Front-line therapy: Update
intraperitoneal therapy

Bradley J. Monk, MD, FACS, FACOG
Arizona Oncology (US Oncology Network)
University of Arizona College of Medicine
Creighton University School of Medicine
at St. Joseph’s Hospital-Phoenix Arizona USA

bradley.monk@usoncology.com
Verbal Disclosures

• My institution has received grants for me from Amgen, Genentech, Eli Lilly, Array, TESARO Inc., Morphotek, and Janssen/Johnson & Johnson.
• I have received honoraria for speakers’ bureaus from Genentech, Roche, AstraZeneca, Myriad, and Janssen/Johnson & Johnson.
• I have received honoraria for my consulting with Merck, TESARO Inc., Gradalis, Advaxis, Amgen, Bayer, Insys, Clovis, Mateon (formally OxiGENE), Roche, Genentech, AstraZeneca, Pfizer and PPD.
• I agree that content of this presentation will be well balanced, unbiased, and evidence-based. Opinions that are not supported by evidence, or are supported by limited or preliminary evidence will be so identified.
What is the standard treatment for newly diagnosed advanced epithelial ovarian cancer?

- Depend on many factors
  - Fitness of the patient
  - Histologic subtype
  - Volume of disease (stage and ascites)
  - Setting (neoadjuvant)
  - Reimbursement and guidelines
**What is the standard treatment for newly diagnosed advanced epithelial ovarian cancer?**

- Many would agree that in stage IV or large volume residual disease (suboptimal), every 3 week carboplatin and paclitaxel with bevacizumab is preferred
  - Reimbursement and cost effectiveness are challenges
What is the standard treatment for newly diagnosed advanced epithelial ovarian cancer?

- **The alternative is weekly chemotherapy**
  - “Dose dense paclitaxel” in the fittest patients
  - “Fractionated” in the infirm and weak patients
What is the standard treatment for newly diagnosed advanced epithelial ovarian cancer?

- Intraperitoneal (IP) is an option in the adjuvant setting when the volume of residual disease is <1cm

- Outline
  - Rationale for IP chemotherapy
  - GOG protocols 114 and 172
  - GOG protocol 252
  - Current recommendations and challenges
Spread of ovarian cancer

- 60-70% Advanced Stage
  - No symptoms because of large peritoneal cavity
  - Peritoneal Dissemination

- Not curative by surgery or radiation therapy

- Importance of Chemotherapy Delivery
  - Infusing a high concentration of anticancer drug appears to be a reasonable approach
What is IP Chemotherapy?

• Perfusion of cytotoxic agent(s) inside the peritoneal cavity

• Primary goal
  – Exposure of tumor tissue to the extremely high concentration
    • Ultrahigh-dose chemotherapy
IP Port-a-Cath Insertion

From Atlas of Procedures in Gynecologic Oncology - Levine, Barakat and Hoskins
Determinant Factors for the Effect of IP Chemotherapy

1. Direct penetration of anticancer agent into the tumor tissue from tumor surface

2. Diffusion of anticancer agent into inner core of tumor tissue through systemic blood circulation
   A. Relationship between IP cavity, systemic circulation, and tumor tissue in terms of IP administered drug pharmacology

3. Antitumor effect of the agent for target tumor
Penetration and diffusion of anticancer drugs into tumor tissue after IP chemotherapy

**Intraperitoneal Cavity**
Very high concentration of Anticancer Agents

**Tumor Tissue**

- **Outer Layer:**
  High Drug Level by Direct Exposure

- **Inner Core:**
  Drug Concentration by Microcirculation through Systemic Circulation
  *Depends on drug pharmacology*

**Blood Vessels**
Penetration of anticancer agent

• Limited to few millimeters from surface

• Penetration studies:
  – Cisplatin:
  – Doxorubicin:
  – Methotrexate:
  – 5-FU:
Theoretical characteristics of anticancer drugs in the peritoneal Cavity

- **Stay Longer**
  - Larger molecules
  - Water **insoluble**

- **Stay Shorter**
  - Smaller molecules
  - Water soluble

(Peritoneal Cavity/Plasma) Ratio of Drug Level

Large  Small
## Pharmacologic Advantage for Intraperitoneal Chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Weight</th>
<th>Water Solubility</th>
<th>Ratio of drug level Peritoneal Cavity/Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peak</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>300.05</td>
<td>+</td>
<td>20</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>371.25</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>334.33</td>
<td>±</td>
<td>71</td>
</tr>
<tr>
<td>Melphalan</td>
<td>305.20</td>
<td>-</td>
<td>93</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>454.44</td>
<td>-</td>
<td>92</td>
</tr>
<tr>
<td>5-FU</td>
<td>130.08</td>
<td>±</td>
<td>298</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>543.53</td>
<td>±</td>
<td>474</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>853.92</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>517.40</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Very effective antitumor effect on target tumor

- Very effective anticancer agents for ovarian cancer are rare

- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- Liposomal Doxorubicin
- Topotecan
- Irinotecan
- Etoposide
- Gemcitabine
Based on the pharmacological characteristics

- **What is the optimal patient situation for IP chemotherapy?**
  - Small Residual Tumor
    - Small amount of inner core of tumors

- **What is the optimal agent for IP chemotherapy?**
  - Large molecules
    - Stay longer in the IP cavity
    - Less systemic toxicity due to lower transportation from IP cavity to systemic circulation
But the reality is........

- Platinum compounds are the most effective agents for ovarian cancer
  - Small molecule
  Therefore,
  - Not the best agents for IP chemotherapy
Good news is
  - Easier to obtain cytotoxic concentration in the inner core of tumor tissue

- Paclitaxel must be given IV as well as IP
  - Large and insoluble molecule
### Previous Large IP Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>IP Regimen</th>
<th>IV Control</th>
<th>PFS</th>
<th>OS</th>
<th>Critique</th>
</tr>
</thead>
</table>
| SWOG 8501 N=546 | Cis IP 100 mg/m²  
Cis IV 100 mg/m²  
Ctx IV 600 mg/m²  
Ctx IV 600 mg/m² | Cis IV 100 mg/m²  
Not reported | IP 49 mos vs 41 mos  
P=.02 | -No paclitaxel  
-0-2 cm residual disease |
| GOG 114 N=462 | Carbo AUC 9 x2  
Cis IP 100 mg/m²  
Pac IV 135@24hr | Cis IV 75 mg/m²  
Pac IV 135@24hr | IP 28 mos vs 22 mos  
P=0.05 | IP 63 mos vs 52 mos  
P=.05 | -High-dose carbo  
-One-tail p value for OS |
| GOG 172 N=415 | Cis IP 100 mg/m²  
Pac IV 135@24 hr d1  
Pac IP 60 mg/m² d8  
Pac IV 135 x 24 hr | Cis IV 75 mg/m²  
Pac IV 135 x 24 hr | IP 24 mos vs 18 mos  
P=0.03 | IP 66 mos vs 50 mos  
P=.03 | -Day 8 Paclitaxel confounds |


Cis = Cisplatin  
Ctx = Cycophosphomide  
Carbo = Carboplatin  
Pac = Paclitaxel  
Mos = Months
GOG Protocol 172

- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy
- Elective Second-Look

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| I   | Cisplatin 75 mg/m²  
Paclitaxel 135 mg/m² (24 h) |
| II  | Cisplatin 100 mg/m² IP d1  
Paclitaxel 135 mg/m² (24 h) IV d1  
Paclitaxel 60 mg/m² IP d8 |

Open: 23-Mar-98
Closed: 29-Jan-01
Accrual: 416 pts (evaluable)

GOG Protocol 172 Survival

**PFS**
- IV: 18 mos
- IP: 24 mos
- HR: 0.80, \( p = .05 \)

**OS**
- IV: 50 mos
- IP: 66 mos
- HR: 0.75, \( p = .03 \)

**Rx Group**
- IV
  - Failed: 50
  - Total: 210
- IP
  - Failed: 63
  - Total: 205

**Proportion PFS (%)**
- Time (mos on study)

**Alive**
- IV: 93
- IP: 117

**Dead**
- IV: 117
- IP: 88

**Total**
- IV: 210
- IP: 205

IV = Intravenous; IP = Intraperitoneal; PFS = progression-free survival; OS = overall survival.

### GOG Protocol 172: Toxicity

<table>
<thead>
<tr>
<th>Grade 3/4 Side Effect</th>
<th>IV, % (N = 210)</th>
<th>IP, % (N = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia*</td>
<td>64</td>
<td>76</td>
</tr>
<tr>
<td>Platelet</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>GI*</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>Renal*</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Neurologic Event*</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Infection*</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Metabolic*</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Pain*</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

*P ≤ 0.05

No difference in QOL at 12 months

IV = Intravenous; IP = Intraperitoneal; GI = Gastrointestinal; QOL = Quality of life.
Treatment Hazard Ratios for Overall Survival
Intraperitoneal vs Intravenous Therapy

- SWOG/GOG—104 (1996): Rel Haz 0.760, Var(\ln(HR)) 0.013, IP regimen better
- GONO (2000): Rel Haz 0.670, Var(\ln(HR)) 0.077, IP regimen better
- GOG—114/SWOG (2001): Rel Haz 0.810, Var(\ln(HR)) 0.012
- Taiwan (2001): Rel Haz 1.130, Var(\ln(HR)) 0.064
- EORTC—55875 (2003): Rel Haz 0.820, Var(\ln(HR)) 0.054
- GOG—172 (2006): Rel Haz 0.750, Var(\ln(HR)) 0.017

Relative hazard

Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study

Devansu Tewari, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog, Bradley J. Monk, and John K. Chan

See accompanying editorial doi: 10.1200/JCO.2014.60.2797

- 876 patients from GOG 114 and 172
- Median follow-up = 10.7 years
- OS IP = 61.8 months (95% CI, 55.5 to 69.5)
- OS IV = 51.4 months (95% CI, 46.0 to 58.2)
- Adjusted HR = 0.77 (95% CI, 0.65 to 0.90; P = .002)
GOG 172: OS by treatment and BRCA1 expression

RETROSPECTIVE SEQUENCING IN GOG 252 IS URGENTLY NEEDED


GOG Protocol 252:
Stage II/III Disease: Small Volume Residual

- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy

I
Carboplatin AUC=6 (IV)
Paclitaxel 80 mg/m^2 (d1, 8, 15 3h)
Bevacizumab (C2+ C22) x 21 days

II
Carboplatin AUC=6 (IP)
Paclitaxel 80 mg/m^2 (d1, 8, 15 3h)
Bevacizumab (C2+ C22) x 21 days

III
Cisplatin 75 mg/m^2 (IP d2)
Paclitaxel 135 mg/m^2 (d1, 3h)
Paclitaxel 60 mg/m^2 (d8, IP)
Bevacizumab (C2+ C22) x 21 days

- Phase III
- PFS primary endpoint

Open: 27 Jul 2009
Closed: 30 Nov 2011
Accrual: 1100
Study Chair: J Walker

ClinicalTrials.gov Identifier: NCT00951496
Strategies by the GOG to reduce toxicity without compromising efficacy of IP Chemo

- Shorten the infusion of paclitaxel and reduce cisplatin dose from 100mg/m² to 75 mg/m²
- Shorten the infusion of paclitaxel and reduce cisplatin dose from 100mg/m² to 75 mg/m² and eliminate the day 8 dose of IP paclitaxel
- Shorten the infusion of paclitaxel and reduce cisplatin dose from 100mg/m² to 75 mg/m² and administer on the same day
Strategies **Not Being Studied** by the GOG to Reduce Toxicity Without Compromising Efficacy of IP Chemo

- Better supportive care
  - Anti-emetics
  - Pain medication
  - Cytoprotection (Amifostine)
  - Growth Factors
- Better techniques of administration
  - Improved catheters
- Improved patient selection
  - Age
  - Bowel resection
  - Performance status
- Substituting carboplatin for cisplatin
GOG Protocol 252: Completion of Assigned Treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>At least 6 cycles of assigned Arm</th>
<th># Bev Cycles</th>
<th>% 6 cycles Plat</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Carbo</td>
<td>65%</td>
<td>20</td>
<td>90%</td>
</tr>
<tr>
<td>IP Carbo</td>
<td>65%</td>
<td>19</td>
<td>90%</td>
</tr>
<tr>
<td>IP Cisp</td>
<td>59%</td>
<td>17</td>
<td>84%</td>
</tr>
</tbody>
</table>

Twice as many patients stopped protocol directed bevacizumab prior to completion of Cycle 6 on the arm 3 IP cisplatin (30% vs 15%)

GOG Protocol 252: PFS (< 1cm)

Stage II or III Optimally Debulked
GOG Protocol 252: PFS (RO)

Stage III with No Gross Residual Disease
## GOG Protocol 252: Toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>IV Carbo</th>
<th>IP Carbo</th>
<th>IP Cisp</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2</td>
<td>&gt;G3</td>
<td>G2</td>
<td>&gt;G3</td>
</tr>
<tr>
<td>Feb/neut</td>
<td>2.5%</td>
<td>2.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Neut</td>
<td>71%</td>
<td>68%</td>
<td>64%</td>
</tr>
<tr>
<td>Platelets</td>
<td>17.6%</td>
<td>15.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>HTN</td>
<td>11.9%</td>
<td>13.8%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Thromb</td>
<td>6.3%</td>
<td>8.4%</td>
<td>9.0%</td>
</tr>
<tr>
<td>N/V</td>
<td>5.1%</td>
<td>4.7%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Fistula</td>
<td>5.3%</td>
<td>3.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Urine Prot</td>
<td>2.7%</td>
<td>3.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Sens Neur</td>
<td>24.1</td>
<td>5.7%</td>
<td>22.6</td>
</tr>
</tbody>
</table>

### GOG Protocol 252: Progression Free Survival (<1cm): Stage II-III (10% stage II)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Event</th>
<th>Median PFS</th>
<th>HR  [95% CI]</th>
<th>Logrank</th>
<th>Logrank</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Carbo</td>
<td>461</td>
<td>303</td>
<td>26.8 months</td>
<td>Reference arm</td>
<td>P-value</td>
<td>Chi square</td>
</tr>
<tr>
<td>IP Carbo</td>
<td>464</td>
<td>300</td>
<td>28.7 months</td>
<td>0.947 [0.808-1.11]</td>
<td>0.416</td>
<td>0.661</td>
</tr>
<tr>
<td>IP Cisp</td>
<td>456</td>
<td>307</td>
<td>27.8 months</td>
<td>1.01 [0.858-1.18]</td>
<td>0.727</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Estimated hazard ratios, and logrank tests are adjusted for stage of disease and size of residual disease micro vs < 1cm

CT required every 6 months for surveillance (not required in GOG 114/172)

Current IV chemotherapy appears at least as effective as modified IP chemotherapy, with median OS exceeding historical data from GOG0172.
Did bevacizumab compromise GOG Protocol 252?

- Lessons learned from GOG Protocol 262

Stage III/IV Disease: Large Volume Residual

Paclitaxel 80 mg/m² IV every week + Carboplatin AUC 6 IV every 3 weeks x 6 cycles with optional Bevacizumab 15 mg/kg IV starting with cycle 2 until disease progression

Paclitaxel 175 mg/m² IV + Carboplatin AUC 6 IV every 3 weeks x 6 cycles with optional Bevacizumab 15 mg/kg IV starting with cycle 2 until disease progression

ClinicalTrials.gov Identifier: NCT01167712
Did bevacizumab compromise GOG Protocol 252?

- Lessons learned from GOG Protocol 262
  - Adding bevacizumab to dose dense weekly chemotherapy does not prolong PFS
  - Without bevacizumab, dose dense weekly chemotherapy prolongs PFS

<table>
<thead>
<tr>
<th>Progression-free Survival</th>
<th>No. of Events</th>
<th>Total No. of Patients</th>
<th>Median (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly paclitaxel</td>
<td>256</td>
<td>346</td>
<td>14.7</td>
</tr>
<tr>
<td>Every-3-wk paclitaxel</td>
<td>272</td>
<td>346</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.89 (95% CI, 0.74–1.06)

\[ P = 0.18 \]

<table>
<thead>
<tr>
<th>Progression-free Survival without Bevacizumab</th>
<th>No. of Events</th>
<th>Total No. of Patients</th>
<th>Median (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly paclitaxel</td>
<td>37</td>
<td>55</td>
<td>14.2</td>
</tr>
<tr>
<td>Every-3-wk paclitaxel</td>
<td>47</td>
<td>57</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.62 (95% CI, 0.40–0.95)

\[ P = 0.03 \]

Did bevacizumab compromise GOG Protocol 252?

- Lessons learned from GOG Protocol 262
  - If yes? Integrate bevacizumab into every 3 week IV therapy!
  - If no? Use either every 3 week IV therapy with bevacizumab or dose dense weekly without!

Potential reasons why GOG 252 results divergent

1. Inclusion of bevacizumab negated the benefit of IP chemo in GOG 252
   i. For positive reasons (in the control arm)
   ii. For negative reasons (in the test arms)

2. Two out of 3 positive trials (GOG114 and GOG 172) did not have equivalent dose intensity in test and control arms

3. Cisplatin dose: All positive studies used 100mg/m² (GOG 252 used cisplatin 75mg/m²)

4. Dose dense paclitaxel in control arm of GOG 252 improved control arm performance so it was equivalent to IP cisplatin (JGOG3016)
iPocc Trial

Stage II to IV ovarian, primary peritoneal, or fallopian tube cancer
Including suboptimal Cases

- Accrual: 655 pts (closed OCT2016)
- Primary Endpoint: PFS
- Secondary Endpoints: OS, Toxicity, QOL, Cost/Benefit

Paclitaxel 80 mg/m²/1h IV, weekly, Cycles 1-6
Carboplatin AUC 6 IV, Day 1, Cycles 1-6

Paclitaxel 80 mg/m²/1h IV, weekly, Cycles 1-6
Carboplatin AUC 6 IP, Day 1, Cycles 1-6
iPocc Trial

Total Accrual

Count

TimeLine

TARGET
COUNT

Presented by: Kosei Hasegawa, M.D., Ph.D. ASCO 2016
Selected ovarian cancer guidelines from outside N America

AGCA Guidelines 2014: ‘Women with stage III ovarian cancer who are optimally debulked at primary surgery should be considered for intraperitoneal (IP) chemotherapy. IP chemotherapy should be provided in a centre with appropriate expertise and potential toxicities fully explained.’

JSGO Guidelines 2015: ‘Intraperitoneal chemotherapy should be considered for patients with advanced cancer who have undergone optimal surgery’
Selected ovarian cancer guidelines from outside N America

NICE Guidelines 2011: ‘Do not offer intraperitoneal chemotherapy to women with ovarian cancer, except as part of a clinical trial.’

ESMO Guidelines 2013: ‘, This treatment has not been adopted as a standard of care in the majority of institutions and countries due to its greater toxicity and difficulty in delivering all of the planned treatment. The absence of the current standard intravenous control arm in these trials has further influenced scepticism, and many clinicians still regard intraperitoneal therapy as experimental, recommending its use only in the context of randomised trials.’
Conclusions

• Until GOG 252, large randomized IP studies have been positive although dose intensity between arms was not always equal

• Biologically, the idea of increasing cancer cell exposure to platinum using IP chemo made sense

• The actual platinum dose may be crucial

• Future studies must select on histology and molecular biology

• Currently the role of IP therapy in treating newly diagnosed advanced ovarian cancer is limited
Session 4: Front-line Therapy

bradley.monk@usoncology.com