Survive and Thrive 2019

Framework for Understanding Rare Tumors in Ovarian Cancer

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Objectives:

- Understand basic classification of rare ovarian cancers
- Review incidence and unique features
- Treatment choices in first line treatment
- Surveillance options
- Role of tumor and somatic genetic testing
- Discuss advocacy for rare tumors

NO DISCLOSURES
Challenges and Opportunities for Rare Ovarian Cancers

- Challenge and frustration of having a rare type of an already rare tumor
- Fewer cases to review and learn
- Harder to accrue and complete clinical trials
- Funding for research
- Diversity of mutations in each cell type
- Opportunities for collaborative research and support networking
- Opportunities for targeted therapies
Not that simple

**Ovarian Cancer is not one disease**

Epithelial ovarian cancer
What is the Cell of origin?
- fallopian tube origin
- ovarian surface lining cells
- endometriosis
- lining of the peritoneal cavity

Epithelial Ovarian Cancers (EOC)

- 80% of ovarian cancers are EOC
  - 80% are Serous carcinomas

- Non EOC
  - Germ Cell Tumors
  - Sex Cord Stromal Tumors
  - Younger age
  - Better outcomes
Types of Ovarian Cancer

- Epithelial Ovarian Cancer
- Fallopian Tube Cancer
- Primary Peritoneal Cancer

5-8% of ovarian cancers

Surface epithelium-stroma
- Serous
- Mucinous
- Endometrioid
- Clear cell
- Transitional cell

Germ cells
- Dysgerminoma
- Yolk sac
- Embryonal carcinoma
- Choriocarcinoma
- Teratoma

Stage IIC Cancer

- Bladder
- Fallopian tube
- Uterus
- Ovary
- Sigmoid colon

Malignant cells in a peritoneal washing

~5%
Rare Ovarian Cancers

- Epithelial Ovarian Cancer (high grade serous) ~ 80%
- Malignant Ovarian Germ Cell Tumors 5%
- Sex Cord Stromal Tumors 1.2%
- Rare Epithelial Ovarian Cancers
  - Clear Cell Carcinoma
  - Endometrioid Carcinoma
  - Mucinous carcinomas
  - Low grade serous carcinomas
Cell types of epithelial ovarian cancers

These cell types may have differences in CLINICAL
• Clinical presentation
  • Age; symptoms
• Optimal treatment regimens
• Recurrence risk
• Response to treatment

BIOLOGIC/MOLECULAR
• Different molecular mutations
• Different pathways that are turned on or off that promote cancer development

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<thead>
<tr>
<th>Type</th>
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Framework:

- Treatment Options
  - Primary
  - Maintenance
  - Recurrence
- Follow-up and Surveillance
- Unique Genetics or tumor mutations
- Novel therapies or clinical trials

Use this framework to ask questions about your specific cancer
Malignant Germ Cell Tumors of the Ovary

- Dysgerminoma
- Yolk Sac Tumors
- Embryonal carcinoma
- Choriocarcinoma
- Immature teratoma
Sex Cord Stromal Malignant Ovarian Tumors 5-8%

- Adult granulosa cell tumor
- Juvenile granulosa cell tumor
- Sertoli-Leydig cell tumors 0.5% of ovarian cancers
- Sex cord tumor with annular tubules

- Indolent, slower growing
- Late recurrences
Sex Cord Stromal Tumors

- **Unique features**
  - Younger patients 20-30s
  - Can secrete hormones (estrogen or testosterone)
  - Average size 16 cm; pelvic mass at presentation

- **Treatment Options**
  - Primary: Surgery; Fertility sparing options; Chemotherapy
  - Recurrence: Repeat surgery; Chemotherapy

- **Follow-up and Surveillance**
  - Tumor markers
  - Decision regarding imaging

- **Unique Genetics**
  - Granulosa cell tumors: Tumor Mutation FOXL2 mutation
  - Sertoli-Leydig cell tumors: DICER 1 genetic mutation

- **Novel therapies or clinical trials**
  - GOG 264
DICER 1 – Hereditary Cancer Mutation

- Inherited germline mutation
- Sertoli-Leydig tumors
- Other cancers: pleuropulmonary blastoma, cervical sarcoma
Rare Epithelial Ovarian Cancers

- Endometrioid carcinoma (10 %)
- Clear cell carcinoma (5-10 %)
- Mucinous carcinoma (3-4 %)
- Low grade serous carcinoma (< 5%)
- Carcinosarcoma (2-5%)
- Transitional cell carcinoma (< 2%)
- Small cell carcinoma (< 3%)
Low grade serous carcinoma

- **Unique features**
  - Younger patients than average EOC
  - Better overall survival may be seen

- **Treatment Options**
  - **Primary**
    - Surgery; Fertility sparing options
    - Chemotherapy
  - **Stage II – IV**
    - Concern for chemoresistance
    - Consider Hormonal maintenance phase

  - **Recurrence**
    - Repeat surgery in select cases
    - Chemotherapy, ex. Doxil, Avastin

- **Follow-up and Surveillance**
  - Tumor markers: CA125
  - Decision regarding imaging

- **Unique Genetics or tumor characteristics**
  - Estrogen or Progesterone receptor positive, hormonal targets
  - Mutations in KRAS/BRAF/MAPK signaling pathway
  - Should get genetic testing but BRCA mutations less common ~5%

- **Novel therapies or clinical trials**
  - Avastin
  - Endocrine therapy
  - MEK inhibitors
Low grade serous carcinoma: Endocrine therapy Options

- Aromatase inhibitors
  - inhibits peripheral conversion of steroids to estrogen

- Tamoxifen
  - Selective estrogen receptor modulator (anti-estrogen effects)

- Fulvestrant (faslodex) - Fulvestrant
  - selective estrogen receptor degrader (SERD)
  - binds to the estrogen receptor and destabilizing it, causing the cell's normal protein degradation processes to destroy it.

- Leuprolide – GnRH agonist – chemical menopause
Low grade serous carcinoma: Biologics

- **Avastin**  The bevacizumab compound binds to the free VEGF and reduces the concentration of the free VEGF. C, The reduction of available VEGF results in diminished blood supply to the tumor and tumor shrinkage.
Low grade serous carcinoma: Targeted therapies

MEK Inhibitors

- GOG 239 Selumetinib, a MEK1/2 inhibitor with a response rate of 15%, with stable disease in 65% and an acceptable toxicity profile

- MILO Study
  - Phase 3 study of binimetinib or a chemotherapy chosen by a physician (liposomal doxorubicin, paclitaxel or topotecan)
  - Did not reach PFS improvement compared to advanced ovarian cancer

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Clear cell carcinoma

- **Unique features**
  - Perimenopausal age range
  - Can be associated with endometriosis
  - Risks of hypercalcemia, blood clots

- **Treatment Options**
  - **Primary**
    - Surgery;
    - Chemotherapy
  - **Concern for chemor esistance**
  - **Recurrence**
    - Chemotherapy
    - rare surgery for secondary

- **Follow-up and Surveillance**
  - Tumor markers
    - CA125
  - Decision regarding imaging

- **Unique Genetics or tumor characteristics**
  - **ARID1 A mutations**
  - **PIK3CA mutations** (noted in 40% of OCCC)
    - Targeting the phosphatidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) pathway

- **Novel therapies or clinical trials**
Clear Cell Carcinoma of the Ovary

- A Phase II Study of Tazemetostat (EPZ-6438) (IND # 138671) in Recurrent or Persistent Endometrioid or Clear Cell Carcinoma of the Ovary, and Recurrent or Persistent Endometrioid Endometrial Adenocarcinoma (CIRB) (NRG-GY014)

GOG trials:

- GOG 254-Phase II evaluation of Sunitinib Malate in the treatment of persistent of recurrent clear cell ovarian carcinoma (Closed to patient entry September 2013; late breaking abstract at 2015 SGO)

- GOG 268 A Phase II Evaluation of Temsirolimus (CCI-779) (NCI Supplied Agent: NSC# 683864, IND# 61010) in Combination with Carboplatin and Paclitaxel followed by Temsirolimus (CCI-779) Consolidation as First-line Therapy in the Treatment of Stage III-IV Clear Cell Carcinoma of the Ovary (Closed to patient entry January 2014)

- GOG 283: A Phase II Trial of DCTD-Sponsored Dasatinib (NSC #732517 IND #73969) in Recurrent/Persistent Ovary, Fallopian Tube, Primary Peritoneal, Endometrial, or Endometriosis-Associated Clear Cell Carcinoma Characterized for the Retention or Loss of BAF250a Expression. (suspended)

- GY-001: A randomized phase II study of XL-184 (cabozantinib) in recurrent clear cell carcinoma (Dr Farley)
  - (VEGFR2 inhibitor)
**Mucinous ovarian carcinoma**

- **Unique features**
  - Presents in early stage often
  - Larger tumors
  - Often can be mets from GI tumors

- **Treatment Options**
  - **Primary**
    - Surgery;
    - Chemotherapy
    - Concern for chemoresistance
  - **Recurrence**
    - Chemotherapy
    - Rare surgery for secondary

- **Follow-up and Surveillance**
  - Tumor markers: CEA
  - Decision regarding imaging

- **Unique Genetics or tumor characteristics**
  - KRAS mutations >75%

- **Novel therapies or clinical trials**
  - GI regimens may show promise
  - Avastin
  - HIPEC