Intraperitoneal therapy in Ovarian Cancer

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# Female Cancers in USA 2006

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>212,920</td>
<td>40,970</td>
</tr>
<tr>
<td>Lung/Bronchus</td>
<td>81,770</td>
<td>72,130</td>
</tr>
<tr>
<td>Colorectal</td>
<td>75,810</td>
<td>27,300</td>
</tr>
<tr>
<td>Endometrium</td>
<td>41,200</td>
<td>7,350</td>
</tr>
<tr>
<td>Ovary</td>
<td>20,180</td>
<td>15,310</td>
</tr>
<tr>
<td>Cervix</td>
<td>9,710</td>
<td>3,700</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,740</td>
<td>880</td>
</tr>
<tr>
<td>Vagina/Other</td>
<td>2,420</td>
<td>820</td>
</tr>
</tbody>
</table>

American Cancer Society Facts and Figures, 2006
Example Case: Newly Diagnosed Ovarian Cancer Patient

- Patient: 72-year-old female
  - Abdominal pressure, bloating for 4 months
  - Ascites, pelvic mass on examination
  - CT with omental cake/carcinomatosis/pelvic mass
  - CA 125 = 1548
Example Case: Newly Diagnosed Ovarian Cancer Patient

- Patient: 72-year-old female
  - Abdominal pressure, bloating for 4 months
  - Ascites, pelvic mass on examination
  - CT with omental cake/carcinomatosis/pelvic mass
  - CA 125 = 1548
  - Debulking laparotomy
Ovarian Cancer: Surgical Treatment for Advanced Disease

- Significant survival advantage for women optimally cytoreduced
- Procedures may include:
  - *En bloc* resection of uterus, ovaries and pelvic tumor
  - Omentectomy
  - Selective lymphadenectomy
  - Bowel resection
  - Removal of diaphragmatic and peritoneal implants
  - Splenectomy, appendectomy
Primary Cytoreduction

- **Meta-analysis:**
  - 53 studies (1989-98)
  - 81 cohorts (Stage III/IV)
  - N = 6885 patients

- **Results**
  - Expert centers have higher optimal rates
  - Each 10% ↑ in cytoreduction = 5.5% ↑ in survival
  - Platinum intensity = NS

Bristow, J Clin Oncol 20:1248, 2002
Survival Outcome in Ovarian Cancer

Stage III

Cumulative survival

Survival time (days)

Optimally Debulked Ovarian Cancer

- Defined as post-op residual < 1 cm
- First-line therapy controversial
- IV Carboplatin AUC 6 - 7.5 plus Paclitaxel 175 mg/m2 over 3 hours

Is there a new standard?
Abdominal Chemotherapy for Ovarian Cancer Improves Survival

Women who received chemotherapy directly in their abdomens as part of treatment for advanced ovarian cancer lived more than a year longer than women who received the same chemotherapy intravenously, researchers reported last week.

The findings confirm and expand recent research showing that intraperitoneal (IP) chemotherapy, which delivers drugs directly to the abdominal cavity through a catheter, can significantly increase survival for some women with the disease.

In the study, women who received chemotherapy intravenously and through an IP route lived on average 16 months longer than women who had IV chemotherapy only, according to findings in the January 5, 2006 issue of the New England Journal of Medicine (NEJM).
Intraperitoneal (IP) chemotherapy is an alternative method of delivery. Chemotherapy administered directly into the abdominal cavity (peritoneal space) through an implanted port.

**Rationale:**
- Provide higher concentration of drug directly within the peritoneal cavity (major route of spread)
- Minimize systemic toxicity of chemotherapeutic agents
- Attempt to control malignant ascites

**Limitations:**
- Poor tumor penetration of bulk disease
- Less exposure of extra-peritoneal disease to drug

**Complications:**
- Obstruction to flow or inadequate distribution
- Infection: peritonitis, abdominal wall or catheter
- Intestinal perforation
Rationale for IP Chemotherapy

- Most women with metastatic ovarian cancer have disease limited to peritoneal space
- Pharmacokinetic advantages when chemo via an IP route
  - Higher IP drug concentrations
  - Longer half-life
  - For cisplatin 10-20-fold greater exposure

Dedrick, R et al, Cancer Treat Rep 1978
Intravenous versus Intraperitoneal Administration of Cisplatin

Pharmacokinetics

Lack of Acceptance of IP Therapy in Community of Oncology

- No Standard Catheter
- No Standard Insertion Technique
- Catheter Complications are Common
- Management of Complications Difficult
- Patient selection uncertain
- IV Carbo/Taxol accepted
IP Catheter Placement

1. Use largest bore IV Port-a-Cath
2. Site important
3. Use standard procedures to access port
IP PORT-A-CATH INSERTION

Images not available
Image not available
Clinical settings evaluated

- Intraoperative at time of primary or secondary surgery (± hyperthermia)
- Post-operative in advanced disease
  - Optimally & suboptimally debulked
- Adjuvant for early-stage disease
- Consolidation
- After neo-adjuvant chemo + surgery
Potential IP approaches

- Standard chemotherapeutic agents
- Radioactive agents (e.g, P32, AU198)
- Immunologic agents
  - Radio-labeled antibodies
  - Cytokines (interferon, etc)
  - Tumor-infiltrating lymphocytes
Early findings

- IP chemotherapy not effective in bulky disease
- Chemotherapeutic agents with higher molecular weight had longer half-lives
- Platinums/taxanes have 10-20 times greater concentration IP than when given IV
Role of IP Chemotherapy for Optimally Debulked Advanced-Stage Ovarian Cancer

**GOG 104** – Improved outcome in CP treated patients when cisplatin administered IP (RR 0.76)

**GOG 114** – Improved outcome in TP treated patients when cisplatin administered IP (RR 0.78)

**GOG 172** – Improved outcome in TP treated patients when paclitaxel and cisplatin administered IP (RR 0.73)

3. ASCO 2002 Abstract # 803
# Results IP Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS (mo)</th>
<th>% Inc.</th>
<th>Median OS (mo)</th>
<th>% Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>IV</td>
<td>IP</td>
<td>IV</td>
<td>IP</td>
</tr>
<tr>
<td>Alberts</td>
<td>--</td>
<td>--</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>INT0051</td>
<td>22</td>
<td>28</td>
<td>27</td>
<td>52</td>
</tr>
<tr>
<td>Markman</td>
<td>18.3</td>
<td>23.8</td>
<td>26</td>
<td>49.5</td>
</tr>
<tr>
<td>GOG 172</td>
<td>18.3</td>
<td>23.8</td>
<td>26</td>
<td>49.5</td>
</tr>
</tbody>
</table>

(All differences statistically significant)
Slide not available
GOG Protocol 172

Ovarian cancer
Optimal (<1cm)
Stage III
Stratify:
Gross residual
Planned 2nd look

BRCA Analysis
DNA Banking

Paclitaxel 135 mg/m²/24h
Cisplatin 75 mg/m²
q 21 days x 6

Paclitaxel 135 mg/m²/24h
Cisplatin 100 mg/m² IP D2
Paclitaxel 60 mg/m² IP D8
q 21 days x 6

Second look Laparotomy (if chosen)
GOG Protocol 172

**Rx Group**

<table>
<thead>
<tr>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>93</td>
<td>117</td>
</tr>
<tr>
<td>IP</td>
<td>117</td>
<td>88</td>
</tr>
</tbody>
</table>

**Proportion Surviving**

- **IV Median Survival** = 49.5 months
- **IP Median Survival** = 66.9 months

**RR of death** 0.71 (95% CI: 0.54, 0.94)  
**P** = 0.0076, one-sided log-rank test
## Number of IP Cycles Completed on GOG Protocol 172 (N=205)

<table>
<thead>
<tr>
<th>No. of IP cycles</th>
<th>No. of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16</td>
<td>8%</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>7%</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>5%</td>
</tr>
<tr>
<td>Failed: &lt;6 cycles</td>
<td>119</td>
<td>58%</td>
</tr>
<tr>
<td>Success: 6 cycles</td>
<td>86</td>
<td>42%</td>
</tr>
<tr>
<td>Total</td>
<td>205</td>
<td>100%</td>
</tr>
</tbody>
</table>

Forty (34%) discontinued IP therapy primarily due to catheter complications
# GOG Protocol 172 Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Condition</th>
<th>IV</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>G4</td>
<td>WBC</td>
<td>14%</td>
<td>31%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Platelet</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>G3/4</td>
<td>GI</td>
<td>24%</td>
<td>46%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Renal</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Neuropathy</td>
<td>9%</td>
<td>19%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Fatigue</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Infection</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Metabolic</td>
<td>7%</td>
<td>27%</td>
</tr>
<tr>
<td>G3/4</td>
<td>Pain</td>
<td>1%</td>
<td>11%</td>
</tr>
</tbody>
</table>

No difference in QoL between arms after 12 months
## Reasons for Discontinuing IP TX
(Not IP Catheter Related)

<table>
<thead>
<tr>
<th>REASON</th>
<th>PRIMARY</th>
<th>SECONDARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal / Metabolic</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34/118 (28.8%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Armstrong et al, NEJM 2006
## Reasons for Discontinuing IP TX (IP Catheter Related)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Primary</th>
<th>Contributing</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP catheter infection</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>IP catheter blocked</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>IP catheter leaked</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Access problems</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Bowel complication</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Fluid out vagina</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>46/118 (36%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Armstrong et al, NEJM 2006
# Reasons for Failing IP (uncertain relationship to catheter)

<table>
<thead>
<tr>
<th>REASON</th>
<th>PRIMARY</th>
<th>SECONDARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Refusal</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Other infection</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38/118 (34.7%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Armstrong et al, NEJM 2006
Toxicity with IP chemotherapy

- Presence of an IP catheter
  - Infection, fever
- IP administration of chemotherapy
  - Abdominal pain, nausea, vomiting
- Chemotherapy
  - Greater hematologic, metabolic, and neurologic toxicity
Patient Education

- Rationale for IP chemotherapy
- Overview of procedure
- Possible adverse effects from agents used
- Possible prolonged effects of treatment
- Activity restrictions during IP therapy
Administration Guidelines

- Have patient void prior to initiation of IP chemotherapy.
- Access port with 19 – 20 gauge right angle needle for optimal flow
- Place patient in semi-fowler position.
  - No higher than 30 °
- Warm NS in warm water bath to 37 ° (approximately 15 minutes)
- Drip IP therapy via gravity as rapidly as possible.
  - Never use infusion pump
- Observe site of needle insertion for swelling, leakage, or redness.
- Observe for unusual local swelling
- Observe pt for complaints of pain, shortness of breath, dyspnea, respiratory distress and cramping.
- After infusion, reposition patient every 15 minutes from side to side for 2 hours post infusion.
Supportive Care Issues

1. IV hydration, diuresis, supplementation
2. Antiemetic regimens
3. Antidepressant regimens
4. Anti-peripheral neuropathy regimens
5. Neutropenia/anemia
6. Pain management
Supportive Care Issues:
IV Fluids

- At least 1 L NS during IP instillation of Cisplatin
  - 1L afterward if no cardiac risk factor
  - Add 12.5gm mannitol to IV saline
  - Magnesium Sulfate supplementation
  - Additional electrolyte supplementation as needed
Supportive Care Issues: Antiemetics

- Palonosetron (Aloxi) 250ug IV before IP CDDP for 72 hours 5HT₃ inhibition
- Aprepitant (Emend) 125 mg Day 2 before IP CDDP, 80 mg Days 3 & 4
- Dexamethasone 20 mg IV before IP CDDP and 8mg po bid on Days 3, 4, and 5
- 5-HT3 antagonist on Days 5, 6, and 7 for breakthrough nausea and vomiting
- If breakthrough nausea/vomiting occurs
  - bring pt back for additional hydration
  - Use antiemetic from different class

See NCCN Guidelines at www.nccn.org
Supportive Care
Antidepressants

- Consider Cymbalta 20-30mg po bid
  - Indicated for mild to moderate depression
  - Indicated for control of diabetic neuropathic pain
- Consider Neurontin 300-600-900mg days 1,2, 3 with escalation up to 1800mg/day po (bid dosing)
  - Indicated for postherpatic neuralgia
Supportive Care Issues:
Anti-peripheral Neuropathy Regimens

- Amifostine
  - Significantly reduced grade 2/3 peripheral neuropathy associated with 100mg/m2 IV cisplatin with no reduction in antitumor efficacy (Kemp, et al. JCP 1996, 14(7): 2101-2112)
  - 740mg/m2 IV bolus before IP Cisplatin
  - Alternative dosing regimen: 500mg IV bolus prior to, immediately after, and at the end of clinic visit (i.e. 1500mg total)

- Glutamine 10gm po bid
  - Limited phase II/III data suggest control of paclitaxel-induced neuropathy

- Cymbalta-QD
  - Indicated for control of diabetic neuropathic pain
  - Can escalate dose to 30mg bid
Supportive Issues
Pain Management

- Consider analgesic for mild to moderate pain
- Tylenol PM or Ambien 5-10 mg on evening of Day 2 (to counteract IV dexamethasone and discomfort associated with abdominal distention)
Current consensus

- The toxicities, inconvenience and cost of IP therapy are justified by the improved survival seen with this treatment.
- New, targeted therapies are likely to be more effective in patients who have an excellent response to chemotherapy.
- While we work to improve the tolerability and toxicities of IP therapy, it remains the most effective means of treating ovarian cancer today.
Unanswered questions

- How to improve efficacy and decrease toxicity
- How to integrate IP with new agents
- How to improve catheters
- Role of IP with optimally debulked stage IV, neoadjuvant, consolidation, recurrence, hyperthermia
THANK YOU!!