Rationale for the treatment of Peritoneal Surface Malignancy
A full circle: acknowledgements
Rationale for the treatment of Peritoneal Surface Malignancy
A *hopeless* operation for a *hopeless* patient with a *hopeless* disease by a *hopeless* surgeon.

"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."
• Natural history
• Pathophysiology
• Shift of the paradigm
• Pharmacologic rationale
• Pharmacologic variables
• Manipulating variables
• Tumor nodule as endpoint
• Rationale for bidirectional chemotherapy
• Individual drug sensitivity
• Conclusions
‘ NATURAL ‘

HISTORY
PERITONEAL CARCINOMATOSIS: HOW ARE WE DOING?

Source: SEER-data, 1988-2010, National Cancer Institute
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. patients</th>
<th>Median survival (months)</th>
<th>Tumor</th>
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<td>1989</td>
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<td>Sadegi et al</td>
<td>2000</td>
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<td>Jayne et al</td>
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<td>Verwaal et al</td>
<td>2003</td>
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**PERITONEAL CARCINOMATOSIS: HOW ARE WE DOING?**
PATHOFYSIOLOGY
PERITONEAL CARCINOMATOSIS: WHY IS PSM DIFFERENT?

THEORETICAL PATTERNS OF TUMOR SPREAD

- Direct tumor growth
- Lymphovascular spread
- Exfoliation of tumor cells

Steps in the peritoneal metastatic cascade:

1. Liberation of cells from tumor mass
2. Transport throughout the peritoneal cavity
3. Adhesion and invasion
4. Systemic spread
Figure 2: Mechanisms of transcoelomic metastasis in ovarian cancer

Step 1: Epithelial ovarian cancer cell (green) detaches after altered gene expression. Step 2: peritoneal or ascitic current (blue arrow) facilitates peritoneal, lymphatic, and haematogenous metastasis. Step 3: immune evasion by complement inhibition and secretion of TGFβ1, TGFβ2, TGFβ3. Step 4: spheroid formation. Step 5: ascites components stimulate further metastatic progression. Step 6: peritoneal activation and implantation. IC: H4=immune cell-inhibitory protein E7-H4; CXCL12=ligand of chemokine (CXC motif) receptor 4 (CXCR4); PHIL-1=factor H-like protein 1; LPA=lyosphosphatidic acid; MMP=matrix metalloproteinase; VEGF=vascular endothelial growth factor.
EM magnification of the milky spot. It is 5-10 µm in diameter and connects with submesothelial lymphatic channels (courtesy: Yonemura Y; Peritoneal Dissemination, Maeda Shoten, Kanazawa, Japan, 1998)
PERITONEAL CARCINOMATOSIS: 'MILKY SPOTS'
Lacunae in diaphragmatic mesothelial lining
SHIFT OF THE PARADIGM
PERITONEAL CARCINOMATOSIS: AGGRESSIVE APPROACH?
Rationale for an aggressive combined surgical – medical approach

*Shift of the paradigm*

Peritoneal carcinomatosis = distant metastasis

Peritoneal carcinomatosis = regional spread

‘ *a locoregional treatment for a locoregional disease makes sense* ‘

PERITONEAL CARCINOMATOSIS: AGGRESSIVE APPROACH

three steps – one procedure

- Combined multi-organ resections
- Peritonectomy-procedures
- Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)

Treatment of MACROSCOPIC disease

Treatment of MICROSCOPIC disease
Loco-regional chemotherapy

CYTOREDUCTIVE SURGERY + INTRACAVITARY CHEMOTHERAPY

HIPEC  Hyperthermic Intraperitoneal Peroperative Chemotherapy

EPIC  Early Postoperative Intraperitoneal Chemotherapy

BIC  Bidirectional Intraoperative Chemotherapy
PERITONEAL CARCINOMATOSIS: AGGRESSIVE APPROACH

- Combined multi-organ resections
- Peritonectomy-procedures

Treatment of MACROSCOPIC disease
PERITONEAL CARCINOMATOSIS: AGGRESSIVE APPROACH
PERITONEAL CARCINOMATOSIS: AGGRESSIVE APPROACH

- Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)

Treatment of MICROSCOPIC disease
• Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC)
PHARMACOLOGIC RATIONALE
Pharmacokinetic rationale

“the peritoneal permeability of a number of hydrophylic anticancer drugs after intraperitoneal administration may be considerably less than the plasma clearance of that same drug”

- pharmacokinetic principle of **DOSE INTENSIFICATION**
- function of molecular weight
- two compartment model

Rate of mass transfer = PA \left( C_P - C_B \right)

Fig. 1. Traditional two-compartment model of peritoneal transport, in which transfer of a drug from the peritoneal cavity to the blood occurs across the "peritoneal membrane." The permeability-area product (PA) governs this transfer and can be calculated by measuring the rate of drug disappearance from the cavity and dividing by the overall concentration difference between the peritoneal cavity and the blood (or plasma). $C_B$ = the free drug concentration in the blood (or plasma); $V_B$ = volume of distribution of the drug in the body; $C_P$ = the free drug concentration in the peritoneal fluid; $V_P$ = volume of the peritoneal cavity.
DOSE - INTENSIFICATION

MMC Dose = 17mg/200cc

MMC (ug/ml)

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<th>0</th>
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<th>2Hrs</th>
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LEVELS
- PLASMA
- PERITONEAL FLUID
Efficacy versus hematological toxicity

Doxorubicin levels in tumor nodules versus normal adjacent tissues
Question: do plasmatic levels predict toxicity?

BI-DIRECTIONAL INTRAOPERATIVE CHEMOTHERAPY
MITOMYCN PLASMA LEVELS
(Grade III/IV Neutropenic Patients vs Average)

Plasma Levels (µg/mL)

Time (minutes)

Peak [PL] = 0.35(±0.07) µg/mL (neutropenic)
Peak [PL] = 0.31(±0.09) µg/mL (average)

Unpublished data
Fig. 1. Peritoneal barrier modeled as blood and lymph capillaries distributed within a tissue space made up of parenchymal cells, interstitial cells, and matrix molecules. The peritoneum, made up of a single layer of mesothelial cells and underlying connective tissue, separates the fluid in the cavity from the underlying tissue space but does not provide a significant barrier to transport. The major resistances to transport are the capillary endothelium and the cell-matrix system surrounding the exchange vessels.
Question: Is P influenced by our surgery?

**Peritoneal Barrier Function**

Figure 4 — H&E stain of frozen sections of rat demonstrating the presence (A) or absence (B) of peritoneum.

Flessner et al PDI 2003

Figure 5 — Osmotic filtration into the transport chamber and loss of mannitol: effect of the presence of peritoneum. The results of one-way ANOVA demonstrate no significance of the presence of the peritoneum for osmotic volume flux (µL/minute/cm², n = 9, p > 0.9, solid bars) or mass transfer coefficient for mannitol (MTC; cm/minute, n = 9, p > 0.4, open bars).
Question: Is P influenced by our surgery?

Fig. 2 Peritoneal and plasma concentration curves of heated intraoperative mitomycin C. The means ± SD of five patients in each group are shown.
PHARMACOLOGIC VARIABLES
<table>
<thead>
<tr>
<th>Pharmacokinetic VR</th>
<th>Pharmacodynamic VR</th>
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<tbody>
<tr>
<td>• DOSE</td>
<td>• TUMOR NODULE SIZE</td>
</tr>
<tr>
<td>• VOLUME</td>
<td>• DENSITY</td>
</tr>
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<td>• DURATION</td>
<td>• VASCULARITY</td>
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<td>• CARRIER SOLUTION</td>
<td>• INTERSTITIAL FLUID PRESSURE</td>
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<td>• PRESSURE</td>
<td>• BINDING</td>
</tr>
<tr>
<td>• MOLECULAR WEIGHT</td>
<td>• TEMPERATURE</td>
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‘what the drug does to the body’  ‘what the body does to the drug’
Question: do peritoneal drug levels accurately predict efficacy? NO
Manipulating Pharmacologic Variables
PK - VARIABLE: PRESSURE

High Intra-abdominal Pressure Enhances the Penetration and Antitumor Effect of Intraperitoneal Cisplatin on Experimental Peritoneal Carcinomatosis

Philippe Equis, MD,∗† David Consolo, MD,‡ Gay Magne, MD,‡ Philippe Pointaire, MD,‡
Philippe Moretto, MD,&Maria Dolores Ynna, MD,¶ Jean-Luc Beltramo, PhD,¶ Carole Dragou,¶
Michel Simonet, MD,∗† Laurent Benoit, MD,∗ Patrick Rat, MD,† and Bruno Chauvaert, MD∗†‡

FIGURE 3. Distribution of platinum into peritoneal tumor nodules after conventional IP or IAP cisplatin treatment. Rats with 21-day-old carcinomatosis (4 per group) were treated with cisplatin through a conventional intraperitoneal injection (IP) or an intraperitoneal infusion with increased intra-abdominal pressure (22 mm Hg for 1 hour; IAP). Local platinum concentration was measured along the radii of peritoneal tumor nodules by the PIXE method. The platinum distribution in 400 × 800 um² analyzed areas was plotted from the periphery to the tumor center. In conventionally treated IP groups, the cisplatin concentration in the peritoneal liquid was either 250 mg/L in 20 mL isotonic saline (5 mg/rat; 15 mg/kg; ●), or 1875 mg/L in 20 mL isotonic saline (37.5 mg/rat; 112.5 mg/kg; ▲) to compare groups exposed to the same concentration or the same total dose of cisplatin. Cisplatin concentration was 250 mg/L in 150 mL isotonic saline (37.5 mg/rat; 112.5 mg/kg) for the IAP-treated group (■). Each point is the mean of 4 determinations ± SD. A significant difference among the 3 IP treatments was detected (P = 0.0125, Kruskal-Wallis test). The Mann-Whitney test indicated that the difference between both of the upper curves was only significant between a depth of 1400 and 1800 um (P = 0.0421).
Laparoscopic HIPEC: initial experience; opportunities and limitations

Kurt DF van der Speeten, M.D.
Department of Digestive Surgery, Ziekenhuis Oost-Limburg, Genk - Belgium

Method

A 45-year-old patient was admitted to the emergency department with a type IIB colon cancer. The patient underwent a laparoscopic total mesorectal excision (TME) and a laparoscopic partial colonic resection of the right colon. The patient was discharged from the hospital on the 7th day after surgery. The patient had a good outcome with no complications.

Results

The patient underwent a laparoscopic HIPEC procedure on the 7th day after surgery. The HIPEC procedure was performed with a perfusion time of 45 minutes. The perfusion time was monitored using a perfusion pump. The perfusion was stopped and restarted twice during the procedure. The patient had a good outcome with no complications.

Discussion

Laparoscopic HIPEC has been shown to be a feasible procedure with good outcomes. The procedure was performed with a perfusion time of 45 minutes. The perfusion time was monitored using a perfusion pump. The perfusion was stopped and restarted twice during the procedure. The patient had a good outcome with no complications.

References


Pharmacokinetic variables

Journal of Surgical Oncology 2009;100:331–334

Laparoscopic Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) in the Management of Refractory Malignant Ascites: A Multi-Institutional Retrospective Analysis in 52 Patients

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2Department of Surgical Oncology, Ziekenhuis Oost-Limburg, Genk, Belgium

Malignant ascites is a debilitating condition affecting cancer patients in their terminal stage of disease. Recently, laparoscopic hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) was introduced as a new approach. From September 2001 to August 2008, 52 patients were treated with this new modality. No treatment-related mortality was observed. Median survival was 98 days. One patient developed a clinical recurrence. Laparoscopic HIPEC is a safe and effective method for palliating malignant ascites.

Pharmacokinetic variables

Fig. 1. Inflow an outflow catheters in place and secured, through trocar port incisions after laparoscopic adhesiolysis.

Fig. 3. Kaplan-Meier survival function of 52 patients treated with laparoscopic HIPEC in the palliation of malignant ascites.
TUMOR NODULE

AS

PHARMACOLOGIC

ENDPOINT
Doxorubicin levels in peritoneal fluid, plasma, tumor nodules and adjacent tissue

TUMOR NODULE AS PHARMACOLOGIC ENDPOINT

Doxorubicin levels in peritoneal fluid, plasma, tumor nodules and adjacent tissue
Fig. 3 Doxorubicin levels in appendiceal tumor tissue showing diffuse peritoneal adenomucinosis (DPAM) versus peritoneal mucinous carcinomatosis (PMCA). Peritoneal fluid concentrations are also shown. TN tumor nodule, PF peritoneal fluid
TUMOR NODULE AS PHARMACOLOGIC ENDPOINT

[Graphs showing the concentration of Doxorubicin, Cisplatin, and Melphalan in Peritoneal Fluid, Plasma, and Tumor nodules over time (minutes).]

DOXORUBCIN  
CISPLATIN  
MELPHALAN
Rationale for
Bidirectional Intraoperative Chemotherapy (BIC)
Introduction: concept of BIC

Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution


One hour before IPCH we delivered systemic intravenous leucovorin 20 mg/m² and 5-FU 400 mg/m² because 5-FU potentiates the action of oxaliplatin [11]. However, as 5-FU cannot be mixed with oxaliplatin in the peritoneal cavity due to pH incompatibility, it was delivered intravenously. Following this systemic perfusion, tumour and healthy tissue were soaked with 5-FU before the beginning of the IPCH. A low dose of 400 mg/m² was chosen to avoid intensifying the aggressiveness of combined complete cytoreductive surgery and IPCH.
Pharmacologic concept of bidirectional (IV and IP) chemotherapy

Modified from Fujiwara K. Int J Gynecol Cancer 2007, 17, 1-20
FIGURE 2: 5-Fluorouracil concentrations in peritoneal fluid and plasma after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=20).

- Rapid distribution to ALL body compartments
- Metabolization restricted to plasma compartment
**FIGURE 3:** 5-Fluorouracil concentrations in plasma, peritoneal fluid, and tumor nodules after intravenous administration during hyperthermic intraperitoneal chemotherapy procedure (N=9).
Rationale for **intravenous** administration of 5-fluorouracil (*augmentative drug*)

- Rapid distribution to all body compartments (including peritoneal cavity)
- Metabolisation confined to plasma compartment
- Pharmacokinetic advantage

**Timing** of intravenous chemotherapy emerges as a new variable

- Pharmacological ‘sink’ phenomenon in the artificial ascites
- Ideal situation for drug synergism with intraperitoneal chemotherapy
- Normothermic administered IV 5-FU = subject to IP hyperthermic augmentation
INDIVIDUAL

DRUG SENSITIVITY
Heterogeneous activity of cytotoxic drugs in patient samples of peritoneal carcinomatosis

H. Mahteme a, A. von Heideman b, B. Grundmark c, B. Tholander d, L. Pålman a, B. Glimelius b,d, R. Larsson c, W. Graf a, P. Nygren b,*

Conclusions: The activity in vitro of cytotoxic drugs commonly used in IPC for PC is very heterogeneous. Efforts for individualizing drug selection for PC patients undergoing IPC seem justified.
NON-METABOLIZERS

Unmetabolized mitomycin C. In the top portion is a representative HPLC chromatogram of mitomycin C and its metabolites in peritoneal fluid, plasma and urine. This pattern of the chromatogram was observed in a great majority of patients. The lower graphs shows the HPLC chromatogram of a single patient who had failure to metabolize the drug. Six patients (4%) had this unusual mitomycin C chromatogram.
TIME FOR A NEW CONCEPTUAL MODEL
Pharmacokinetics and Pharmacodynamics of Perioperative Cancer Chemotherapy in Peritoneal Surface Malignancy

Kurt Van der Speeten, MD,* Oswald A. Stuart, BS,† and Paul H. Sugarbaker, MD†
CONCLUSIONS
• PSM is a locoregional disease and as such warrants a locoregional approach.

• CRS addresses macroscopic disease and the subsequent intraperitoneal chemotherapy eliminates residual microscopic disease

• Dose intensification (IP/IV) is the driving force

• Tumor nodules emerges as the pharmacologic endpoint

• Timing of IV chemotherapy emerges as a new pharmacologic variable

• Individual drug sensitivity ?
THANK YOU