Intraperitoneal Chemotherapy for Stage IV Gastric Cancer

Andrew M. Blakely, MD

November 7, 2020
Outline

• Rationale for catheter-based intraperitoneal chemotherapy

• Comparison to other intraperitoneal treatment approaches

• Clinical trial at the National Cancer Institute

• Future directions
Clinical Need

• Cytoreduction and HIPEC are reserved for low-volume disease

• However, many patients will present with more extensive disease

  • Some may become candidates for CRS/HIPEC after effective treatment
Why an Intraperitoneal Approach?

- **IV CDDP 100 mg/m²**
  - Plasma: Low
  - Peritoneal fluid: Moderate

- **IP CDDP 90 mg/m²**
  - Plasma: Low
  - Peritoneal fluid: High
Rationale for Catheter-Based Chemotherapy

• Allows for use of chemotherapy drugs that:
  
  • Do not require heat to improve efficacy
  
  • Are cell-cycle specific
# Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight</th>
<th>Type</th>
<th>AUC ratio</th>
<th>T\textsuperscript{1/2} (mins)</th>
<th>T\textsuperscript{90%} (mins)</th>
<th>Dose</th>
<th>Carrier solution</th>
<th>Incompat-ability in solution</th>
<th>Heat synergy</th>
<th>Heat stability</th>
<th>Depth of penetrative</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>579.99</td>
<td>Antitumor antibiotic</td>
<td>230</td>
<td>20</td>
<td>80</td>
<td>15 mg/m²</td>
<td>1.5% dextrose dialysis solution</td>
<td>Heparin, fluorouracil</td>
<td>Yes</td>
<td>42 °C</td>
<td>4-6 cell layers</td>
<td>4-6 cell layers</td>
</tr>
<tr>
<td>DOXIL (liposomal doxorubicin)</td>
<td>579.99</td>
<td>Antitumor antibiotic</td>
<td>1,040</td>
<td>180</td>
<td>NA</td>
<td>100 mg/m²</td>
<td>1.5% dextrose dialysis solution</td>
<td>Heparin, fluorouracil</td>
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<td>42 °C</td>
<td>4-6 cell layers</td>
<td>4-6 cell layers</td>
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<tr>
<td>Etoposide</td>
<td>588.58</td>
<td>Antitumor antibiotic</td>
<td>65</td>
<td>NA</td>
<td>NA</td>
<td>25-350 mg/m²</td>
<td>5% dextrose</td>
<td>Plastic devices; acryls; antibiotics</td>
<td>Yes</td>
<td>42 °C</td>
<td>NA</td>
<td>0.2 mm</td>
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<tr>
<td>5-fluorouracil</td>
<td>130.08</td>
<td>Anti-metabolite</td>
<td>280</td>
<td>30</td>
<td>75</td>
<td>650 mg/m² (x5 days)</td>
<td>0.9% sodium chloride; 1.5% dextrose dialysis solution</td>
<td>Icodextrin</td>
<td>Minimal</td>
<td>43 °C</td>
<td>2,000 µm</td>
<td>NA</td>
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<tr>
<td>Flururidine (FUDR)</td>
<td>246.2</td>
<td>Anti-metabolite</td>
<td>75</td>
<td>NA</td>
<td>NA</td>
<td>500 mg/m² twice daily (x3 days)</td>
<td>0.9% sodium chloride</td>
<td>NA</td>
<td>Minimal</td>
<td>43 °C</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Gemcitabine</td>
<td>299.5</td>
<td>Pyrimidine antagonist</td>
<td>205</td>
<td>40</td>
<td>75</td>
<td>1,000 mg/m²</td>
<td>0.9% sodium chloride</td>
<td>NA</td>
<td>At 48 hours</td>
<td>42.5 °C</td>
<td>NA</td>
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<td>Iromotecan</td>
<td>677.19</td>
<td>Antitumor antibiotic</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>200 mg/m²</td>
<td>1.5% dextrose dialysis solution</td>
<td>NA</td>
<td>No</td>
<td>44 °C</td>
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<td>NA</td>
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<tr>
<td>Melphalan</td>
<td>305.2</td>
<td>Alkylator</td>
<td>56</td>
<td>33</td>
<td>69</td>
<td>70 mg/m²</td>
<td>0.9% sodium chloride</td>
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<td>Marked</td>
<td>42 °C</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Mitomycin C</td>
<td>334.3</td>
<td>Antitumor antibiotic</td>
<td>27</td>
<td>40</td>
<td>90</td>
<td>15 mg/m²</td>
<td>1.5% dextrose dialysis solution</td>
<td>Bleomycin</td>
<td>Yes</td>
<td>42.5 °C</td>
<td>2,000 μm</td>
<td>NA</td>
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<tr>
<td>Mitoxantrone</td>
<td>517.41</td>
<td>Antitumor antibiotic</td>
<td>115-255</td>
<td>NA</td>
<td>NA</td>
<td>28 mg/m²</td>
<td>0.9% sodium chloride; lactated Ringer’s solution</td>
<td>Heparin</td>
<td>Yes</td>
<td>43 °C</td>
<td>5-6 cell layers</td>
<td>NA</td>
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<td>Pemetrexed</td>
<td>471.4</td>
<td>Multitargeted antifolate</td>
<td>70</td>
<td>90</td>
<td>260</td>
<td>500 mg/m²</td>
<td>1.5% dextrose dialysis solution</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Carboplatin</td>
<td>371.25</td>
<td>Alkylator</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>300 mg/m²</td>
<td>0.9% sodium chloride</td>
<td>NA</td>
<td>Yes</td>
<td>41.5 °C</td>
<td>0.5 mm</td>
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<tr>
<td>Cisplatin</td>
<td>300.1</td>
<td>Alkylator</td>
<td>10</td>
<td>30</td>
<td>90</td>
<td>90 mg/m²</td>
<td>0.9% sodium chloride</td>
<td>NA</td>
<td>Yes</td>
<td>41.5 °C</td>
<td>1-3 mm</td>
<td>NA</td>
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<tr>
<td>Oxaliplatin</td>
<td>397.3</td>
<td>Alkylator</td>
<td>16</td>
<td>40</td>
<td>60</td>
<td>460 mg/m²</td>
<td>5% dextrose</td>
<td>Aluminum alkaline or NaCl</td>
<td>Yes</td>
<td>46 °C</td>
<td>1-2 mm</td>
<td>NA</td>
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<tr>
<td>Paclitaxel</td>
<td>853.9</td>
<td>Antimiotic</td>
<td>1,000</td>
<td>NA</td>
<td>NA</td>
<td>120-180 mg (total dose)</td>
<td>1.5% dextrose dialysis solution; 6% hetastarch</td>
<td>Plastic containers and tubes</td>
<td>No</td>
<td>42.5 °C</td>
<td>&gt;80 cell layers</td>
<td>PA</td>
</tr>
</tbody>
</table>
Why Paclitaxel?

- High molecular weight, hydrophobic
- Targets cells that are actively dividing
- Effects are seen as early as 6 hours, last as long as 72 hours
- Ideal agent for bidirectional therapy
Rationale for Bidirectional Therapy

• Treat peritoneal nodules using intraperitoneal and intravenous drugs

• IV chemotherapy is thought to diffuse into the peritoneal space
  • Leakage facilitated by the increased vascularity of tumor nodules

• Co-administration of IP chemo injures or collapses blood vessels
  • This leads to increased cell death in the outer layers of the nodules
Intraperitoneal Chemotherapy: Advantages

**Catheter-Based**
- Does not require the OR
- Can be given with IV chemo

**Laparoscopy-Based**
- Ability to control perfusion
- Can augment with heat
Intraperitoneal Chemotherapy: Disadvantages

**Catheter-Based**
- Inability to control perfusion
- Cannot augment with heat
- Catheter-related complications

**Laparoscopy-Based**
- Does require the OR
- Timing offset with IV chemo
# Prior Experience in Gastric Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial Design</th>
<th>Intervention</th>
<th>Recommended Dose</th>
<th>Accrual</th>
<th>Toxicity</th>
<th>Treatment Response</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>Ishigami, H. et al (2009)</td>
<td>Phase 1</td>
<td>PAX (IP/IV) S-1 (PO)</td>
<td>PAX IV 50mg/m²&lt;br&gt;PAX IP 20mg/m² S-1 PO 80mg/m²/day</td>
<td>n = 9</td>
<td>Dose level 1 - n = 4 grade 3/4 (leukopenia/neutropenia)&lt;br&gt;Dose level 2 - n = 4 grade 3 (leukopenia/neutropenia/diarrhea)</td>
<td>6/7 patients converted to negative cytology</td>
<td>N/A</td>
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<tr>
<td>Kurita, N. et al (2011)</td>
<td>Phase 1</td>
<td>PAX (IP) S-1 (PO) Gastrectomy</td>
<td>PAX IV 40mg/m² S-1 PO 80mg-100mg/day</td>
<td>n = 18</td>
<td>Dose level 2 - n=1 grade 3 (leukopenia)&lt;br&gt;Dose level 5 - n=2 grade 3 (leukopenia)</td>
<td>2/18 patients converted to negative cytology, 2/18 PR, 15/18 SD</td>
<td>Median OS 11mo</td>
</tr>
<tr>
<td>Ishigami, H. et al (2009)</td>
<td>Phase II</td>
<td>PAX (IV/IP) S-1 (PO)</td>
<td>PAX IV 50mg/m²&lt;br&gt;PAX IP 20mg/m² S-1 PO 80mg/m²</td>
<td>n = 40</td>
<td>Grade 3/4 - leukopenia (18%), neutropenia (38%), anemia (10%), Anorexia (5%), N/V (8%), diarrhea (3%)</td>
<td>24/40 patients converted to negative cytology, 10/40 PR, 6/40 SD</td>
<td>1-yr OS 78%, Median OS 22.5mo</td>
</tr>
<tr>
<td>Imano, M et al (2012)</td>
<td>Phase II</td>
<td>PAX (IP) One Dose PAX (IV) S-1 (PO)</td>
<td>PAX IV 80mg/m²&lt;br&gt;PAX IP 80mg/m² S-1 PO 80mg/m²/day</td>
<td>n = 35</td>
<td>Grade 3/4 - anemia (5.7%), leukopenia (8.6%), neutropenia (22.8%), ALT elevation (5.7%)</td>
<td>15/22 reduction in gastric wall thickening 1/8 Target Lesion CR 1/7 Target Lesion PR</td>
<td>1yr OS 68.6%, Median OS 21.3mo</td>
</tr>
<tr>
<td>Yamaguchi, H et al (2013)</td>
<td>Phase II</td>
<td>PAX (IP/IV) S-1 (PO)</td>
<td>PAX IV 50mg/m²&lt;br&gt;PAX IP 20mg/m² S-1 PO 80mg/m²</td>
<td>n = 35</td>
<td>Grade 3/4 - neutropenia (34%), leukopenia (23%), anemia (9%)</td>
<td>5/7 Target Lesion OR 28/35 converted to negative cytology</td>
<td>1yr OS 77.1%, 2yr OS 44.8%, Media OS 17.6mo</td>
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</tbody>
</table>
Clinical Question:

Can we replicate the successes reported in previous studies?
Clinical Trial Objectives

• To evaluate bidirectional therapy for peritoneal metastasis

• Assess progression-free survival

• Evaluate ability to downstage patients to be eligible for HIPEC
Protocol Design

Dx Laparoscopy #1
Peritoneal Bx

Dx Laparoscopy #2
IP Catheter

IP, IV paclitaxel
PO capecitabine
X3 Cycles

Dx Laparoscopy #3
Peritoneal Bx

Resectable

Unresectable

IP, IV paclitaxel
PO capecitabine
X3 Cycles

Unresectable, Responding
or Stable

Dx Laparoscopy
Peritoneal Bx

Progressing

End treatment

Resectable

Off treatment

Unresectable

Responding or Stable
## Protocol Treatment

### Chemotherapy Calendar

<table>
<thead>
<tr>
<th>Cycles 1 and 4</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
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</tbody>
</table>

* = IP paclitaxel; # = IV paclitaxel; ✓ = PO capecitabine

Diagnostic laparoscopy, biopsies (between days 1 and 7)
Inclusion/Exclusion Criteria

Inclusion:
• ≥18 years of age
• Confirmation of GE junction or gastric adenocarcinoma
• ECOG status ≤1

Exclusion:
• Extra-abdominal disease
• Allergy to therapeutic agent
• Prior intraperitoneal therapy
• Existing peripheral neuropathy
Future Directions

• Dose-escalation studies of paclitaxel

• Evaluation of nab-paclitaxel (Abraxane®)

• Identify other IP/IV/PO drug combinations

• Exploration of early or adjuvant IP chemotherapy
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