USA Trials in the Treatment of Peritoneal Carcinomatosis from Colorectal Cancer

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USA
Outcome of Peritoneal Surface Malignancies of Colo-Rectal Origin

- Glehen, August 15 2004, JCO
  506 patients
  271 patients with a complete cytoreduction
  Median Survival: 32.4 months

- Verwaal, January 2005, Ann Surg Onc
  117 patients
  59 patients with a complete cytoreduction
  Median Survival: 42.9 months
  45% 5-yr survival (2008 update)
## Incomplete Cytoreductions

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glehen</td>
<td>2004</td>
<td>129</td>
<td>8.4 m</td>
</tr>
<tr>
<td>Zoetmulder</td>
<td>2004</td>
<td>10</td>
<td>5.4 m</td>
</tr>
<tr>
<td>Sugarbaker</td>
<td>2004</td>
<td>174</td>
<td>20 m</td>
</tr>
<tr>
<td>Verwaal</td>
<td>2005</td>
<td>17</td>
<td>5 m</td>
</tr>
</tbody>
</table>
Systemic Chemotherapy in the treatment of Metastatic Colorectal Cancer

- 1959  5-FU/LV  12.6 months
- 2000  Saltz (IFL)  14.8 months
- 2002  FOLFOX-4  16.0 months
- 2004  IFL-Bevacizumab  20.3 months
- 2008  All of the above  > 24 months
You need a complete cytoreduction.

Having a complete cytoreduction does not guarantee a good outcome.

We are able to achieve complete cytoreductions in about 50% of patients.

More than likely, the complications are due to the extent of Surgery and not the HIPEC with Mitomycin
Stage IV is Stage IV
No need for subsets
Do not recognize that intracoelomic dissemination is different than hematogenous dissemination
However, we know that hematogenous dissemination is different than lymphatic dissemination
We know that 1 positive LN is very different than 10 positive LN
We know that 1 liver met is very different than 10 liver metastases
USA Guidelines

- American Cancer Society
- American Society of Clinical Oncology
- National Cancer Institute
- National Comprehensive Cancer Network

If you have colon cancer with carcinomatosis and ask them for options
If you are the medical oncologist and ask them for options
“We have two buckets; one full of luck and one empty of experience. We need to fill up the latter without emptying the former”

Gabriel Ruiz

First BASE-jumper of El Cañón del Sumidero
Current HIPEC Situation in the US

“We have two buckets; one full of enthusiasm and one empty of data. We need to fill up the latter without emptying the former”

Jesus Esquivel
Who visited El Cañón del Sumidero
(But did not jump)
How are we going to get there

- By filling up the bucket with Data
- Practice Altering Data (PAD)
- Data with positive p values but, p values that are not only statistically significant but clinically significant.
- Prospective Randomized Trials that are powered to show PAD
Data, Precious Data

- The Power of Data
  - Good Data is expensive, labor intense, takes too much time. (it can get old)
  - Not needed in the opinion of some.

- The Power of NO Data
  - Reduces cost for the insurance companies (short term)
  - Prevents the establishment of guidelines which would clearly simplify patient care
PC in Colorectal and Gastric Cancer

- CRS and HIPEC is the gold standard treatment for colorectal cancer with PC.... when optimal CRS is achieved in an experienced center.

PC (stage 1-2) from gastric cancer could be treated with CRS and HIPEC within clinical trials: … still under evaluation.

2008 French NCI recommendation.
Policy Statement

Medically Necessary:

Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of gastrointestinal origin is considered medically necessary for the treatment of pseudomyxoma peritonei.

Investigational/Not Medically Necessary:

Cytoreduction and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis of gastrointestinal origin is considered investigational/not medically necessary for all other indications.
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith and Jill P Pell

BMJ 2003;327:1459-1461
doi:10.1136/bmj.327.7429.1459
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomized controlled trials.
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomized controlled trials.
Liver patients with R0 resection
Carcinomatosis patients with complete cytoreduction

Sugarbaker PH, JCO 21(5)762,2003
Cytoreductive surgery and perioperative intraperitoneal chemotherapy for isolated colorectal peritoneal carcinomatosis: experimental therapy or standard of care?

Yan TD, Morris DL.

University of New South Wales, Department of Surgery, St. George Hospital, Sydney, Australia.

The combined treatment for patients with isolated colorectal peritoneal carcinomatosis should be considered to be the current standard of care.
HAI and HAIPEC

- HAI has continued to show benefits in the treatment of isolated hepatic metastases from colorectal cancer. Pharmacokinetic advantage. 100-400 fold FUDR

- The treatment requires multidisciplinary coordination between surgical oncology and medical oncology, technical expertise for safe dosing....

- Further trials are planned to explore HAI and systemic therapy to improve survival....

Loco-Regional Therapy

- HAI 1757 publications
- EPIC
- NIPS
- HIPEC
- NIPC for ovarian cancer

The summary is: More talked about than actually done
PROGRESS

- Pause
- Re-direct goals and objectives
- Organize
- Gather
- Resources
- Enthusiasm
- Smile
- Start Sweating
The Journey

- Milano December 2006
- Presented the initial idea of a randomized trial
February and March 2007
USMCI-Peritoneal Surface Malignancy Group
Proposed Phase III Trial

Limited Peritoneal Surface Malignancy of Colonic Origin with No prior Cytoreduction

Prior Chemo

No Prior Chemo

Best Systemic Therapy
N=164

Cytoreduction + HIPEC (MMC) + Best Systemic Rx
N=164

Primary Outcome
1. Peritoneal Progression Free Survival

Secondary Outcomes
1. PFS
2. Overall Survival
3. Toxicity burden
4. QOL appraisal
5. CTC during Rx
Phase III Trial continued…..

- Right after SSO in Washington, DC.
- Industry support (2 million dollars).
- DoD endorsement.
- CALGB turns us down.
- Duke University to run the trial stats.
- July 2007, The cost? 9 million dollars
- Avastin and Erbitux makers: No Thanks.
Phase III Trial continued…..

- September 18, 2007 presented to the NIH.
- Colon Cancer Task Force (25)
- GI Steering Committee
- CTEP
Limited Peritoneal Surface Malignancy of Colonic Origin with No prior Cytoreduction

USMCI-Peritoneal Surface Malignancy Group Proposed Phase III Trial

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Best Systemic Therapy
N=164

Cytoreduction + HIPEC (MMC) + Best Systemic Rx
N=164

Cross Over At Progression

Prior Chemo
No Prior Chemo
MEMORANDUM

To: CTEP Protocol and Information Office

From: Meg Mooney, MD, CIB, CTEP, DCTD

Date: October 14, 2008


14 pages requiring a response to 39 comments
Limited Peritoneal Surface Malignancy of Colonic Origin with No prior Cytoreduction

Stratify

Sync Vs Met

Measurable Vs Not meas.

Perf Status

Cytotoxic Biologics

RandomIZE

Best Systemic Therapy

N=155

Cross Over At Progression

Cytoreduction + HIPEC (MMC)

+ Best Systemic Rx

N=155

Primary Outcome
1. Overall Survival

Secondary Outcomes
1. PFS
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3. QOL appraisal
4. CTC during Rx

USMCI-ACOSOG-NCI Pilot/Phase III Trial
Version 24+ October 25, 2008
Ideal Therapy in PSM

Efficient

Reproducible

Questioned
Efficient

- C: Maximize effectiveness and minimize toxicity.
- C: Data, not opinions, should lead to guidelines.
- A: Phase III USMCI-PSMG-ACOSOG
- A: Feasibility study of Laparoscopic CRS+HIPEC in limited PSM
Reproducible

- C: If there is a surgical technique that constitutes the primary treatment modality, we have the obligation to teach it.

- A: We are starting a pilot training program in CRS and HIPEC for military Surgical Oncologists using STAT
Questioned

- Can the treatment strategy improve?.
- Need to evolve based on new data?.
Future Directions

- American Society of Peritoneal Surface Malignancies
- Non for profit organization
- Goal: Establish guidelines of care based on protocol generated data
- www.americansocietypsm.org
- Open access Journal of PSM
Caution

- It is funny how research data can change today's truth into tomorrow’s inaccuracies
- Breast Cancer and ultra-radical mastectomy
- Anal Cancer and abdomino-perineal resection
- Rectal Cancer, if you can feel it = APR