urinary urgency
- Tissue biopsy confirms diagnosis
  - 90% of epithelial origin (cells surrounding ovary)
- Surgery confirms staging/extent of disease
Tumor Staging

Stage I
Tumor confined to ovaries or fallopian tubes

Stage II
Tumor spreads within the pelvic region

Stage III
Tumor spreads to peritoneum outside the pelvis and/or metastasis to retroperitoneal lymph nodes

*Typical stage of diagnosis*

Stage IV
Tumor spreads beyond the peritoneum and includes distant metastases
Risk Factors

Increased Risk

- Early menarche, older age at menopause
- Post-menopausal hormone use
- Genetics/family history of breast or ovarian cancer
- Obesity

Decreased Risk

- Oral contraceptive use in women <65
- 20% decrease with first birth, 10% decrease with each birth thereafter
- Oophorectomy, hysterectomy, tubal ligation

Torre, et al. CA Cancer J Clin 2018
Genetics

• BRCA1, BRCA2 (Breast cancer type susceptibility protein) – 17% germline and 8.7% somatic
  • Encode proteins necessary for DNA repair
  • Associated with early age of disease onset

• BRCA2 mutation increases sensitivity to treatment leading to improved survival – positive prognostic factor
  • Platinum agents
  • PARP inhibitors

Neff et al. Ther Adv Med Oncol 2017;9(8):519-531
Treatment for Advanced Stage Disease

Primary Surgical Cytoreduction (De-bulking surgery)

Combination Chemotherapy

Platinum Agent: Carboplatin or Cisplatin

Taxane Agent: Paclitaxel or Docetaxel

Every 3 weeks x 6 cycles

Observation

Recurrence

• >80% of advanced-stage ovarian cancer will experience recurrence
  • Generally incurable therefore goal is to maintain quality of life and prolong progression free survival

• Factors influencing treatment choice:
  • Disease burden, complications from previous chemo, organ function, BRCA status, patient goals (quality of life), platinum agent sensitivity
    • <6 months since treatment = platinum resistant
    • >6 months since treatment = platinum sensitive

• Historical strategy – additional/different chemotherapy
Targeted Agents

- Novel mechanisms of action
- Goal: to help lower the recurrence rate and lengthen the time between progression episodes
- Bevacizumab – initial therapy and maintenance
- PARP Inhibitors – maintenance therapy, recurrent treatment
Question 1

How does having a BRCA2 mutation affect survival and effectiveness of PARP inhibitors?

• A. Increases survival, PARP inhibitors less effective
• B. Increases survival, PARP inhibitors more effective
• C. Decreases survival, PARP inhibitors less effective
• D. Decreases survival, PARP inhibitors more effective
Bevacizumab
Bevacizumab: Vascular Endothelial Growth Factor (VEGF) Inhibitor

- Blood vessel
- Tumor Cells
- Oxygen
- Nutrients
- VEGF

Bevacizumab [package insert]. San Francisco, CA: Genetech, Inc; 2018
Bevacizumab: Vascular Endothelial Growth Factor (VEGF) Inhibitor

= Bevacizumab

Blood vessel

Tumor Cells

Bevacizumab [package insert]. San Francisco, CA: Genetech, Inc; 2018

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Adverse Events and Monitoring

Black Box Warnings
- Delayed wound healing – hold for 28 days prior to elective surgery
- GI perforations (0.3-3% incidence)
- Hemorrhage – potentially fatal

Other adverse effects
- Hypertension (19-42%)
- Thromboembolism
- Bleeding (epistaxis, GI, CNS)
- Proteinuria, nephrotic syndrome

GI = gastrointestinal
CNS = central nervous system
Bevacizumab (Avastin®) - Indications

Ovarian Cancer – Initial Treatment
*New indication as of June 2018*

Carboplatin + Paclitaxel + Bevacizumab 15mg/kg
every 3 weeks x 6 cycles

Bevacizumab 15mg/kg every 3 weeks x 22 cycles or disease progression

Maintenance

x 6 cycles
Trials that led to Bevacizumab FDA approval in ovarian cancer

ICON7 Trial
NEJM December 2011

GOG-0218 Trial
NEJM December 2011

European Approval 2011

FDA Approval 2018

Perren, et al. NEJM 2011;365:2484-96
Burger, et al. NEJM 2011;365:2473-83
# Phase III Trial Comparison

<table>
<thead>
<tr>
<th></th>
<th>ICON7</th>
<th>GOG-0218</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td><strong>Open-label</strong>, randomized, two-armed</td>
<td>Randomized, <strong>double-blind</strong>, placebo controlled, three-armed</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>• 1528 women, 11 countries</td>
<td>• 1873 women, four countries</td>
</tr>
<tr>
<td></td>
<td>• Newly diagnosed ovarian cancer</td>
<td>• Newly diagnosed ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>• High-risk <strong>early stage disease</strong> (none residual) or more advanced (stage Iib-IV)</td>
<td>• **Stage III (incompletely resectable) or stage IV epithelial ovarian cancer</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>• Carboplatin + paclitaxel every 3 weeks x 6 cycles</td>
<td>• Carboplatin + paclitaxel every 3 weeks x 6 cycles</td>
</tr>
<tr>
<td></td>
<td>• Same + Bevacizumab 7.5mg/kg (+12 more weeks)</td>
<td>• Same + Bevacizumab 15mg/kg (+16 more weeks)</td>
</tr>
</tbody>
</table>

Perren, et al. NEJM 2011;365:2484-96
Burger, et al. NEJM 2011;365:2473-83
## Phase III Trial Comparison (continued)

<table>
<thead>
<tr>
<th></th>
<th>ICON7</th>
<th>GOG-0218</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1° - PFS</strong></td>
<td>• 19.8 vs. 17.4</td>
<td>• 14.1 vs. 10.3</td>
</tr>
<tr>
<td></td>
<td>• HR 0.87, p=0.004</td>
<td>• HR 0.717, p&lt;0.001</td>
</tr>
<tr>
<td><strong>2° - OS</strong></td>
<td>• OS: Not significant</td>
<td>• OS: Not significant</td>
</tr>
<tr>
<td></td>
<td>• OS high risk: 39.7 vs. 30.2</td>
<td>• No significant differences</td>
</tr>
<tr>
<td></td>
<td>• HR 0.78, p=0.03</td>
<td>in quality of life scoring</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>• 4 deaths related to GI perforation,</td>
<td>• Fatal ADE in 14 patients</td>
</tr>
<tr>
<td></td>
<td>intracerebral hemorrhage</td>
<td>• Proteinuria, GI perforation,</td>
</tr>
<tr>
<td></td>
<td>• 66% vs. 56% had grade 3-4 ADE (HTN,</td>
<td>were similar between groups but higher than</td>
</tr>
<tr>
<td></td>
<td>bleeding, thrombosis, GI perforations)</td>
<td>ICON7 trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HTN significant (but only 2.4% led to D/C)</td>
</tr>
</tbody>
</table>

PFS = progression free survival  
OS = overall survival  
HR = hazard ratio  
ADE = adverse events  
HTN = hypertension  
Perren, et al. NEJM 2011;365:2484-96  
Burger, et al. NEJM 2011;365:2473-83
Bevacizumab Clinical Application

- Seems to benefit patients with more advanced ovarian cancer (stage III-IV) as an initial therapy
  - Potentially related to ascites formation in this population
- Caution with timing of surgery
- Not for use in patients at risk for GI perforation
  - Potentially not good for patients at high risk of bleeding
  - Trials excluded patients with uncontrolled HTN
- Questions remain
  - Dose (7.5 vs. 15mg/kg), optimal duration, cost-effectiveness of adding to standard therapy

Question 2

Which of these patients would benefit most from the addition of bevacizumab to their treatment?

• A. Newly diagnosed stage II, no residual disease after de-bulking surgery
• B. Stage IV, just completed 6 cycles of carboplatin/paclitaxel, in remission
• C. Newly diagnosed stage III, estimated creatinine clearance 30 mL/min
• D. Newly diagnosed stage IV, BP 161/90 on amlodipine and lisinopril
PARP (poly ADP ribose polymerase) Inhibitors
PARP Inhibitors Mechanism of Action

Normal DNA

- PARP Enzyme

Cancer Cell with PARP inhibitor

- PARP Enzyme
- BRCA
- PARP Inhibitor

2 unrepaired DNA strand breaks = cell death
FDA Approval of PARP Inhibitors

- **Olaparib (Lynparza®)**
  - FDA approved in 2014 for treatment of **BRCA-mutated** with at least 3 prior chemo treatments
  - FDA approved Aug 2017 (SOLO-2)

- **Rucaparib (Rubraca®)**
  - FDA approved in 2016 for treatment of **BRCA-mutated** with at least 2 prior chemo treatments
  - FDA approved April 2018 (ARIEL3)

- **Niraparib (Zejula®)**
  - FDA approved March 2017 (NOVA)
  - Maintenance therapy in recurrent ovarian cancer that is in a complete or partial response to platinum-based chemotherapy (Regardless of BRCA status)
  - NCCN recommends at least 2 prior platinum-based therapies
Olaparib SOLO2/ENGOT-Ov21 Trial

- Randomized, double-blind, placebo-controlled, phase 3

Platinum sensitive, high-grade, ovarian cancer, two prior treatments with complete or partial response *BRCA mutation required*

Randomize

2:1

N=196

Olaparib 300mg BID

N=99

Placebo

Continued until disease progression or toxicity

Allowed dose interruptions for up to 14 days

Up to 2 dose reductions allowed for grade 3/4 ADE (50mg intervals)

ADE = adverse events

SOLO2 Outcomes (Olaparib)

### Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Olaparib vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression free survival (PFS) months</td>
<td>19.1 vs. 5.5</td>
</tr>
<tr>
<td></td>
<td>HR 0.30, p&lt;0.001</td>
</tr>
</tbody>
</table>

### Safety

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 ADE</td>
<td>36% (anemia)</td>
<td>18%</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>25%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>11%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Conclusion:** Olaparib showed a significantly increased progression free survival when used for maintenance therapy in platinum-sensitive patients with a BRCA-mutation and 2 prior treatments.
Rucaparib ARIEL3 Trial

- Randomized, double-blind, placebo-controlled, phase 3

Platinum sensitive, high-grade, ovarian cancer, two prior treatments with complete or partial response

Randomize

2:1

N=372
Rucaparib 600mg BID

N=189
Placebo

Stratified based on genetic status (BRCA mutation)

Continued until disease progression or toxicity
Up to 2 dose reductions allowed for grade 3/4 ADE (120mg intervals)
### ARIEL3 Outcomes (Rucaparib)

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>BRCA-mutation only</th>
<th>Intent-to-treat population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression free survival (PFS) months</td>
<td>16.6 vs. 5.4 in placebo HR 0.23, p&lt;0.001</td>
<td>10.8 vs. 5.4 in placebo HR 0.36, p&lt;0.001 <em>Included BRCA mutations</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety</th>
<th>Rucaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 ADE</td>
<td>56% vs. 15% (thrombocytopenia, anemia, increased LFTs)</td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>55%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Conclusion: Rucaparib showed a significant increase in PFS in patients with platinum-sensitive, advanced ovarian cancer, with at least partial response to 2 prior treatments regardless of BRCA status.  
*Of note, no analysis done in only non-BRCA mutation patients*  
*Dose-adjustments in >50% of patients*
Niraparib NOVA Trial

- Randomized, double-blind, placebo-controlled, phase 3

Platinum sensitive, high grade, ovarian cancer, two prior treatments with complete or partial response

BRCA mutation
2:1

N=136
Niraparib 300mg

N=65
Placebo

N=231
Niraparib 300mg

N=114
Placebo

No mutation
2:1

Continued until disease progression or toxicity

Dose reductions allowed for hematologic toxicity

BRCA = Breast cancer susceptibility gene

### NOVA Outcomes (Niraparib)

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>BRCA-mutation</th>
<th>No mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Survival (PFS) - months</td>
<td>21.0 vs. 5.5</td>
<td>9.3 vs. 3.9</td>
</tr>
<tr>
<td></td>
<td>HR 0.27, p&lt;0.001</td>
<td>HR 0.45, p&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety</th>
<th>Niraparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reduction</td>
<td>66.5%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>14.7%</td>
<td>2.2%</td>
</tr>
<tr>
<td>QOL survey</td>
<td>Similar QOL scores</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Niraparib significantly prolonged progression free survival in platinum-sensitive, recurrent ovarian cancer patients, regardless of BRCA-mutation presence.

*Dose reductions in >50%*

QOL = quality of Life

# PARP Inhibitor Comparison

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>300mg BID</td>
<td>600mg BID</td>
<td>300mg <strong>daily</strong></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Major CYP3A4 substrate (mainly hepatic)</td>
<td>Minor substrate of CYP2D6,1A2 and 3A4 (mainly hepatic)</td>
<td>Carboxylesterases metabolize to inactive metabolite</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td><em>Carboxylesterases</em></td>
<td><em>Carboxylesterases</em></td>
<td><em>Carboxylesterases</em></td>
</tr>
<tr>
<td><strong>Organ Function</strong></td>
<td><strong>CrCl 31-50:</strong> 200mg BID</td>
<td><strong>CrCl≤30:</strong> not studied</td>
<td><strong>CrCl≤30:</strong> not studied</td>
</tr>
<tr>
<td><strong>Common Toxicities</strong></td>
<td>Myelosuppression, &lt;2% risk AML or MDS (hematologic toxicity), Nausea/Vomiting (moderate emetic potential)</td>
<td>Myelosuppression, &lt;2% risk AML or MDS (hematologic toxicity), Nausea/Vomiting (moderate emetic potential)</td>
<td>Myelosuppression, &lt;2% risk AML or MDS (hematologic toxicity), Nausea/Vomiting (moderate emetic potential)</td>
</tr>
<tr>
<td><strong>Unique Toxicities</strong></td>
<td>• SCr increase</td>
<td>• SCr increase</td>
<td>• Palpitations, hypertension</td>
</tr>
<tr>
<td></td>
<td>• Pneumonitis (2%)</td>
<td>• LFT increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &gt;20% risk nasopharyngitis and URTI</td>
<td>• Cholesterol increase</td>
<td></td>
</tr>
</tbody>
</table>
PARP Inhibitors Summary and Clinical Implications

• Oral, maintenance monotherapy option in platinum-sensitive patients
  • Use regardless of BRCA status, but better in BRCA-mutated patients
  • Unique toxicities for each drug

• Questions still remaining
  • Comparative efficacy?
  • Cross-resistance?
  • Optimal length of treatment? Best place in course?
  • Combinations with other agents?
    • Caution with over-lapping myelosuppression
Question 3

Which PARP inhibitor would be best for a patient on a strong CYP3A4 inducer and concern for liver dysfunction?

• A. Olaparib
• B. Rucaparib
• C. Niraparib
• D. Any of the above
Conclusion

- Targeted therapy offers novel mechanisms of action for the treatment of advanced ovarian cancer
- Carefully selecting a drug based on patient specific factors and goals of care will be important to gaining full benefit from these drugs
Questions & Discussion
Supplemental Slides
Basic Tumor Staging

- T (tumor), N (lymph nodes), M (metastases)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (T)</td>
<td>Tumor confined to ovaries or fallopian tubes</td>
</tr>
<tr>
<td>II (T – extensive)</td>
<td>Tumor involves one/both ovaries or fallopian tubes with pelvic extension below the pelvic brim or primary peritoneal cancer</td>
</tr>
<tr>
<td>III (T, N)</td>
<td>Spread to peritoneum outside the pelvis and/or metastasis to retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>IV (T, N, M)</td>
<td>Distant metastasis excluding peritoneal metastases</td>
</tr>
</tbody>
</table>
Classification by Cell/Site of Origin

Ovarian Cancer

- Non-epithelial (10%)
- Epithelial (various histologies) (90%)

Type I
- Large, unilateral, cystic tumors with indolent behavior

Type II
- Usually both ovaries, extraovarian disease and ascites, aggressive, low survival

~70% of cancers
Classification

• Cell/site of origin, pathologic grade

• 90% - epithelial cancer
  • Tumor cell histology: serous (52%), endometrioid (10%), mucinous (6%), clear cell (6%), unspecified (25%)

• Epithelial malignancies grouped as type I or type II
  • Type I usually large, unilateral, cystic tumors with indolent behavior – low grade
  • Type II has genetic instability
    • High grade, usually involve both ovaries, aggressive, late stage at diagnosis, low survival
    • Usually present with extraovarian disease and ascites
    • Usually high grade serous carcinomas – most common type diagnosed
Bevacizumab Cost-considerations

- AWP = $233.25 for a 400mg vial
  - 15mg/kg x 70kg = ~1200mg → ~$700 per cycle

- Pharmacoeconomic studies have not found the addition of bevacizumab to primary therapy + maintenance to be cost-effective due to the lack of overall-survival benefit found
  - Cost of standard therapy= $2.5 million
  - Adding Bevacizumab = $78.3 million
    - Additional $401,088 per progression free year of life saved (ICER per PF-LYS)

ICER = incremental cost-effectiveness ratios
PF-LYS = progression free year of life saved
Chan et al. The Oncologist 2014;19:523-527
Cost Considerations – PARP Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost (Average Wholesale Price)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>$138.86 for a 150mg tablet 300mg BID x 28 days = $15,552.32 monthly</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>$147.02 for a 300mg tablet 600mg BID x 28 days = $16,466.24 monthly</td>
</tr>
<tr>
<td>Niraparib</td>
<td>$212.40 for a 100mg tablet 300mg daily x 28 days = $17,841.60 monthly</td>
</tr>
</tbody>
</table>

- Not found to be cost-effective in pharmacoeconomic studies

Smith et al. Gynecologic Oncology 2015;139:59-62
Liu et al. Gynecologic Oncology Abstracts 2018;124:9