Intraperitoneal Chemo
An interesting Concept or a New Standard for Treatment of Ovarian Cancer?
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Outline

• Ovarian Cancer Types
• Current Standard IV Treatment
• Exploring IP Chemotherapy
• OV.21 Trial
• Potential Future Standards
Ovarian Cancer Types

- Germ Cells
- Cord-Stromal Cells
- Epithelial
Epithelial Ovarian Cancer - Subtypes

- Serous
- Endometrioid
- Clear cell
- Mucinous

Ovarian EOC Subtypes
Symptoms of Ovarian Cancer

- Recent unexplained increased abdominal size
- Abdominal distension
- Post-menopausal bleeding or menstrual irregularities
- Back or abdominal pain
- Pelvic pressure or pain
- Bloating
- Fatigue
- Changes in bowel habit (constipation or diarrhea)
- Urinary symptoms (frequency or urgency)
- Unexplained weight gain or loss
- Appetite Loss and/or feeling full quickly
- Difficulty eating
- Rectal Bleeding
- Suspected new dx of IBS (particularly if >50yo)
Management of Epithelial Ovarian Cancer

• Standard treatment:
  ➢ Primary cytoreductive surgery
  ➢ Followed by adjuvant IV chemotherapy with a platinum / taxane combination
    ➢ Typically Carboplatin & Paclitaxel
Management of Epithelial Ovarian Cancer

- Other approaches explored:
  - Neoadjuvant chemotherapy
    - ~3 Cycles of Carboplatin/Paclitaxel IV
    - Followed by delayed (interval) debulking surgery
    - Completed with another 3+ Cycles of IV Chemotherapy
  - Intraperitoneal chemotherapy
IP vs IV Chemotherapy

Drawbacks

Potential Increase Chance of Toxicity with IP:

- IP catheter related
  - Local or systemic infection
  - Catheter blockage
  - Leakage
  - Access problems
  - Bowel perforation
  - Drainage per vagina
  - Chemical peritonitis

- Adverse Effects
  - Abdominal pain
  - N&V

- Toxicity
  - Hematologic
  - Metabolic
  - Neurologic
IP vs IV Chemotherapy
Benefits

- ↑ dose intensity delivered to tumour
- ↑ intraperitoneal concentration of drug
- Longer half-life in peritoneal cavity
- Overall increase in length of survival
Randomized trials conducted between 1994 and 2005 assessing IP chemotherapy after primary surgery for treatment of ovarian cancer

<table>
<thead>
<tr>
<th>Study Identifier / Year Published / ref</th>
<th>Control Regimen</th>
<th>Experimental Regimen</th>
<th>Eligible patients</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994 [Kirmani 1994]</td>
<td>Cisplatin 100 mg/m² IV; cyclophosphamide 600 mg/m²  Q 3 weeks x 6</td>
<td>Cisplatin 200 mg/m² IP; etoposide 350 mg/m² IP Q 4 weeks x 6</td>
<td>Stage IIC-IV</td>
<td>62</td>
</tr>
<tr>
<td>SWOG 8501/ GOG 104 1996 [Alberts 1996]</td>
<td>Cisplatin 100 mg/m² IV; cyclophosphamide 600 mg/m² IV Q 3 weeks x 6</td>
<td>Cisplatin 100 mg/m² IP; cyclophosphamide 600 mg/m² IV Q 4 weeks x 6</td>
<td>Stage III, ≤ 2 cm residual</td>
<td>546</td>
</tr>
<tr>
<td>Greek 1999 [Ozols 2003]</td>
<td>Carboplatin 350 mg/m² IV; cyclophosphamide 600 mg/m² IV Q 3 weeks x 6</td>
<td>Carboplatin 350 mg/m² IP; cyclophosphamide 600 mg/m² IV Q 3 weeks x 6</td>
<td>Stage III</td>
<td>90</td>
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<tr>
<td>GONO 2000 [Gadducci 2000]</td>
<td>Cisplatin 50 mg/m² IV; cyclophosphamide 600 mg/m² IV; epidoxorubicin 60 mg/m² IV Q 4 weeks x 6</td>
<td>Cisplatin 50 mg/m² IP; cyclophosphamide 600 mg/m² IV; epidoxorubicin 60 mg/m² IV Q 4 weeks x 6</td>
<td>Stage II-IV, ≤ 2 cm residual</td>
<td>113</td>
</tr>
<tr>
<td>GOG 114/ SWOG 9227 2001 [Markman 2001]</td>
<td>Cisplatin 75 mg/m² IV paclitaxel 135 mg/m² (24 hr) IV Q 3 weeks x 6</td>
<td>Carboplatin (AUC9) IV q 28 days x 2; cisplatin 100 mg/m² IP; paclitaxel 135 mg/m² (24 hr) IV Q 3 weeks x 6</td>
<td>Stage III, ≤ 1 cm residual</td>
<td>462</td>
</tr>
<tr>
<td>Taiwan 2001 [Yen 2001]</td>
<td>Cisplatin 50 mg/m² IV; cyclophosphamide 50 mg/m² IV; epidoroxorubin/ Doxorubicin 50 mg/m² IV Q 3 weeks x 6</td>
<td>Cisplatin 100 mg/m² IP; cyclophosphamide 500 mg/m² IV; epidoxorubicin / Doxorubicin 50 mg/m² IV Q 3 weeks x 6</td>
<td>Stage III, ≤ 1 cm residual</td>
<td>118</td>
</tr>
<tr>
<td>GOG 172 2005 [Armstrong 2006]</td>
<td>Cisplatin 75 mg/m² IV; paclitaxel 135 mg/m² (24 hr) IV Q 3 weeks x 6</td>
<td>Paclitaxel 135 mg/m² (24 hr) IV; cisplatin 100 mg/m² IP; paclitaxel 60 mg/m² IP on day 8 Q 3 weeks x 6</td>
<td>Stage III, ≤ 1 cm residual</td>
<td>415</td>
</tr>
</tbody>
</table>
NCIC CTG Experiences

• **OV.11:**
  - Phase II Trial
  - **IP** Cisplatin and Paclitaxel after Primary Optimally-Debulked
  - Stage III EOC

• **OV.13:**
  - Phase III Study
  - Comparing Upfront Debulking Surgery vs. Interval Debulking following Neo-adjuvant IV Chemo
  - Stage IIIC or IV EOC
NCIC CTG Experiences

- Previous trial outcomes:
  - Survival is ↑ through optimal surgical cytoreduction after neoadjuvant chemo.
  - Optimal debulking at primary surgery shows superior outcomes with IP chemo than with traditional IV chemo.

- Still to be explored:
  - IP chemo vs. IV in patients who undergo optimal debulking following IV neoadjuvant chemotherapy?
  - OV.21 Trial
Study Population

Stratification and Randomization

Phase II Portion

**ARM 1**
- **Day 1**: Paclitaxel 135 mg/m² IV + Carboplatin AUC 5 or 6 IV;
- **Day 8**: Paclitaxel 60 mg/m² IV
  - Q 21 days x 3 cycles

**ARM 2**
- **Day 1**: Paclitaxel 135 mg/m² IV + Cisplatin 75 mg/m² IP;
- **Day 8**: Paclitaxel 60 mg/m² IP
  - Q 21 days x 3 cycles

**ARM 3**
- **Day 1**: Paclitaxel 135 mg/m² IV + Carboplatin AUC 5 or 6 IP;
- **Day 8**: Paclitaxel 60 mg/m² IP
  - Q 21 days x 3 cycles

Assess Phase II Outcomes
  - (Sample Size = 150)
  - Proceed to Phase III Portion

Stratification and Randomization

Arm 1

Winner of Arm 2 and Arm 3

Assess Phase III Outcomes
  - (Total Sample Size = 830)
# Treatment Plan – Arm 1

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m²</td>
<td>IV</td>
<td>3 hours</td>
<td>Day 1, every 21 days, 3 cycles in total</td>
</tr>
<tr>
<td></td>
<td>60 mg/m²</td>
<td></td>
<td>1 hour</td>
<td>Day 8</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 5 if measured GFR (use AUC 6 if calculated GFR)</td>
<td>IV</td>
<td>30 minutes*</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

* or according to local practice

**N.B.** Carboplatin should be given immediately after paclitaxel infusion
# Treatment Plan – Arm 2

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Schedule</th>
<th>Repeat</th>
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</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m²</td>
<td>IV</td>
<td>3 hours</td>
<td>Day 1</td>
<td>Every 21 days, 3 cycles in total</td>
</tr>
<tr>
<td></td>
<td>60 mg/m²</td>
<td>IP</td>
<td>By gravity as rapidly as possible</td>
<td>Day 8</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m²</td>
<td>IP</td>
<td>By gravity as rapidly as possible</td>
<td>Day 1</td>
<td></td>
</tr>
</tbody>
</table>

*N.B.* IP Cisplatin should be given immediately after IV paclitaxel infusion.
# Treatment Plan – Arm 3

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m²</td>
<td>IV</td>
<td>3 hours</td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>60 mg/m²</td>
<td>IP</td>
<td>By gravity as rapidly as possible</td>
<td>Day 8</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 5 if measured GFR (use AUC 6 if calculated GFR)</td>
<td>IP</td>
<td>By gravity as rapidly as possible</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

**Every 21 days, 3 cycles in total**

_N.B._ IP Carboplatin should be given immediately after IV paclitaxel infusion.
Participating Centres

- Lead group – NCIC CTG
- Collaborators – NCRI (UK), GEICO (Spain)
Phase II

• **Objective:**
  - to identify which of the two IP arms will continue into the phase III portion

• **Stats:**
  - Sample size: 150
  - Accrual: ~ 150 / yr over ~ 1 yr

• **Comparison of Endpoints:**
  - 9-month progression rate post randomization
  - Completion rate of treatment
  - Toxic effects
  - Feasibility
**OV.21 Schema**

**Study Population**

**Stratification and Randomization**

**Phase II Portion**

**ARM 1**
- **Day 1**: Paclitaxel 135 mg/m² IV + Carboplatin AUC 5 or 6 IV;
- **Day 8**: Paclitaxel 60 mg/m² IV Q 21 days x 3 cycles

**ARM 2**
- **Day 1**: Paclitaxel 135 mg/m² IV + Cisplatin 75 mg/m² IP;
- **Day 8**: Paclitaxel 60 mg/m² IP Q 21 days x 3 cycles

**ARM 3**
- **Day 1**: Paclitaxel 135 mg/m² IV + Carboplatin AUC 5 or 6 IP;
- **Day 8**: Paclitaxel 60 mg/m² IP Q 21 days x 3 cycles

**Assess Phase II Outcomes**
(Sample Size = 150)
Proceed to Phase III Portion

**Stratification and Randomization**

**Arm 1**

**Winner of Arm 2 and Arm 3**

**Assess Phase III Outcomes**
(Total Sample Size = 830)
Phase III

• Objective
  - To compare efficacy of selected IP plus IV chemo regimen vs IV Carboplatin plus Paclitaxel in patients with EOC optimally debulked at surgery following neoadjuvant IV chemo

• Stats
  - Sample size: additional 680 (Total of 830)
  - Accrual: will continue in waiting period b/w phase II & III. 150-200/yr over ~ 4 yrs
  - Total duration: 7.7 years
Eligibility Criteria

• Epithelial Ovarian, Peritoneal or Fallopian tube carcinoma
  
  ➢ FIGO Stage IIIB-III at initial stage of disease
  
  ➢ Stage IV if only criterion for is presence of pleural effusion with +ve cytology for ovarian cancer
Eligibility Criteria

• Completed 3-4 cycles of platinum-based neoadjuvant chemo prior to debulking surgery

• ‘Delayed primary debulking’
  ➢ TAH BSO, omentectomy etc
  ➢ Must achieve maximal cytoreduction
  ➢ Residual disease of ≤ 1 cm
Baseline Evaluation

• Within 7 days prior to randomization:
  - History, PE and ECOG
  - Hematology, Biochemistry, CA125

• AFTER surgery but before start of protocol therapy:
  - chest xray or CT scan
  - abdominal/ pelvic CT scan or MRI
  - other scans/xrays as necessary to document disease
## Evaluation During Treatment

<table>
<thead>
<tr>
<th>Evaluation Category</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE, ECOG, Weight</td>
<td>Day 1 each cycle</td>
</tr>
<tr>
<td>Hematology</td>
<td>Day 1, 8 and 22 each cycle</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Day 1 each cycle</td>
</tr>
<tr>
<td>CA 125</td>
<td>Day 1 each cycle, at end of last cycle</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>After each cycle</td>
</tr>
<tr>
<td>Radiology</td>
<td>At end of last cycle (earlier if clinically indicated)</td>
</tr>
<tr>
<td>QoL</td>
<td>Day 1 cycles 2 and 3 / At end of last cycle</td>
</tr>
<tr>
<td>Nursing Practices in IP Administration</td>
<td>Each cycle of IP treatment at EACH IP administration</td>
</tr>
<tr>
<td>Other Investigations</td>
<td>As clinically indicated</td>
</tr>
</tbody>
</table>
Nursing Practices Study

• Objective
  ➢ To evaluate the potential association of various nursing practices with certain patient outcomes
    • Patient positioning during and after administration of IP therapy
    • The pre-warming of IP fluid
    • The use of home hydration practices after administration of IP therapy.
## Evaluation After Treatment

| PE, ECOG, Weight | Before progression or initiation of second-line therapy*:  
|                 | at 6 wks after completing protocol therapy, then every 3 months (beginning 3 months after completing protocol therapy) for 2 years, every 6 months for 2 additional years and then annually until death  
|                 | After progression or initiation of second-line therapy:  
|                 | as indicated  
| CA 125          | (Same as above)  
| Radiology       | (Same as above)  
| Adverse Events  | At 6 weeks post treatment, then every 3 mos for 2 yrs, every 6 mos for 2 additional yrs and then annually until progression or death  
| QoL             | 3, 6 and 12 mos after protocol treatment then beginning 12 mos after protocol treatment, assess annually until disease progression or death  
| Other           | Information of catheter removal  
|                 | All others as clinically indicated  

* At 6 wks after completing protocol therapy, then every 3 months (beginning 3 months after completing protocol therapy) for 2 years, every 6 months for 2 additional years and then annually until death.
Decide on a New Standard?

- **Primary Endpoint**
  - Progression free survival
- **Secondary Endpoints**
  - Overall survival
  - Toxic effects
  - Quality of life
  - Correlative biological studies
  - Economic evaluation
  - Nursing-related practices
Questions?

- NCIC CTG OV.21 website
  - www.ctg.queensu.ca

- Ovarian Cancer Canada website
  - www.ovariancanada.org

- Canadian Cancer Society
  - www.cancer.ca

- Cancer Care Manitoba
  - www.cancercare.mb.ca