Primary Mucinous Ovarian Cancer (PMOC)

Michael Frumovitz
Epithelial Subtypes

- Serous
- Endometrioid
- Mucinous
- Transitional
- Clear Cell
- Mixed
- Undifferentiated
- Squamous
Ovarian Surface Epithelium
Subclassification of Epithelial Ovarian Cancers

<table>
<thead>
<tr>
<th></th>
<th>Serous</th>
<th>Endometrioid</th>
<th>Mucinous</th>
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</tr>
</thead>
<tbody>
<tr>
<td>LMP</td>
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<tr>
<td>GR 1</td>
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<td>GR 2</td>
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<td>GR 3</td>
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Gilks, 2004
Landmark Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Mucinous</th>
<th>Regimen</th>
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<tbody>
<tr>
<td>GOG 111</td>
<td>3.4%</td>
<td>Cisplat and Cyclo vs. Cisplat and Paclitaxel</td>
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<td>OV-10</td>
<td>4.4%</td>
<td>Cisplat and Cyclo vs. Cisplat and Paclitaxel</td>
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<tr>
<td>GOG 132</td>
<td>2.6%</td>
<td>Cisplat vs. Paclitaxel vs. Cisplat and Paclitaxel</td>
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<tr>
<td>GOG 182</td>
<td>1.6%</td>
<td>5-arm, platinum-based regimens</td>
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Mucinous Epithelial Ovarian Cancer: A Separate Entity Requiring Specific Treatment

Viviane Hess, Roger A’Her, Nazar Nasiri, D. Michael King, Peter R. Blake, Desmond P.J. Barton, John H. Shepherd, T. Ord, J. Bridges, K. Harrington, Stanley B. Kaye, and Martin E. Gore

Abstract

Purpose
Invasive mucinous carcinoma of the ovary (mucinous epithelial ovarian cancer [mEOC]) is a histologic subgroup of epithelial ovarian cancer (EOC). Chemotherapy for mEOC is chosen according to guidelines established for EOC. The purpose of this study is to determine whether this is appropriate.

Patients and Methods
Women with advanced mEOC (International Federation of Gynecology and Obstetrics stage III or IV) who underwent first-line platinum-based chemotherapy were compared with women with other histologic subtypes of EOC in a case-controlled study.

Results
Eighty-one patients (27 cases, 54 controls) treated with platinum-based regimens were analyzed. The response rates for cases and controls were 26.3% (95% CI, 9.2% to 51.2%) and 64.9% (95% CI, 47.5% to 79.8%), respectively (P = .01). The odds ratio for complete or partial response to chemotherapy for mEOC was 0.19 (95% CI, 0.06 to 0.66; P = .009) compared with other histologic subtypes of EOC. Median progression-free survival was 5.7 months (95% CI, 1.9 to 9.6 months) versus 14.1 months (95% CI, 12.0 to 16.2 months; P < .001) and overall survival was 12.0 months (95% CI, 8.0 to 15.6 months) versus 36.7 months (95% CI, 25.2 to 48.2 months; P < .001) for cases and controls, respectively. The hazard ratio for progression and death was 2.94 (95% CI, 1.71 to 5.07; P < .001) and 3.08 (95% CI, 1.69 to 5.6; P < .001), respectively, for mEOC patients as compared with controls.

Conclusion
Patients with advanced mEOC have a poorer response to platinum-based first-line chemotherapy compared with patients with other histologic subtypes of EOC, and their survival is worse. Specific alternative therapeutic approaches should be sought for this group of patients, perhaps involving fluorouracil-based chemotherapy.
Stage III/IV Mucinous vs. Epithelial Ovarian Cancers

Median PFS (95% CI)
Mucinous 5.7 mos (1.9-9.6)
Control 14.1 mos (12-16.2)
$P < .001$

Hess et al., 2004
Stage III/IV Mucinous vs. Epithelial Ovarian Cancers

Median OS (95% CI)
Mucinous 12.0 mos (8.0-15.6)
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$P < .001$

Hess et al., 2004
Subclassification of Epithelial Ovarian Cancers

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</table>

Gilks, 2004
Microscopic Differences

Serous Carcinoma

Mucinous Carcinoma
Molecular Differences
Gene Expression Analysis

Matsuo et al., CCR, 2011
### Summary of Genetic Alterations

<table>
<thead>
<tr>
<th></th>
<th>Serous</th>
<th>Mucinuous</th>
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<tbody>
<tr>
<td>BRCA</td>
<td>64%</td>
<td>2%</td>
</tr>
<tr>
<td>P53</td>
<td>59%</td>
<td>16%</td>
</tr>
<tr>
<td>KRAS</td>
<td>5%</td>
<td>50%</td>
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Clinical Findings
# Incidence

<table>
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<th>Type</th>
<th>Literature</th>
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<tr>
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<tr>
<td>Mucinous</td>
<td>11%</td>
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<tr>
<td>Endometrioid</td>
<td>19%</td>
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<td>Clear Cell</td>
<td>7%</td>
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<tr>
<td>Transitional</td>
<td>&lt;1%</td>
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<tr>
<td>Mixed</td>
<td>4%</td>
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<tr>
<td>Undifferentiated</td>
<td>7%</td>
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## Incidence

<table>
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<th>Type</th>
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<th>WHC</th>
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<tr>
<td>Serous</td>
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<td>68%</td>
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<tr>
<td>Mucinous</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Transitional</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Mixed</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>7%</td>
<td>1%</td>
</tr>
</tbody>
</table>

WHC – Washington Hospital Center

Seidman et al., 2004
Literature’s Overestimation

1) Mistaken gastrointestinal primaries
Literature’s Overestimation

1) Mistaken gastrointestinal primaries
2) Overcalled mucinous borderline tumors
Literature’s Overestimation

1) Mistaken gastrointestinal primaries
2) Overcalled mucinous borderline tumors
3) Standardized classification of pseudomyxoma peritoneii as intestinal in origin
Literature’s Overestimation

1) Mistaken gastrointestinal primaries
2) Overcalled mucinous borderline tumors
3) Standardized classification of pseudomyxoma peritonei as intestinal in origin
4) Published literature mainly from referral centers
# Metastatic Disease to Ovary

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Gastrointestinal</td>
<td>45%</td>
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<tr>
<td>Pancreas</td>
<td>20%</td>
</tr>
<tr>
<td>Cervix</td>
<td>13%</td>
</tr>
<tr>
<td>Breast</td>
<td>8%</td>
</tr>
<tr>
<td>Uterus</td>
<td>5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>10%</td>
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</table>

Seidman et al., 2003
Mucinous Ovarian Cancer More Likely to Be Early Stage

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Stage I</th>
</tr>
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<tbody>
<tr>
<td>Mucinous</td>
<td>83%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>57%</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>36%</td>
</tr>
<tr>
<td>Serous</td>
<td>4%</td>
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</table>

Seidman et al., 2004
Lymph Node Dissection Likely Not Necessary in Early Disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Women with gross stage I disease</th>
<th>Number with nodal mets</th>
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<tbody>
<tr>
<td>Cho</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>Roger</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Schmeler</td>
<td>51</td>
<td>0</td>
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</table>
### Early Stage = Better Prognosis

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>n</th>
<th>OS (mo)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>1407</td>
<td>34</td>
<td>1.00</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>154</td>
<td>31</td>
<td>0.96</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>207</td>
<td>66</td>
<td>0.59</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>607</td>
<td>65</td>
<td>0.55</td>
</tr>
<tr>
<td>Mucinous</td>
<td>473</td>
<td>70</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Ji et al., 2008
Early Stage, Less Recurrence

- Stage I/II Recurrence Rates
  - Mucinous: 13%
  - Serous: 30%

\[ p = 0.009 \]

- OR for Recurrence: 0.33

Matsuo et al., CCR, 2011
## Stage at Presentation

<table>
<thead>
<tr>
<th>Type</th>
<th>Stage I</th>
<th>Stages II-IV</th>
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<tbody>
<tr>
<td>Mucinous</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>Mixed</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>7%</td>
<td>94%</td>
</tr>
<tr>
<td>Serous</td>
<td>4%</td>
<td>96%</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Seidman et al., 2004
Late Stage, Less Survival

- Stage III/IV
- No difference in PFS
- Median OS
  
  Mucinous: 1.7 years  
  Serous: 3.4 years  

\[ p = 0.002 \]

Matsuo et al., CCR, 2011
PMOC are Platinum Resistant

Median PFS (95% CI)
Mucinous 5.7 mos (1.9-9.6)
Control 14.1 mos (12-16.2)
P < 0.001

Hess et al., 2004
PMOC are Platinum Resistant

Median OS (95% CI)
Mucinous 12.0 mos (8.0-15.6)
Control 36.7 mos (25.2-48.2)

\( P < .001 \)

Hess et al., 2004
PMOC are Platinum Resistant

- Stage III epithelial ovarian cancer
- Six GOG studies of primary surgery followed by cisplatinum + paclitaxel
- 1,895 total patients
  - Serous 74%
  - Endometrioid 9%
  - Clear cell 3%
  - Mucinous 2%
  - Mixed 8%

Winter et al., 2007
PMOC are Platinum Resistant

Progression Free Survival

Winter et al., 2007
PMOC are Platinum Resistant

Overall Survival

Winter et al., 2007
**PMOC are Platinum Resistant**

Response to chemotherapy of mucinous and serous adenocarcinoma of the ovary

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous (n = 24)</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>14</td>
<td>12.5%</td>
</tr>
<tr>
<td>Serous (n = 189)</td>
<td>54</td>
<td>74</td>
<td>34</td>
<td>27</td>
<td>67.7%</td>
</tr>
</tbody>
</table>

Shimada *et al.*, 2009
Recurrent MOC are Platinum Resistant

<table>
<thead>
<tr>
<th></th>
<th>Mucinous (n=20)</th>
<th>Others (n=388)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Response</td>
<td>36%</td>
<td>63%</td>
<td>0.04</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>4.5</td>
<td>8</td>
<td>0.03</td>
</tr>
<tr>
<td>OS (months)</td>
<td>17.9</td>
<td>28.8</td>
<td>0.003</td>
</tr>
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</table>

Pignata et al., 2008
Clinical Trial
GOG-0241 Schema

Stage II-IV or recurrent stage I PMOC

RANDOMIZE

Carbo/paclitaxel x 6 cycles
- No Bev
- + Bev
  - Bevacizumab Consolidation x 12 mo

Capecitabine/oxaliplatin x 6 cycles
- + Bev
- No Bev
5-FU/Oxaliplatin in Cell Lines

• Five PMOC cell lines
• Evaluated:
  – Cisplatinum
  – Paclitaxel
  – 5-FU
  – Oxaliplatin
  – Etoposide
  – Irinotecan
• All cisplatinum and paclitaxel resistant

Sato et al., 2009
5-FU/Oxaliplatin in Cell Lines

Sato et al., 2009
5-FU/Oxaliplatin in Cell Lines

Sato et al., 2009
5-FU/Oxaliplatin in Cell Lines

Sato et al., 2009
New Approaches
Role of Src Kinase

- Non-receptor tyrosine kinase
- Regulates tumor progression via multiple signaling pathways
  - Cell survival (AKT)
  - Growth (Ras/MEK/ERK)
  - Metastasis (FAK/Paxillin/c-Jun)
  - Angiogenesis (STAT3/VEGF)
- Overexpressed in colorectal, pancreatic, and other cancers
- May contribute to chemoresistance
Oxaliplatin Induces Src Kinase Activity

Matsuo et al., CCR, 2011
Oxalplatin and Dasatinib Have Anti-Tumor Effect on PMOC

Matsuo et al., CCR, 2011
Future Directions
Targeting Src and Tubulin in Mucinous Ovarian Carcinoma

Tao Liu\textsuperscript{1,8}, Wei Hu\textsuperscript{1}, Heather J. Dalton\textsuperscript{1}, Hyun Jin Choi\textsuperscript{1}, Jie Huang\textsuperscript{1}, Yu Kang\textsuperscript{1,9}, Sunila Pradeep\textsuperscript{1}, Takahito Miyake\textsuperscript{1}, Jian H. Song\textsuperscript{2}, Yunfei Wen\textsuperscript{1}, Chunhua Lu\textsuperscript{1}, Chad V. Pecot\textsuperscript{5}, Justin Bottsford-Miller\textsuperscript{1}, Behrouz Zand\textsuperscript{1}, Nicholas B. Jennings\textsuperscript{1}, Cristina Ivan\textsuperscript{1,6}, Gary E. Gallick\textsuperscript{2}, Keith A. Baggerly\textsuperscript{3}, David G. Hangauer\textsuperscript{7}, Robert L. Coleman\textsuperscript{1}, Michael Frumovitz\textsuperscript{1}, and Anil K. Sood\textsuperscript{1,4,6}

Clin Cancer Res; 19(23) December 1, 2013
Ovarian SPORE Developmental Grant

• KX01 – a dual mechanism biologic agent
  – Inhibition of Src kinase signaling
  – Pre-tubulin inhibition
• Evaluate effect of KX01 in PMOC models
  – Cell
  – Mouse
RMUG-S-ip2

**Migration**

Con  KX-01  Oxaliplatin  KX-01+Oxa

**Invasion**

Con  KX-01  Oxaliplatin  KX-01+Oxa

---

Graph showing cell number comparisons:
- Control vs. KX-01, P<0.01
- Control vs. Oxaliplatin, P<0.01
- Control vs. KX-01+Oxa, P<0.01
PMOC Summary

- Unique subtype of ovarian cancer
PMOC Summary

- Unique subtype of ovarian cancer
- Good prognosis overall due to high prevalence of early stage disease
PMOC Summary

• Unique subtype of ovarian cancer
• Good prognosis overall due to high prevalence of early stage disease
• Late stage and recurrent disease has very poor prognosis
  – Seemingly platinum resistant
PMOC Summary

- Unique subtype of ovarian cancer
- Good prognosis overall due to high prevalence of early stage disease
- Late stage and recurrent disease has very poor prognosis
  - Seemingly platinum resistant
- GOG/GCIG phase III study closed 😞
  - MDACC treats off protocol with oxaliplatin/capecitabine +/- bevacizumab
Thank You!

mfrumovitz@mdanderson.org