Intraperitoneal Chemotherapy for Carcinomatosis...

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USELESS
Objectives

- Incidence/Pathogenesis
- Therapeutic Options
- Lack of Standardization
- Lack of Scientific Method
- Extreme Morbidity and Mortality
- Lack of Evidence
- Netherlands Trial
- Preoperative Appointment
- Conclusions
### Incidence

<table>
<thead>
<tr>
<th>Primary</th>
<th>Incidence (cases/yr)</th>
<th>% PD</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>130,000</td>
<td>10-15</td>
<td>5.2</td>
</tr>
<tr>
<td>Ovarian</td>
<td>27,000</td>
<td>75</td>
<td>36</td>
</tr>
<tr>
<td>Gastric</td>
<td>22,000</td>
<td>50</td>
<td>3.1</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>1500</td>
<td>100</td>
<td>12-17</td>
</tr>
<tr>
<td>Appendiceal</td>
<td>500</td>
<td>31</td>
<td>NA</td>
</tr>
</tbody>
</table>

- 25% peritoneum only metastatic site
- 2-year survival chemo/symptomatic surgery: 10%

Pathogenesis

- Multistep process: Direct extension, peritoneal flow, surgical manipulation/trauma
- Lymphatic stomata, milky spots
- Submesothelial lymphatic space
- **Stomata:** diaphragm, small bowel mesentery, greater omentum, appendix epipliociae of large bowel, pelvic peritoneum
- **No stomata:** liver capsule, splenic surface, serosa of small bowel and stomach

Therapeutic Options

- Systemic chemotherapy
- Intraperitoneal chemotherapy
  - Early Postoperative Intraperitoneal Chemotherapy (EPIC)
  - Intraoperative Hyperthermic Chemotherapy (IPHC)
- Palliative surgery
- Cytoreductive surgery
Lack of Standardization

What is this called again?…

• “Sugarbaker”

• Early Postoperative Intraperitoneal Chemotherapy (EPIC)

• Intraoperative Hyperthermic Chemotherapy (IPHC)

• Hyperthermic Intraperitoneal Chemotherapy (HIPC/HIPEC)

• Heated Intraoperative Intraperitoneal Chemotherapy (HIIC)

• Continuous Hyperthermic Peritoneal Perfusion (CHPP)

• Intraoperative Hyperthermic Intraperitoneal Chemotherapy (IHIC)

Yan T. Journal of Clinical Oncology 2006; 24(24): 4011-4018
Lack of Standardization

- Gilly Peritoneal Carcinomatosis Staging
- Peritoneal Cancer Index (PCI)
- Dutch Simplified Peritoneal Cancer Index (SPCI)
- Computerized Tomographic Peritoneal Cancer Index (CTPCI)
- Carcinomatosis staging by the Japanese Research Society for Gastric Cancer
- Completeness of Cytoreduction Score
- Prior Surgical Score

Harmon R. International Seminars in Surgical Oncology 2005; 2(3): 1-10
## Lack of Consistency

<table>
<thead>
<tr>
<th>Author</th>
<th>P</th>
<th>#</th>
<th>Tumor</th>
<th>Chemotherapy Regimen</th>
<th>Temp</th>
<th>Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilati 2003</td>
<td>II</td>
<td>34</td>
<td>C</td>
<td>M 20.1-31.6 mg, C 193.7 mg</td>
<td>41.5° C</td>
<td>90</td>
</tr>
<tr>
<td>Glehen 2003</td>
<td>II</td>
<td>56</td>
<td>G,O,C,M,PP</td>
<td>M 0.7 mg/kg, C 1 mg/kg</td>
<td>46-48° C</td>
<td>90</td>
</tr>
<tr>
<td>Shen 2004</td>
<td>II</td>
<td>77</td>
<td>C</td>
<td>M 40 mg</td>
<td>40.5° C</td>
<td>120</td>
</tr>
<tr>
<td>Elias 2004</td>
<td>II</td>
<td>24</td>
<td>C</td>
<td>O 460 mg/m² in 5% dextrose</td>
<td>43° C</td>
<td>30</td>
</tr>
<tr>
<td>Deraco 2004</td>
<td>II</td>
<td>33</td>
<td>PP</td>
<td>C 25 mg/m², M 3.3 mg/m²</td>
<td>42.5° C</td>
<td>60</td>
</tr>
<tr>
<td>Verwaal 2005</td>
<td>II</td>
<td>117</td>
<td>C</td>
<td>M 35 mg/m²</td>
<td>40-41° C</td>
<td>90</td>
</tr>
<tr>
<td>Zanon 2006</td>
<td>II</td>
<td>25</td>
<td>C</td>
<td>M 15 mg/m²</td>
<td>42° C</td>
<td>60</td>
</tr>
</tbody>
</table>
Where is the SCIENCE?
Optimal chemotherapy?

- Stewart et al. 2005 review
- Peritoneal clearance $1/\sqrt{\text{MW}}$: High molecular weight, lipophilic

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW (Da)</th>
<th>Ratio PF:Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitomycin C</td>
<td>334</td>
<td>75:1</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>130</td>
<td>300:1</td>
</tr>
<tr>
<td>Floxuridine</td>
<td>246</td>
<td>2000:1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>544</td>
<td>975:1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>300</td>
<td>20:1</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>808</td>
<td>1000:1</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>397</td>
<td>25:1</td>
</tr>
</tbody>
</table>
Where is the SCIENCE?

Why use hyperthermia?

Giovanella et al. 1976: Selective Lethal Effect of Supranormal Temperatures on Human Neoplastic Cells

- Hyman embryos
- Colon carcinoma lines (SW 620 SW40)
- Nude thymus-deficient mice
- Graded temperature bath
- Neoplastic cells more susceptible
- 42.5-43°C effective killing of all cell types

Giovanella B. Cancer Research 1976. 36: 3944-3950
Excessive Complications

- University of Minnesota prospective trial 35 patients
- Appendix (19), Colon (7), Mesothelioma (3), Stomach (2), Small Bowel (2), Gallbladder (1), Unknown (1)
- Mitomycin C (variable dose)
- 40°C, 90 minute infusion
- Median survival time: 21.4 months
- Hospitalized 30 days: 34%
- Adverse events: 51%
## Excessive Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal fistula</td>
<td>11%</td>
</tr>
<tr>
<td>Intraabdominal abscess</td>
<td>11%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>6%</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>6%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>6%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3%</td>
</tr>
<tr>
<td>Infected ascites</td>
<td>3%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3%</td>
</tr>
</tbody>
</table>

Tuttle T. Annals of Surgical Oncology 2006; 13(12): 1627-1632
Smeenk et al. 2007

- 1996-2006
- 323 procedures: 184 colorectal cancer, 139 pseudomyxoma peritonei
  - Rate of complete cytoreduction 35.6% to 65.1% (p = 0.012)
  - Morbidity 71.2% to 34.1% (p < 0.001)
  - Hospital stay 24 to 17 days
- Learning curve 130 procedures

Smeenk R. British Journal of Surgery 2007; 94: 1408-1414
Yan et al. 2006
Systematic review of 14 studies
• 530 studies total, 64 “potentially relevant”
• IPHC for colorectal carcinomatosis
• Median Survival 28-60 months
• Overall Morbidity 23%-44%
• Overall Mortality 0%-12%

Yan T. Journal of Clinical Oncology 2006; 24(24): 4011-4018
“The level of evidence was LOW in 13 of the 14 eligible studies.”

-Yan, Black, Savady, Sugarbaker
Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

By Vic J. Verwaal, Serge van Ruth, Eelco de Bree, Gooi Ke W. van Slooten, Harm van Tinteren, Henk Boot, and Frans A.N. Zoetmulder

- 105 patients
- Fluorouracil-leucovorin +/- palliative surgery V.S. HIPEC followed by systemic chemotherapy
- Mytomycin C 17.5 mg/m² to 8.8 mg/m² q 30 min (70 mg max)
- 41-42°C for 90 minutes
- Median follow up 21.6 months
- Median standard survival: 12.6 months
- Median experimental survival: 22.3 months

Verwaal V. Journal of Clinical Oncology 2003; 21(20): 3737-3743
“Swiss Cheese”

- Selection criteria
- Study changed after 1 year
- Short follow up
- Under Powered
- Chemotherapy outdated
- Control Surgery: Bypass or stoma
- Experimental Surgery: Gastrostomy and transgastric jejunal feeding tubes
- No control for visceral resections
Inadequate Power

- 80% Power detect a 20% difference in survival
- **100** patients minimum for $P < .05$

Verwaal V. Journal of Clinical Oncology 2003; 21(20): 3737-3743
Inadequate Chemotherapy

- Fluorouracil and Leucovorin
- FOLFOX/FOLFIRI/Bevacizumab+Cetuximab

Hriesik C. Journal of the American College of Surgeons 2007; 205(3); 468-479
Severe Morbidity

- Median blood loss 4 liters (0.5-30 l)
- Median hospital stay 29 days (6-166 d)
- Median duration HIPEC 485 minutes (8 hours) (315-765 min)
- Mean 1.8 visceral resections: rectum, small bowel, colon, gallbladder, stomach, spleen, omentum
- National Cancer Institute Common Toxicity Criteria (NCI CTC) 65% Grade 3-5
- Overall complication rate 35% of patients, 45% needed prolonged ICU care

Verwaal V. Journal of Surgical Oncology 2004; 85:61 61-67
Severe Mortality

- **8%** Mortality
- 6 or 7 regions median survival of **5.4 months** after therapy
- After 21.6 months: **20** pts from control and **30** pts from HIPEC group were still alive

Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC)
“Patients with 6 or 7 regions involved and in those in whom complete cytoreduction cannot be reached are probably BETTER OFF WITHOUT THIS TREATMENT”

- Verwaal, Tinteren, Ruth, Zoetmulder

PreOp Visit:
Conclusions:

- Data is flawed, biased, and outdated
- Minimal scientific logic
- Old chemotherapy regimens
- Morbidity and Mortality prohibitively high
- Steep learning curve
- Excessive costs
- Useless


