From Research to Practice: What’s New in Gynecologic Cancers?

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Disclosure

• Speakers Bureau: AstraZeneca
Outline

• New cancer basics
• Ovarian cancer achievements
  – Surgical modifications
  – Chemotherapy and targeted therapy
• Cervical and endometrial cancer surgery
  – Robotic
  – Sentinel node sampling
• Targeted therapy for cervical cancer
• NCI Match trial
"I think you should be more explicit here in step two."
“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?”
- President Obama, January 30, 2015
• Cancer is an infectious disease
• Cancer is a disease of aging
• Cancer is an environmental disease

*Ultimately, all cancers are a genetic disease*
Genetic Basis of Cancer

• Germline mutations - inherited
• Somatic mutations - occur in individual cells after conception
• Cancer is caused by an accumulation of mutations that affect gene expression in a single cell
• Cancer is an immortalized cell line that no longer responds to the normal mechanism that control cell proliferation
Our concept of ovarian cancer until 2011
Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*

Importance to ovarian cancer, subtype 1

Lesser importance

Greater importance

Cancer gene status

Validated cancer genes

Unknown

Functional categories

- Protein transport
- Fibroblast growth factor
- Cytoskeletal
- Caspase pathway
- β-catenin signaling

HumanNet interaction score

Lower confidence

Higher confidence
Transformation of the Fallopian Tube Secretory Epithelium Leads to High-Grade Serous Ovarian Cancer in Brca;Tp53;Pten Models

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Documented preinvasive to invasive HGSOC
"Whoa! That was a good one! Try it, Hobbs — just poke his brain right where my finger is."
Ovarian Cancer: Surgical Treatment for Advanced Disease

• Significant survival advantage for women who are optimally cytoreduced
• Procedures may include:
  – *En bloc* resection of uterus, ovaries and pelvic tumor
  – Omentectomy
  – Bowel resection
  – Removal of diaphragmatic and peritoneal implants
  – Splenectomy, appendectomy
  – Possible intraperitoneal port placement
Ovarian Cancer: Survival by Residual Disease

GOG Protocols (PR) 52 and 97
MSK Experience

9/98 to 12/06

No gross 69
Residual $\leq 1$ cm 134
Residual $> 1$ cm 82

Chi et al Gynecol Oncol 2012
EORTC Neoadjuvant Chemotherapy Trial

- Randomization to primary debulking vs 3 cycles of therapy, surgery, and 3 more cycles
- 632 subjects with extensive St IIIc or St IV disease – lesions > 5 cm in 74% and > 10 cm in 62%
- Residual tumor ≤ 1 cm in 42% of primary surgical cases and in 81% following interval debulking
- PFS (median: 12 vs 12 mo) and OS (median: 29 vs 30 mo) were no different between the two groups
- Complete resection of all gross disease was the strongest predictor of survival for primary and interval surgery

Vergote, NEJM 2010
MRC CHORUS Trial

• Randomization similar to the EORTC trial
• 552 stage III/IV subjects randomized, 25% w/ stage IV
• Median tumor size: 8 cm, 20% WHO PS of 2 or 3
• Residual tumor burden
  – No gross dz: 16% primary surg vs 40% neoadjuvant
  – < 1 cm: 41% primary surg vs 75% neoadjuvant
• Fewer complications in the neoadjuvant arm
• No difference in median PFS (10.3 vs 11.7 mo) or median OS (22.8 vs 24.5 mo)
Ovarian Cancer Surgery
MD Anderson Cooper Protocol

• Goal: complete resection of gross disease
• Physical examination
• CT imaging of chest, abdomen and pelvis
  – Mesenteric implants are particularly ominous
  – Moderate or large pleural effusions – pleural implants
• Laparoscopic evaluation
  – Six item scoring system
  – If not a candidate for laparotomy, obtain a biopsy of the tumor and place an IV portacath
## Laparoscopic Scoring System

- **Laparoscopic Features**: 2 pts/finding

<table>
<thead>
<tr>
<th>Peritoneal Carcinomatosis</th>
<th>Omental Cake</th>
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<tbody>
<tr>
<td>Diaphragmatic Carcinomatosis</td>
<td>Bowel and/or Stomach Infiltration</td>
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<tr>
<td>Superficial <strong>Spleen</strong> &amp;/or Liver Carcinomatosis</td>
<td>Mesenteric retraction</td>
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</table>

- Preliminary study by Fagotti indicated that for a score ≥8, 100% could not be debulked

- Evaluation in Houston yielded an increase in complete resection with primary surgery from 20% to 88%
"We’ve found a mass. The good news is we have weapons of mass destruction."
Primary Chemotherapy for Ovarian Cancer

- **Primary therapy**
  - Carboplatin/taxane q3 wks x 6 cycles
  - Carboplatin q3 wks*/Taxol wkly x 6 cycles
  - Cisplatin/Taxol IV/IP q3 wks x 6 cycles

- Bevacizumab (Avastin) can be added to the IV regimens and is continued as consolidation therapy

- Response rate of approximately 80%

- 75% of patients will recur
Targeted Therapy

• ACTIONABLE

• Small molecule drugs (-ib)
  – Enter cells and interact with target proteins

• Monoclonal antibodies (-mab)
  – Bind to target proteins on surface of cancer cells so immune system can locate and destroy
Biomarkers: Functional Definitions

Prognostic Markers
- Correlate with disease outcome regardless of intervention
  - e.g. Clinical: stage, PS
  - e.g. Lab: LDH in non-Hodgkin’s lymphoma

Predictive Markers
- Predict outcome with specific therapy - match drugs with appropriate pts
  - e.g. KRAS mutations and anti-EGFR monoclonal antibodies in colorectal cancer

Pharmacodynamic Markers
- Confirm biologic activity
  - e.g. ↓ pERK with a targeted agent (such as a MEK inhibitor)
• Cancers secrete vascular endothelial growth factor (VEGF) to stimulate the development of new blood vessels
• Bevacizumab is an antibody that binds to VEGF to reverse angiogenesis
• Primary therapy: no effect on overall survival
Recurrent Ovarian Cancer—
Definition of Disease Sensitivity

Time to recurrence, months

PREVIOUS TREATMENT

Refractory

Resistant

Sensitive

Very sensitive
# NCCN Guidelines Version 2.2015
## Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

### ACCEPTABLE RECURRENCE THERAPIES (1 OF 2)\(^a\)

<table>
<thead>
<tr>
<th>Preferred Single Agents or Combinations</th>
<th>Cytotoxic Therapy (In alphabetical order)</th>
<th>Hormonal Therapy</th>
<th>Targeted Therapy</th>
<th>Radiation Therapy</th>
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</thead>
<tbody>
<tr>
<td><strong>Platinum-Sensitive Disease</strong>(^b,c)</td>
<td>Carboplatin(^1)</td>
<td></td>
<td>Bevacizumab(^d,e,17,18) Olaparib(^g,19,20)</td>
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<td>Carboplatin/docetaxel(^2,3)</td>
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<td>Carboplatin/gemcitabine(^1)</td>
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<td>Carboplatin/gemcitabine/bevacizumab(^d,e) (category 2B)(^4)</td>
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<td>Bevacizumab(^d,e,17,18) Olaparib(^g,19,20)</td>
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<td>Carboplatin/liposomal doxorubicin(^5) (category 1)</td>
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<td>Carboplatin/paclitaxel (category 1)(^6)</td>
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<td>Carboplatin/paclitaxel (weekly)(^7)</td>
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<td>Cisplatin(^6)</td>
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<td>Cisplatin/gemcitabine(^8)</td>
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<tr>
<td><strong>Platinum-Resistant Disease</strong></td>
<td>Docetaxel(^9)</td>
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<td>Bevacizumab(^d,e,17,18) Olaparib(^g,19,20)</td>
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<td></td>
<td>Etoposide, or(^a)(^10)</td>
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<td></td>
<td>Gemcitabine(^11,12)</td>
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<td>Liposomal doxorubicin(^11,12)</td>
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<td>Liposomal doxorubicin/bevacizumab(^d,e,13)</td>
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<td>Paclitaxel (weekly)(^14)</td>
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<td></td>
<td>Paclitaxel (weekly)/bevacizumab(^d,e,13)</td>
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<td>Topotecan(^15,16)</td>
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<td></td>
<td>Topotecan/bevacizumab(^d,e,13)</td>
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<tr>
<td><strong>Other Potentially Active Agents</strong>(^f)</td>
<td><strong>Single Agents</strong>(^21)</td>
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<td></td>
<td>Altemisine</td>
<td>Melphalan</td>
<td>Aromatase inhibitors</td>
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<td></td>
<td>Capecitabine</td>
<td>Oxaliplatin</td>
<td>Leuprolide acetate</td>
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<td></td>
<td>Cyclophosphamide</td>
<td>Paclitaxel</td>
<td>Megestrol acetate</td>
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<tr>
<td></td>
<td>Doxorubicin</td>
<td>Paclitaxel, albumin bound (nab-paclitaxel)</td>
<td>Tamoxifen</td>
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<td></td>
<td>Ifosfamide</td>
<td>Pemetrexed</td>
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<td></td>
<td>Irinotecan</td>
<td>Vinorelbine</td>
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</table>
Antiangiogenesis Agents for Recurrent Ovarian Cancer

Table 2. Efficacy Comparisons: Angiogenesis Inhibitors in Platinum-Pretreated Ovarian Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>TRINOVA-1&lt;sup&gt;8&lt;/sup&gt;</th>
<th>AURELIA&lt;sup&gt;5,6&lt;/sup&gt;</th>
<th>OCEANS&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>trebananib + paclitaxel</td>
<td>paclitaxel</td>
<td>Avastin + Chemo</td>
</tr>
<tr>
<td>Platinum-Free Interval (PFI)</td>
<td>&lt; 12 months</td>
<td>&lt; 6 months</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>mPFS (months)</td>
<td>7.2</td>
<td>5.4</td>
<td>6.7</td>
</tr>
<tr>
<td>PFS HR, p-value</td>
<td>HR: 0.66, p&lt;0.001</td>
<td>HR: 0.48, p&lt;0.001</td>
<td>HR: 0.484, p&lt;0.001</td>
</tr>
<tr>
<td>mOS (months)</td>
<td>19.0</td>
<td>17.3</td>
<td>16.6</td>
</tr>
<tr>
<td>OS HR, p-value</td>
<td>HR: 0.86, p=0.19*</td>
<td>HR: 0.85, p=0.174</td>
<td>HR: 1.027*</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Edema, Ascites, Pleural Effusion</td>
<td>Hypertension, Proteinuria, GI Perforation</td>
<td>Hypertension, Proteinuria, Bleeding, Thromboembolic event</td>
</tr>
</tbody>
</table>

*Based on an interim analysis, data are not yet mature

Exploratory analysis of Aurelia results: wTaxol v. wTaxol/bev
PFS: 3.9 v 9.6 mo (HR 0.47 CI 0.31, 0.72)
OS: 13.2 v 22.4 mo (HR 0.64 CI 0.41, 1.01)
PARP Inhibitors: Mechanism of Action

Homologous Recombination
- BRCA1/2
- Rad51
- FA proteins
- XRCC3
- Others (PTEN)

DNA Damage

PARP1

NHEJ
- DNA-PK
- Artemis

Error-prone Repair

Error-free Repair

Cell Survival

• Genomic Instability
• Chromosome rearrangement

Cell Death

Modified from Patel, et al., PNAS (2011)
Study 19: Maintenance Olaparib

**Patient eligibility:**
- Platinum-sensitive high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy: platinum-based with a maintained response
- Stable CA125 at trial entry
- Randomization stratification factors:
  - Time to disease progression on penultimate platinum therapy
  - Objective response to last platinum therapy
  - Ethnic descent
- Primary ENDPOINT: PFS

**Treatment:**
- Olaparib
  - 400 mg po bid
- Placebo
  - po bid

Treatment until disease progression

Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer

- Patients were randomized after response to platinum-based chemotherapy

**Primary analysis**
(58% maturity; n=154/265)

PFS hazard ratio=0.35
(95% CI, 0.25–0.49)

\( P<0.00001 \)

*Patients were treated until disease progression


• Interim OS analysis (38% maturity): HR=0.94; 95% CI, 0.63–1.39; \( P=0.75 \)
Overall survival: interim analysis*

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Olaparib</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0.6</td>
<td>0.1</td>
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<td>3</td>
<td>0.8</td>
<td>0.2</td>
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<td>6</td>
<td>0.9</td>
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<td>9</td>
<td>0.7</td>
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<td>0.5</td>
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Hazard ratio 0.94
(95% CI, 0.63–1.39); P=0.75

Median OS (months): Olaparib 29.7, Placebo 29.9

At risk (n):
- Olaparib: 136, 132, 128, 124, 117, 109, 94, 79, 45, 24, 4, 0, 0
- Placebo: 129, 127, 120, 111, 108, 96, 86, 78, 44, 21, 3, 1, 0

38% events
67% planned

*Performed at 38% maturity

• 82% reduction in risk of disease progression or death with olaparib
OS in BRCAm patients

- Deaths: total pts (%)
  - Olaparib: 37:74 (50.0)
  - Placebo: 34:62 (54.8)

- Median OS, months
  - Olaparib: 34.9
  - Placebo: 31.9

- HR=0.74
  - 95% CI (0.46, 1.19)
  - P=0.208

- Number at risk
<table>
<thead>
<tr>
<th>Olaparib BRCAm</th>
<th>Placebo BRCAm</th>
</tr>
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<tbody>
<tr>
<td>74</td>
<td>62</td>
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<td>71</td>
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- OS in BRCAwt patients: HR=0.98; 95% CI, 0.62–1.55; P=0.946
  - Median OS: olaparib, 24.5 months; placebo, 26.2 months

- 14/62 (22.6%) placebo patients switched to a PARP inhibitor
ARIEL2: Evaluation of BRCAness Signature
Treatment of recurrent ovarian cancer with Rucaparib

The optimal companion diagnostic in ovarian cancer looks beyond gBRCA mutations

- Patients with germ-line (17%) and somatic (8%) BRCA mutations respond equally to rucaparib
- Tissue test (not blood) required to identify somatic mutations

- Tissue test also required to detect BRCAness (42%)
- Clovis developed a proprietary BRCAness signature
- Signature prospectively and successfully applied in an interim look at 200-patient ARIEL2 study
- Signature allows analysis of archival or fresh tissue – interesting differences observed
- Signature being applied prospectively in ARIEL3
- Foundation Medicine a key collaborator

RR 70%
RR 40%
RR 8%
Famous Robots From History
da Vinci Robot System
da Vinci Features
Minimally Invasive Surgery

**Benefits**
- Faster recovery with shorter hospitalization
- Less time to resumption of normal daily activities
- Decreased blood loss
- Less postoperative pain
- Improved cosmesis

**Robotic Advantages**
- 3-D visualization
- “Wristed” instruments with 7 degrees of freedom
- Natural movements
- Downscaling of surgeon’s movements (i.e., 3:1 ratio)
- Improved ergonomics
Management Early Stage Cervical Cancer
Radical hysterectomy – standard since mid1900’s
Associated with a high complication rate
GOG Study 278 – Cervical Cancer

- St Ia1 (LVSI) – Ib1 (≤2 cm), DOI ≤10 mm, clean margins
- Simple hysterectomy (cone biopsy if fertility desired) with pelvic lymph node dissection
- Risk for parametrial involvement with these parameters is <1% with a relapse rate of 4%. Our Cooper data corroborates this.
- This study assumes simple hysterectomy to be the equivalent of a radical hysterectomy in regard to disease control
- Purpose is to evaluate QOL parameters
Lymph Node Dissection for Endometrial Cancer
Mayo Clinic Criteria

• Frozen section criteria allowing omission of nodal dissection
  – Type I endometrial cancer
  – Grade 1 or 2 histology
  – <50% myometrial invasion
  – Gross lesion size ≤2 cm
  – Lesion confined to the uterine corpus
This concept is based on the orderly and sequential progression of tumor cells through the lymphatic system. The first set of nodes to receive drainage from a tumor are referred to as the sentinel nodes. If spread of disease has occurred, a sentinel node should be involved.
Sentinel Node Sampling

- Established in melanoma, breast and vulvar cancers
- Minimizes morbidity such as lymphedema associated with a full lymphadenectomy
- More accurate identification of the 10% of sentinel nodes in non-standard locations
- Radioactive tracer, blue dye or near-infrared fluorescence imaging (NIR) used
- Ongoing studies in cervical and uterine cancers demonstrate high sensitivity for nodal detection and a low false negative rate
Bevacizumab for Cervical Cancer
GOG 240

- 252 subjects randomized to either cisplatin/Taxol or Topotecan/Taxol +/- bevacizumab
- Improved PFS & OS with bevacizumab
- No difference was noted between the two chemo regimens
This precision medicine trial explores treating patients based on the molecular profiles of their tumors.

NCI-MATCH* is for adults with:
- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment

About 3,000 cancer patients will be screened with a tumor biopsy.

The biopsied tumor tissue will undergo gene sequencing.

Gene sequencing will look for changes in 143 genes.

*NCI-MATCH: National Cancer Institute's Cancer Targeted Medicine (CTM) Initiative
IF A PATIENT'S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH.

NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED.

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY.
Thank You