Management of Recurrent Epithelial Ovarian Cancer: Current Standard & Novel approach

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Korea University School of Medicine
Overview

- Natural history of advanced ovarian cancer
- Secondary cytoreductive surgery
- Platinum-sensitive recurrent ovarian cancer
- Platinum-resistant recurrent ovarian cancer
- Future directions and new frontiers
New cancer cases and deaths in Korean women

Annual report of the Korea central cancer registry 2002
Standards for Newly Diagnosed Disease

- **Limited (stage I-II) disease**
  - Resection and careful surgical staging
  - Low-risk disease: observation
  - High-risk disease: paclitaxel/carboplatin
  
<table>
<thead>
<tr>
<th>Incidence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>73%</td>
</tr>
<tr>
<td>5%</td>
<td>45%</td>
</tr>
</tbody>
</table>

- **Advanced (stage III-IV) disease**
  - Optimal surgical cytoreduction
  - Chemotherapy
    - Paclitaxel/carboplatin for 6 cycles
    - Consider IP therapy for small-volume residual disease
    - Consider maintenance paclitaxel in cCR
  
<table>
<thead>
<tr>
<th>Incidence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>58%</td>
<td>21%</td>
</tr>
<tr>
<td>17%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Natural History of Advanced Ovarian Cancer

Primary treatment

Clinical remission 70-80%
(1 to 3 years average)

Relapse (70-80%)

Goals of Treatment
Control of disease-related symptoms
Minimize treatment-related symptoms
Maintain or improve quality of life
Delay time to progression
Prolong survival

Clinical remission
(6-12 months average)

Relapse (100%)

keep it stable for as long as possible

Secondary Cytoreductive Surgery

- **Surgery plays only a minor role** due to
  - Technical complexity with repetitive abdominal procedures
  - Lack of conclusive evidence
- **Paucity of studies**
  - Most studies have been retrospective
  - Included heterogenous patient populations with considerable variation in tumor biology
  - Variability in the extent of previous surgery, the extent and type of previous chemotherapy, the time to diagnosis, and the extent of disease at the time of diagnosis of recurrence
AGO DESKTOP OVAR Trial

Jan 2000 - Dec 2003, 267 patients
Median survival: RD=0mm 45.2  RD 1-10mm 19.6  RD > 10mm 19.7
Completely resected tumors showed a significantly longer survival
The size of residual tumor did not impact survival in patients not completely debulked

# AGO DESKTOP OVAR Trial

## TABLE 3. Multivariate analysis of prognostic factors for survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cooperative Oncology Group (ECOG)</td>
<td>.13</td>
<td>.25</td>
<td>1.15</td>
<td>.70–1.88</td>
<td>.588</td>
</tr>
<tr>
<td>Residual disease after primary surgery</td>
<td>.03</td>
<td>.27</td>
<td>.97</td>
<td>.57–1.67</td>
<td>.915</td>
</tr>
<tr>
<td>Ascites</td>
<td>.83</td>
<td>.29</td>
<td>2.30</td>
<td>1.31–4.04</td>
<td>.004</td>
</tr>
<tr>
<td>Localization of recurrence in preoperative diagnostics in pelvis</td>
<td>.54</td>
<td>.32</td>
<td>1.72</td>
<td>0.92–3.20</td>
<td>.090</td>
</tr>
<tr>
<td>Residual disease after surgery for recurrence</td>
<td>1.08</td>
<td>.29</td>
<td>2.94</td>
<td>1.68–5.17</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Platinum-based chemotherapy after surgery for recurrence</td>
<td>.61</td>
<td>.25</td>
<td>1.84</td>
<td>1.13–3.01</td>
<td>.015</td>
</tr>
<tr>
<td>Treatment-free interval &lt; 6 months vs. 6–12 months</td>
<td>.04</td>
<td>.34</td>
<td>.96</td>
<td>.49–1.86</td>
<td>.897</td>
</tr>
<tr>
<td>Treatment-free interval &lt; 6 months vs. &gt; 12 months</td>
<td>.07</td>
<td>.35</td>
<td>.93</td>
<td>.47–1.86</td>
<td>.837</td>
</tr>
</tbody>
</table>

*OR odds ratio, CI confidence interval.

## TABLE 5. Multivariate analysis of factors for achieving complete resection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cooperative Oncology Group (ECOG)</td>
<td>.98</td>
<td>2.65</td>
<td>1.56–4.52</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Residual disease after primary surgery (mm)*</td>
<td>.90</td>
<td>2.46</td>
<td>1.45–4.20</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ascites</td>
<td>1.63</td>
<td>5.08</td>
<td>1.97–13.16</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Localization of recurrence in preoperative diagnostics</td>
<td>.44</td>
<td>1.55</td>
<td>.85–2.82</td>
<td>.155</td>
</tr>
</tbody>
</table>

*OR odds ratio, CI confidence interval.

* Alternatively International Federation of Gynecology and Obstetrics (FIGO) stage if residual disease after primary surgery is unknown [hazard ratio (HR) 1.87 (95% CI 1.04–3.37); P = .036].
AGO DESKTOP OVAR II Trial

Patients with disease-free-interval > 6 months, informed consent, and:
- good performance status (ECOG = 0)
- no residuals after primary surgery (if unknown FIGO stage I/II initially)
- No or small volume of ascites (estimation: < 500 ml)

Eligibility/Selection criteria

- Disease-free interval of at least 12 months
- Response to first-line chemotherapy
- Potential for complete resection based on preoperative evaluation
- Good performance status
- Younger age

=> based more on expert’s opinions than on valid data
The role of secondary cytoreductive surgery

- Controversial
- Better survival - maximal cytoreduction
- Need large prospective randomized study
  - Selection criteria
  - Prognostic factor
Agents for Recurrent Disease

**Frequently used:**
- Carboplatin
- Cisplatin
- Topotecan**
- Paclitaxel
- Docetaxel
- Liposomal doxorubicin**
- Oral etoposide
- Gemcitabine**+ Carboplatin
- Tamoxifen
- Cyclophosphamide
- Hexamethylmelamine**

**Under Review:**
- Oxaliplatin
- Vinorelbine
- 5-FU/leucovorin
- Irinotecan
- Ifosfamide
- Capecitabine

** FDA approved for the treatment of recurrent ovarian cancer.**
Chemotherapy for Recurrent Disease

Definition of Sensitivity

- Refractory
- Resistant
- Sensitive
- Very Sensitive
## Major Trials in Patients with Platinum-Sensitive Recurrent Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON 4/AGO-OVAR 2.2</td>
<td>Carboplatin ± paclitaxel</td>
</tr>
<tr>
<td>GCIG OVAR 2.5</td>
<td>Carboplatin ± gemcitabine</td>
</tr>
<tr>
<td>PLD/Topotecan</td>
<td>PLD vs topotecan</td>
</tr>
</tbody>
</table>
ICON 4/AGO-OVAR 2.2

- 2 parallel randomized, multicenter trials

Patients with platinum-sensitive recurrent ovarian cancer
TFI ≥ 6 months
(N = 802)

Paclitaxel + Platinum-based chemotherapy
(n = 392)

Platinum-based chemotherapy
(n = 410)

## ICON 4/AGO-OVAR 2.2: Toxicity

<table>
<thead>
<tr>
<th>Toxicity, %</th>
<th>Platinum (n = 410)</th>
<th>Paclitaxel/Platinum (n = 392)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic (grade ≥ 2)</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Hematologic*</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>Infection*</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Renal*</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Mucositis (grade ≥ 2)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Nausea and vomiting (grade ≥ 2)</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Alopecia (grade ≥ 2)</td>
<td>25</td>
<td>86</td>
</tr>
</tbody>
</table>

Progression-Free Survival

- Hazard ratio: 0.76 (95% CI: 0.66-0.89; \( P = .0004 \))
- Absolute difference at 1 year: 10% (95% CI: 4-15)
- 50% (paclitaxel/platinum) vs 40%

Overall Survival

- Hazard ratio: 0.82 (95% CI: 0.69-0.97; \( P = .023 \))
- Absolute difference at 2 years: 7% (95% CI: 1-12)
- 57% (paclitaxel/platinum) vs 50%

AG0-OVAR 2.5 (GCIG): Gemcitabine/Carboplatin vs Carboplatin

- Randomized, phase III trial

*Patients with platinum-sensitive recurrent ovarian cancer*

≥ 6 months out from initial platinum therapy

(N = 356)

**Gemcitabine** (1000 mg/m²) Days 1 and 8
**Carboplatin** (AUC = 4) Day 1
every 21 days x 6 cycles
(n = 178)

**Carboplatin** (AUC = 5) Day 1
every 21 days x 6 cycles
(n = 178)

# AGO-OVAR 2.5 (GCIG): Grade 3/4 Toxicity and Supportive Care

<table>
<thead>
<tr>
<th>Parameter, %</th>
<th>Gemcitabine/Carboplatin (n = 175)</th>
<th>Carboplatin (n = 174)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 hematologic toxicity</td>
<td>78.3</td>
<td>24.7</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>• Anemia</td>
<td>27.4</td>
<td>8.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>34.9</td>
<td>11.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>• Neutropenia</td>
<td>70.3</td>
<td>12.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>• Febrile neutropenia</td>
<td>1.1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Infections</td>
<td>0.6</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Supportive care (n = 178)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• G-CSF or GM-CSF</td>
<td>23.6</td>
<td>10.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>• Parenteral antibiotics</td>
<td>8.4</td>
<td>5.1</td>
<td>NS</td>
</tr>
<tr>
<td>• RBCs</td>
<td>27.0</td>
<td>6.7</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

AGO-OVAR 2.5 (GCIG):

Median PFS
- Gemcitabine plus carboplatin: 8.6 months
- Carboplatin: 5.8 months

Response rate
- Gemcitabine plus carboplatin: 47.2%
- Carboplatin: 30.9%

HR for overall survival was 0.96 (95% CI, 0.75 -1.23; P = .7349).

Patients with advanced ovarian cancer (90% stage II/IV)
Recurrent or failed platinum-based therapy
Measurable disease
Median age: 60 years (range: 25-87) (N = 474)

Platinum-sensitive

Stratification by platinum sensitivity and presence/absence of bulky disease

Topotecan 1.5 mg/m²/d IV for 5 consecutive days every 3 weeks

## PLD vs Topotecan: Therapy-Related Adverse Events (Grade 3/4)

<table>
<thead>
<tr>
<th>Grade 3/4 Adverse Event, %</th>
<th>PLD (n = 239)</th>
<th>Topotecan (n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>12</td>
<td>77</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8.0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

PLD vs Topotecan:

Median Survival
PLD: 62.7 weeks
Topotecan: 59.7 weeks
HR: 1.23 (95% CI: 1.01-1.50; \( P = .038 \))

Median Survival
PLD: 107.9 weeks
Topotecan: 70.1 weeks
HR: 1.432 (95% CI: 1.066-1.923; \( P = .017 \))

(Platinum-Sensitive Disease)

Chemosensitive Disease: Principles

- Repeat platinum doublet on further relapse for patients with clinical CR and TFI > 6 mos
- **Carboplatin doublet regimen of choice**
  - Paclitaxel/carboplatin
  - Gemcitabine/carboplatin
  - PLD/carboplatin
- Treatment to progression, unacceptable toxicity, clinical complete remission (vs defined treatment duration)
The Traditional Treatment Paradigm of Recurrent Ovarian Cancer

- **Platinum sensitive**
  - > 6 months
  - Platinum*
    - retreatment

- **Platinum refractory/resistant**
  - < 6 months
  - Nonplatinum treatment
Platinum-resistant disease

• Treatment efforts are directed at **palliation and quality of life**, rather than cure
• Retreatment with platinum is rarely effective
• Generally treated with **single-agent therapy** rather than combination chemotherapy, because of higher toxicity and the lack of a clear survival benefit with combination treatment
Therapeutic Approaches for Relapsed Platinum-Resistant Disease

- Pegylated liposomal doxorubicin*
- Weekly topotecan*
- Weekly paclitaxel*
- Docetaxel
- Gemcitabine + Carboplatin*
- Oral etoposide
- Bevacizumab

*Approved by the US Food and Drug Administration.

- Clinical trial
  - GOG 126 (cytotoxic) series
  - GOG 170 (biologic) series
  - Trabectedin
  - Patupilone
  - Phenoxodiol
  - TLK286
# PLD in relapsed ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>RR(%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muggia et al. J Clin Oncol, 1997</td>
<td>35</td>
<td>PLD 50 mg/m2 q 28 days</td>
<td>25.7</td>
<td>5.7 months</td>
<td>11 months</td>
</tr>
<tr>
<td>Gordon et al. J Clin Oncol, 2000</td>
<td>89</td>
<td>PLD 50 mg/m2 q 28 days</td>
<td>16.9</td>
<td>19.3 weeks</td>
<td>NR</td>
</tr>
<tr>
<td>Gordon et al. J Clin Oncol, 2001</td>
<td>474</td>
<td>PLD 50 mg/m2 q 28 days vs Topotecan 1.5 mg/m2 5 days q 21 days</td>
<td>19.7</td>
<td>16.1 weeks</td>
<td>63 weeks</td>
</tr>
<tr>
<td>Gordon and Teitelbaum. Eur J Cancer, 2003</td>
<td>214</td>
<td>PLD 50 mg/m2 q 28 days vs Paclitaxel 175 mg/m2 q 21 days</td>
<td>17.0</td>
<td>17.0 weeks</td>
<td>60 weeks</td>
</tr>
<tr>
<td>O’Byrne et al. Proc Am Soc Clin Oncol ,2002</td>
<td></td>
<td></td>
<td>17.8</td>
<td>21.7 weeks</td>
<td>45.7 weeks</td>
</tr>
</tbody>
</table>

not significantly different
Single-agent Gemcitabine was well-tolerated and had demonstrable activity

<table>
<thead>
<tr>
<th>study</th>
<th>N</th>
<th>Dose</th>
<th>RR (%)</th>
<th>Grade 3/4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markman et al. Gynecol Oncol, 2003</td>
<td>51</td>
<td>1000 mg/m2 day 1,8,15 q 28days</td>
<td>16</td>
<td>Neutrophils, platelets, fever, chills, fatigue</td>
</tr>
<tr>
<td>D’Agostino et al. Gynecol Oncol, 2003</td>
<td>41</td>
<td>1000 mg/m2 day 1,8,15 q 28days</td>
<td>17</td>
<td>Neutrophils, platelets, anemia, ↑LFTs</td>
</tr>
</tbody>
</table>
## Gemcitabine combination therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>RR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jungnelius et al. ASCO</td>
<td>39</td>
<td>Gemcitabine(1250mg/m2, days1,8 q 21 days) Paclitaxel(175mg/m2, day 1 q 21 days),</td>
<td>41</td>
</tr>
<tr>
<td>Garcia et al. Gynecol Oncol, 2004</td>
<td>19</td>
<td>Gemcitabine(1000mg/m2, days1,8,15), Paclitaxel(80mg/m2, day 1,8,15) q 28 days</td>
<td>42</td>
</tr>
<tr>
<td>D'Agostino et al. Br J Cancer, 2004</td>
<td>67</td>
<td>Gemcitabine(1000mg/m2, day 1,8), PLD(30mg/m2, day 1) q 21 days</td>
<td>34</td>
</tr>
<tr>
<td>Tobias et al. ASCO</td>
<td>14</td>
<td>Gemcitabine(650mg/m2, day 1,8), PLD(25mg/m2, day 1) q 21 days</td>
<td>43</td>
</tr>
<tr>
<td>Greggi et al. Oncology, 2001</td>
<td>24</td>
<td>Gemcitabine(600mg/m2, day 1,3), Topotecan(0.9mg/m2, day 1-5) q 28 days</td>
<td>13</td>
</tr>
<tr>
<td>Sehouli et al. J Obstet Gynecol Res, 2003</td>
<td>12</td>
<td>Gemcitabine(800mg/m2, day 1,8), Topotecan(0.5 mg/m2, day 1-5) q 21 days</td>
<td>50</td>
</tr>
<tr>
<td>Nagourney et al. Gynecol Oncol, 2003</td>
<td>27</td>
<td>Gemcitabine(600-750mg/m2, day 1,8), Cisplatin(30mg/m2, day 1,8) q 21 days</td>
<td>70</td>
</tr>
<tr>
<td>Rose et al. Gynecol Oncol, 2003</td>
<td>36</td>
<td>Gemcitabine(750mg/m2, day 1,8), Cisplatin(30mg/m2, day 1,8) q 21 days</td>
<td>43</td>
</tr>
</tbody>
</table>

- High dose > Low dose(<800mg/m2)
- Combination > Single therapy
- Reverse or overcome platinum resistance
- Synergy between Gemcitabine and Cisplatin
Patients with advanced ovarian cancer (90% stage II/IV)
Recurrent or failed platinum-based therapy
Measurable disease
Median age: 60 (range: 25-87) (N = 474)

Topotecan 1.5 mg/m²/day IV for 5 consecutive days every 3 weeks
PLD 50 mg/m² IV every 4 weeks

Stratification: platinum sensitivity and presence or absence of bulky disease

## Topotecan vs PLD

### Adverse Event,* %

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Topotecan (n = 235)</th>
<th>PLD (n = 239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia†</td>
<td>77</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonhematologic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0.4</td>
<td>8.0</td>
</tr>
</tbody>
</table>

### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>CR, %</th>
<th>PR, %</th>
<th>SD, %</th>
<th>CB, %</th>
<th>Median PFS, wks</th>
<th>Median OS, wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan</td>
<td>124</td>
<td>0.8</td>
<td>5.6</td>
<td>42.7</td>
<td>49.1</td>
<td>13.6</td>
<td>41.3</td>
</tr>
<tr>
<td>PLD</td>
<td>130</td>
<td>0.8</td>
<td>11.5</td>
<td>27.7</td>
<td>40.0</td>
<td>9.1</td>
<td>35.6</td>
</tr>
</tbody>
</table>

*P value: 0.733, 0.455

### GOG-126: Phase II Trial Series in Platinum Resistant/Refractory Ov Ca

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>Principal Grade 3/4 Toxicity</th>
<th>ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 126-N [1]</td>
<td>48</td>
<td>Paclitaxel 80 mg/m² weekly</td>
<td>Neuropathy (grade 3): 4%</td>
<td>20.9</td>
</tr>
<tr>
<td>GOG 126-J [2]</td>
<td>60</td>
<td>Docetaxel 100 mg/m² q 3 weeks</td>
<td>Neutropenia (grade 4): 75%</td>
<td>22.4</td>
</tr>
<tr>
<td>GOG 126-H [3]</td>
<td>41</td>
<td>Oral etoposide 50 mg/m² 21 of 28 days</td>
<td>Neutropenia (grade 3: 20%; grade 4: 25%)</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Phase II: Weekly Topotecan


Each treatment given for up to 2 cycles after CR attained

*Optional; allowed in case of progressive disease, undue toxicity, or cumulative PLD dose of 500 mg/m².

Gemcitabine (median: 15.6 weeks)
PLD (median: 13.3 weeks)
Log-rank P = 0.87

Future Directions and New Frontiers in Individualized Therapeutic Approaches
TLK286 (canfosfamide): Cytotoxic Prodrug

- Glutathione S-transferase P1-1 (GST P1-1)
  - Overexpressed in ovarian cancer
  - Associated with chemoresistance (eg, alkylators, platinum)

- TLK286
  - Small-molecule prodrug
  - Activates when it binds GST P1-1
ASSIST-3

Patients with platinum-refractory or resistant ovarian cancer who progressed on first-line therapy

(Planned N = 244)

TLK286 + Carboplatin

PLD

Topotecan

ASSIST-5

Patients with platinum-refractory or resistant ovarian cancer who progressed on first-line therapy

(N = 244)

TLK286 + PLD

PLD

ASSIST-1

Patients with platinum-refractory or resistant ovarian cancer who progressed on second-line therapy

(N = 440)

TLK286

PLD

Topotecan

Results pending
Unique Binding of Trabectedin to DNA

- Binds selectively to the minor groove of DNA
- Specific 3-base sequence (5’-PuGC-3’ or 5’-PyrGC-3’)
- Bends macromolecule toward major groove
- Most active in G1 phase
- Synergistic with platinum without overlapping toxicity

Trabectedin After Failure of Platinum and Taxanes

- Trabectedin 1.65 mg/m² every 3 weeks (N = 59)
- Platinum-sensitive disease (n = 29; 23 assessable)
  - 43% RR (95% CI: 23% to 65%)
  - Median PFS: 7.9 mo (range: 7.5-14.1)
- Platinum-resistant disease (n = 30; 28 assessable)
  - 7% RR

<table>
<thead>
<tr>
<th>Toxicity, % (n = 41)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>27</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>39</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17</td>
</tr>
<tr>
<td>Thrombo-cytopenia</td>
<td>20</td>
</tr>
</tbody>
</table>

Trabectedin With PLD vs PLD Alone: Phase III Ovarian Cancer Study

Patients with advanced recurrent epithelial ovarian cancer
1 prior platinum-based chemotherapy regimen
Platinum sensitive or resistant
(Planned N = 650)

- Opened to accrual April 2005
- Primary endpoint: OS
- Other endpoints: PFS, RR, safety

http://www.clinicaltrials.gov/ct/show/NCT00113607
Phenoxodiol Reverses Chemotherapy Resistance

- Efficient inducer of cell death in ovarian cancer cells
- Sensitizes cancer cells to Fas-mediated apoptosis
- Restores sensitivity in docetaxel-resistant epithelial ovarian cancer cells

Phenoxodiol With Platinum: Phase III Study (OVATURE)

Patients with advanced recurrent ovarian, fallopian, or peritoneal cancer
Refractory to ≥ 2 prior platinum regimens
Measurable disease (N = 470)

- Primary endpoint: PFS
- Interim analysis planned after 95 progression “events”

http://clinicaltrials.gov/ct/show/NCT00382811
## GOG Trials of Biologic Agents in Recurrent Ovarian Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Not active</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Active</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Too early</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Too early</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Angiogenesis pivotal in ovarian cancer development and progression

Bevacizumab: recombinant humanized monoclonal antibody to VEGF

Bevacizumab in Persistent/Recurrent Ovarian Cancer: GOG 170D

- Patients with recurrent or persistent ovarian carcinoma and up to 2 prior regimens (N = 62)
- Bevacizumab 15 mg/kg IV every 21 days
- **Response rate:** 17.7%
  - CR: 3 patients (4.8%)
  - PR: 8 patients (12.9%)
- 6-month PFS: 38.7%
- Now part of randomized phase III trial

## GI Perforations With Bevacizumab in Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Gastrointestinal Perforations, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burger (GOG-170D)</td>
<td>0/62 (0)</td>
</tr>
<tr>
<td>Garcia (ASCO 2005)</td>
<td>2/29 (6.9)</td>
</tr>
<tr>
<td>Cannistra (ASCO 2006)</td>
<td>5/44 (11.4)</td>
</tr>
<tr>
<td>Wright (ASCO 2006)</td>
<td>4/62 (6.5)</td>
</tr>
<tr>
<td>Penson (ASCO 2006)</td>
<td>0/30 (0)</td>
</tr>
<tr>
<td>Friberg (ASCO 2006)</td>
<td>2/13 (15.4)</td>
</tr>
<tr>
<td>Monk (Gynecol Oncol 2006)</td>
<td>1/32 (3.1)</td>
</tr>
<tr>
<td>Wright (Cancer 2006)</td>
<td>2/23 (8.7)</td>
</tr>
<tr>
<td>Bidus (Gynecol Oncol 2006)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16/299 (5.4%)</td>
</tr>
</tbody>
</table>

Predicting Response to Therapy

- Gene expression profiling
- Ex vivo chemoresponse assay and PFS
- Histoculture drug response assay and clinical response to platinum
- P53 status and response to platinum and taxanes
- Proposed GOG trial
Predicting Response to Therapy: Chemoresistance Assay

- Retrospective analysis
  - Choice of chemotherapy based on extreme drug resistance assay results
  - Control subjects treated empirically
- Outcomes improved in platinum-sensitive patients \(n = 31\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Assay-Directed Therapy Pts (n = 31)</th>
<th>Controls (n = 31)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>65</td>
<td>35</td>
<td>.02</td>
</tr>
<tr>
<td>Progression-free survival (median), mos</td>
<td>15</td>
<td>7</td>
<td>.0002</td>
</tr>
<tr>
<td>Overall survival (median), mos</td>
<td>38</td>
<td>21</td>
<td>.005</td>
</tr>
</tbody>
</table>

Predicting Response to Therapy: Gene Expression Model

- Ovarian cancer patients likely resistant to primary platinum-based chemotherapy identified using gene expression profiles
  - Accuracy: > 80%
- In patients with platinum-resistant disease: Gene expression signatures consistent with Src and Rb/E2F activation
- Potential application: stratify patients based on predicted response to primary chemotherapy/oncogenic pathway deregulation

Results of gene expression analysis: *Likely to respond?*
- yes
- no

GOG Trial: EDR Assay in Selection of Second-Line Therapy

- Fresh primary tumor obtained at time of primary cytoreductive surgery
  - Biopsy sent for EDR testing
  - Results blinded
- If disease progression on primary therapy or within 6 months of completion (platinum resistant):
  - Randomize to EDR-directed therapy or physician’s therapy of choice
- Endpoints: ability of EDR to improve PFS, predict primary tumor resistance
What Is the Good News?

- Greater awareness of ovarian cancer
- **Number of new ovarian cancer cases has declined over past 5-7 years**
  - From 27,000 to 20,000 cases
- **Patients are living longer**
  - 32,000 women from SEER 1973-1997
  - **5-year survival**
    - 1973-1979: 37%
    - 1980-1989: 39%
    - 1990-1997: 43%

New Agents to Study

- **Microtubule inhibitors**
  - Nanoparticle paclitaxel
  - Paclitaxel polyglumex
  - RPR 109881A
  - Vinflunine

- **Sorafenib**
  - Oral multikinase inhibitor
  - Blocks tyrosine kinase receptors involved in progression
Key Points

- Secondary cytoreduction might be considered in select patients with isolated masses, and a long disease free interval of at least 12 months.

- Treatment of recurrent ovarian cancer is often decided by the interval from previous platinum treatment.

- Future trials are needed to establish the role of molecular targeted compounds, sequential versus combination chemotherapy, role of assay-directed therapy and secondary cytoreduction in recurrent ovarian cancer.