Managing Recurrence

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Recurrent Ovarian Cancer
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Disclosures

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  University of New Mexico Comprehensive Cancer Center
Outline

1. What are the chances that ovarian cancer will return after initial treatment?
2. What symptoms might suggest recurrent disease?
3. How is a recurrence diagnosed or confirmed?
4. What treatment options are available and what factors affect decisions about which to choose? *update on PARP-inhibitors and immune therapy*
5. Are there benefits to enrolling in a clinical trial?
Ovarian cancer subtypes

- Most ovarian cancers arise from the lining of the ovary – the epithelial layer.
- Cancers arising from germ cells (eggs) or stromal cells are less common.
- In this presentation, I will focus on epithelial cancers (ovarian, tubal, peritoneal).
Ovarian cancer subtypes

- Accumulating data indicates that serous ovarian cancers may actually develop in the fallopian tubes and then spread to the ovary.
Initial treatment: *curative intent*

Primary treatment:
- Debulking or cytoreductive surgery
- Chemotherapy
  - Neo-adjuvant chemotherapy (chemotherapy before surgery)
  - Primary adjuvant chemotherapy (chemotherapy after surgery)
**Initial treatment: curative intent**

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[Maintenance therapy: ongoing chemotherapy to reduce the risk of recurrence]
PARP-inhibitor maintenance therapy

- Improved progression-free survival in women with and without germline BRCA mutations
- Improved “PFS2” – survival in response to second-line chemotherapy

### Initial treatment: *curative intent*

#### Primary treatment:
- Debulking or cytoreductive surgery
- Chemotherapy
  - Neo-adjuvant chemotherapy (chemotherapy before surgery)
  - Primary adjuvant chemotherapy (chemotherapy after surgery)

[Maintenance therapy: ongoing chemotherapy to reduce the risk of recurrence]

#### Cancer surveillance:
- 3-month intervals for two years
- 4-month intervals for the third year
- 6-month intervals for up to 10 years
What are the chances that ovarian cancer will return after initial treatment?
Ovarian cancer recurrence

Approximate Percentage of Recurrence

Stage I

Stage II

Stage III (optimal)

Stage III (suboptimal)

Stage IV

Approximate Percentage of Recurrence
What symptoms might suggest recurrent disease?
Symptoms associated with ovarian cancer recurrence

- Bloating, abdominal fullness, increased girth, indigestion
- Pelvic pain
- Change in bowel or bladder habits
- Early satiety
- Vaginal discharge or bleeding
- Pain with intercourse
- Lymphedema / leg swelling
- Shortness of breath
- Nausea, vomiting

*Any new or persistent symptoms should be reported to your oncologist*
How is a recurrence diagnosed or confirmed?
Physical exam

- Physical exam
  - Evaluation of lymph nodes
  - Chest exam for pleural fluid
  - Abdominal exam for masses, fullness, fluid accumulation, pain
  - Pelvic exam for masses or nodularity
  - Extremities for swelling, tenderness, range of motion

- 35% who presented with symptoms had a normal physical exam
CA125

• 61% of women are diagnosed with recurrence based on an elevated CA125 level

  – Rises in CA125 may precede symptomatic relapse by a median of 4.5 months (range 0.5-29.5 months)

  – Doubling of CA125 has a sensitivity of 86% and a specificity of 91% for detecting progression.

  – A second confirmatory value reduces the false-negative rate to <2%.

  – Even a rise within the normal range is associated with a high risk of relapse.
Imaging

- CT or MRI scan can be used to evaluate for recurrence
  - Imaging is indicated in response to new symptoms or a rise in CA125
  - Sensitivity ranges from 40-93%
  - It may be difficult to detect peritoneal or serosal disease

- PET sensitivity of 88-90%

- Directed biopsy may be performed to confirm recurrence
What treatment options are available and what factors affect decisions about which to choose?
Treatment goals for recurrent disease

- Recurrent ovarian cancer is unlikely to be cured with currently available chemotherapeutics, radiation or surgery.

**Goal of treatment in the setting of recurrent disease is to prolong disease-free and overall survival and to palliate symptoms**

- Options include surgery, chemotherapy, targeted therapeutics, immune therapy, hormones, radiation, observation
Surgery

• Secondary (or tertiary) debulking surgery
  – Rationale is based on benefit seen with primary debulking
  – Studies of secondary surgery are limited by patient selection

Generally, surgery is reserved for women with:
• Platinum-sensitive disease
• Limited sites of recurrence
• Long treatment-free intervals (>24 mos)
• Absence of ascites
• Good performance status

• As with primary surgery, the best outcomes are seen in patients who can be optimally debulked

• Minimally invasive options (robotic or laparoscopic surgery) may reduce morbidity for eligible women
Chemotherapy

• Most patients do respond to second-line chemotherapy

• Response to second-line chemotherapy is predicted by:
  
  – Tumor type, size, and number of disease sites
  
  – Duration of response to previous platinum-based regimen, platinum-free interval and treatment-free interval (TFI)
    • TFI <12 mos: Response Rate 24-35%
    • TFI >12 mos: Response Rate 52-62%
Platinum sensitivity

Most women with ovarian cancer receive a platinum drug (carboplatin, cisplatin, oxaloplatin) as part of their primary chemotherapy regimen.

The time to recurrence after platinum treatment determines “platinum sensitivity”

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<th>Response to platinum</th>
<th>Likely secondary treatment</th>
<th>Examples</th>
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<td>Platinum sensitive</td>
<td>&gt;6 months without recurrence</td>
<td>Another platinum-based regimen</td>
<td>Carboplatin alone or in combination with another drug</td>
</tr>
<tr>
<td>Platinum resistant</td>
<td>&lt; 6 months until recurrence</td>
<td>A non-platinum drug</td>
<td>Doxil, Taxol, Gemzar, Topotecan</td>
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<td>Platinum refractory</td>
<td>Failure to achieve remission</td>
<td>A non-platinum drug</td>
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Clinical trials in **platinum-sensitive** patients with recurrent ovarian cancer

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<th>Study (number of patients)</th>
<th>Agents</th>
<th>Response Rate (%)</th>
<th>Median progression free survival (months)</th>
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<td>ICON 4 (802)</td>
<td>Carboplatin Carboplatin + Taxol</td>
<td>54% 66%</td>
<td>9 12*</td>
<td>24 29*</td>
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<td>AGO (366)</td>
<td>Carboplatin Carboplatin + Gemcitabine</td>
<td>31% 47%</td>
<td>5.8 8.6*</td>
<td>17.3 18</td>
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<td>CALYPSO (976)</td>
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<td>OCEANS (484)</td>
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<td>57% 79%</td>
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Response rates to second-line treatment are high among women with platinum – sensitive disease.

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Platinum-sensitive patients are usually treated with another platinum-containing regimen – often carboplatin in combination with a second drug.

Most-frequently used agents in **platinum-resistant disease**

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<tr>
<th>Agent</th>
<th>Response Rate (%)</th>
<th>Median progression free survival (months)</th>
<th>Median overall survival (months)</th>
<th>Side effects</th>
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<tr>
<td>Doxil</td>
<td>10-20%</td>
<td>3-4</td>
<td>10-12</td>
<td>Hand-foot syndrome, mucositis</td>
</tr>
<tr>
<td>Topotecan</td>
<td>12-18%</td>
<td>3-4</td>
<td>10-12</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Taxotere</td>
<td>22%</td>
<td>3.5</td>
<td>12.7</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Gemzar</td>
<td>15%</td>
<td>4-5</td>
<td>11.8-12.7</td>
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</tr>
<tr>
<td>Etoposide</td>
<td>6-27%</td>
<td>4-5</td>
<td>10-11</td>
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<tr>
<td>Taxol</td>
<td>10-30%</td>
<td>4-6</td>
<td>13</td>
<td>Myelosuppression, neuropathy</td>
</tr>
<tr>
<td>Avastin</td>
<td>21%</td>
<td>4.7</td>
<td>17</td>
<td>Hypertension, blood clots</td>
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Because of the more limited prognosis associated with platinum-resistant disease, reducing toxicity becomes a primary goal, and typically single agent protocols are used.

Targeted agents

• Advantages:
  – Different (often more limited) toxicity profile
  – May be active in chemotherapy resistant disease
  – Better understood mechanism of action

• Bevacizumab (Avastin):
  – blocks blood vessel formation in tumors
  – Also has immune modulatory effects
  – response rate greater than 20% (6 mo PFS 28-40%)

• PARP-inhibitors:
  – block single-stranded DNA repair
  – best response is among women with BRCA gene mutations
  – response rates as high as 40% in recurrent EOC
PARP-inhibitors for recurrent ovarian cancer
Immune therapy

• Advantages:
  – Toxicity profile is different than cytotoxic chemotherapy
  – Adaptive effects and potential for long-term benefit

• Currently available primarily through clinical trials

• Examples:
  – Cancer vaccines
  – T cell therapy
  – Immune checkpoint blockade antibodies
A model for the induction of an anti-tumor T cell response
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A model for the induction of an anti-tumor T cell response
The goal of immune therapy is to amplify the anti-tumor T cell response.

Example: Tumor vaccines
The goal of immune therapy is to amplify the anti-tumor T cell response.

Examples:
Adoptive T cell therapy
CAR T cell therapy (Chimeric Antigen Receptor)
Immune checkpoint antibodies
Goals of immune therapy

• Elicit or boost an adaptive anti-tumor immune response

• Induce immune memory for protection against cancer recurrence

• Current interest in combining immune therapy with tumor-directed therapy or chemotherapy to optimize outcomes
Hormone therapy

• Advantages:
  – Lower toxicity
  – Oral administration

• Tamoxifen:
  – Response rate of 17-20% among women with recurrent ovarian cancer

• Fulvestrant (selective estrogen receptor modulator)
  – Maintained disease stability in 50-64% of patients, 30% at 90 days

• Aromatase Inhibitors
  – Modest objective RR of 8-15%, stability in 19-24%
  – Evidence for efficacy in low grade serous cancers
Radiotherapy

• Whole abdominal radiation therapy is associated with significant toxicity and has limited efficacy in the treatment of recurrent disease

• Localized radiation may be effective
  – Good for symptom control
  – Best for deposits in the pelvis, at the vaginal vault, on the abdominal wall.
  – Median remission of 4.8 months.
Observation -

*When should treatment be initiated?*

- Many oncologists believe that early diagnosis and treatment of recurrent disease improves outcomes for women with ovarian cancer
  - Better surgical outcomes
  - Smaller tumors are more susceptible to chemotherapeutics
  - Better symptom control
Observation -
*When should treatment be initiated?*

• Many oncologists believe that early diagnosis and treatment of recurrent disease improves outcomes for women with ovarian cancer
  – Better surgical outcomes
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• 2010 European study: *Does earlier treatment improve survival?*
When should treatment be initiated?

2010 European study: *Does earlier treatment improve survival?*

1442 women with ovarian cancer
- complete remission
- normal CA125 levels
- platinum-based primary chemotherapy.

Underwent CA125 testing every 3 months

529 experienced a doubling in CA125 and were randomized

265 assigned to the “early treatment” group
- Clinicians and patients notified of the rise in CA125
- Treatment initiated

264 assigned to “delayed treatment” group
- Clinicians and patients blinded to CA125 levels
- Treatment initiated when symptoms or clinical findings suggested recurrence

Evaluated for the length of treatment-free intervals, overall survival, and quality of life

*Rustin GJ, et al, Lancet 2010*
When should treatment be initiated?

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Evaluated for the length of treatment-free intervals, overall survival, and quality of life

Rustin GJ, et al, Lancet 2010
Results:

- No difference in overall survival
- Women in the early treatment group underwent more courses of chemotherapy
- Delayed treatment was associated with better quality of life scores.

Rustin GJ, et al, Lancet 2010
Are there benefits to enrolling in a clinical trial?
Standard health care vs. clinical trials

- **Standard health care**: interventions designed solely to enhance the well-being of the patient that have a reasonable expectation of success

- **Research (Clinical trial)**: an activity designed to test a hypothesis, permit conclusions to be drawn, develop or contribute to generalizable knowledge
Clinical Trials

• Oversight and protection of subjects
  – Institutional Review Boards (IRB)
    • Protect the rights and welfare of research subjects
    • Include members of the community
  – Informed consent
    • Benefits, risks and discomforts
    • Alternatives to participation
    • Must be voluntary and un-coerced

• Strategies to optimize results
  – Randomization
    • Process by which participants are assigned to treatment groups
    • Placebo control is optimal to evaluate new treatments
  – Blinding
    • Single-blind: treating physician knows but patient doesn’t
    • Double-blind: neither the treating physician nor the patient knows
## Goals of clinical trials

### Phase I Trials:
- Safety and tolerability
- Uncontrolled, unblinded
- Not randomized
## Goals of clinical trials

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<th>Phase IV Trials:</th>
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<td>post-marketing surveillance (safety)</td>
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### Benefits of clinical trials

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<th>Phase I trials</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<td>Access to newest therapeutic agents</td>
<td>Dose escalation may mean that a lower dose is given to early participants</td>
</tr>
<tr>
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<td>Usually not randomized or blinded</td>
<td>Primary outcome is safety and tolerability</td>
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<td>Smaller studies, results may be available sooner</td>
<td>May or may not be given with known active agents</td>
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<tr>
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<td>Protocol already tested in prior phase I/II with evidence of efficacy</td>
<td>Often randomized Often blinded</td>
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<td>Often given with active agents; control arm is usually standard treatment</td>
<td>Large scale studies – may take years to learn results</td>
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- **Additional benefits:**
  - Oversight by a team of physicians, nurses, study personnel – both locally and often at a national level
  - Expanded options for treatment
  - Benefit to other women with ovarian cancer by advancing our understanding of treatment options and cancer biology
Questions to ask if you are considering enrolling in a clinical trial:

- What is the scientific rationale for conducting the trial?
- What are the objectives of the trial?
- In what phase is the trial? How many participants will there be?
- What are the eligibility requirements?
- What is the intervention, and what is its duration and schedule?
- What are the possible risks, side effects and benefits?
- What medical tests and follow-up tests will participants undergo? How often?
- What are the endpoints (measurable outcomes that indicate an intervention’s effectiveness)?
- Who is sponsoring the trial?
- What is the contact information to inquire about the trial?
There are many options available to manage ovarian cancer recurrence

• Several factors affect choice of treatment including the presence of symptoms, response to prior treatment, availability of a clinical trial, patient preference

• Goal of treatment is to optimize quality of life and to prolong remission

• For more information about available clinical trials: www.ocrf.org/clinicaltrials
Thank you – questions?