Does HIPEC improve Survival in Advanced Ovarian Cancer? CON

Ignace Vergote, MD PhD

University Hospitals Leuven, Leuven Cancer Institute, Leuven, European Union
HIPEC CON

Thanks

• Philipp Harter
• Luis Chiva
• Andreas du Bois
• Fotopoulou Christina
• Sehouli Jalid
• Mahner Sven
• Van Nieuwenhuysen Els
• Gonzalez-Martin Antonio
• ...

Harter Ph et al, Arch Gynecol Obstet 2018; 298(5): 859-60
Why Intraperitoneal Instead of Intravenous?

Some theoretical hypotheses

- Ovarian cancer typically spreads intraperitoneally BUT
  - retroperitoneal disease and, with better imaging, extra-abdominal disease, is present in the majority of patients.
  - In addition, adhesions prevent spread of the drugs in the cavity
- Higher drug concentration directly to the tumor, BUT depth of drug penetration is very superficial.
- Heat would enhance the cytotoxic effect of chemo
- Numerous retrospective reports on IP, HIPEC and PIPAC, BUT

Let’s concentrate on randomised trials
Higher drug concentration to the tumor?

2 options:
- Intraperitoneally (IP)
- Higher intravenous (IV) dose (high-dose chemotherapy)

HIDOC
EUROPEAN INTERGROUP STUDY

Epithelial ovarian cancer
Surgical debulking
FIGO IIb/III - IV ≤65 years

Surgery

Arm A
Multicycle high dose chemotherapy

Arm B
Standard dose chemotherapy

FIGO, International Federation of Gynecology and Obstetrics; HIDOC, High-Dose Ovarian Cancer

HIDOC European Intergroup Study

Highdose chemotherapy without any benefit in advanced ovarian cancer

Median OS
HD = 54.4; Control = 62.8 months
HR = 1.17 (0.71-1.94); P = .54

Intraperitoneal?

3 TRIALS, BUT

Too toxic, differences in dosages and schedules

Old control arm

Too toxic

Phase III Trial of Standard-Dose Intravenous Cisplatin Plus Paclitaxel Versus Moderately High-Dose Carboplatin Followed by Intravenous Paclitaxel and Intraperitoneal Cisplatin in Small-Volume Stage III Ovarian Carcinoma: An Intergroup Study of the Gynecologic Oncology Group.

Year 1996
GOG 104
<2 cm
N=564

Year 2001- GOG 114
<1 cm N=462

Year 2006-GOG 172
<1 cm N=415

18% on IP received <3 courses due to toxicity

43% on IP received <3 courses due to toxicity
After primary surgery, women with optimally-debulked FIGO stage III ovarian cancer should be counseled about the clinical benefit associated with combined IB and IP administration of chemotherapy. Based on the most recent trials, strong consideration should be given to a regimen containing IP cisplatin (100 mg/m2) and a taxane, whether given by an IV only or IV plus IP.

Women should not be subjected to intraperitoneal chemotherapy outside the context of properly designed clinical trials. These trials must either assess IP therapy in comparison to standard treatment or address the issue of route of administration for equivalent doses and schedules of the same drugs, not a mosaic of these questions.

In the meantime, can someone come up with a sensible IP regimen?
Careful Strategic Planning Is Needed
Randomization

Epithelial ovarian cancer
Optimal Stage III
No Prior therapy

Part A: Cycles 1 - 6*
Paclitaxel 80 mg/m² iv day 1,8,15
Carboplatin iv AUC 6 day 1
Bevacizumab 15 mg/kg iv day 1**

Part B: Cycles 7 - 22*
Paclitaxel 80 mg/m² iv day 1,8,15
Carboplatin ip AUC 6 day 1
Bevacizumab 15 mg/kg iv day 1**
Paclitaxel 135 mg/m² iv day 1
Cisplatin ip 75 mg/m² day 2
Bevacizumab 15 mg/kg iv day 1**
Bevacizumab 15 mg/kg iv day 1 cycles 7 - 22

*Continue regimen every 3 weeks for 6 cycles of chemotherapy and a total of 22 cycles including bevacizumab unless toxicity or progression intervenes

**Beginning on cycle 2

N = 1560

Walker J SGO 2016
**GOG 252**

**Progression-Free Survival by Treatment Group**

*Stage II or III Optimally Debulked*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb(IV)+T+Bev</td>
<td>303</td>
<td>461</td>
<td>26.8</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>300</td>
<td>464</td>
<td>28.7</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>307</td>
<td>456</td>
<td>27.8</td>
</tr>
</tbody>
</table>

**Walker J SGO 2016**
Why was GOG-252 negative?

Suggestions of J Walker:

• Is bevacizumab masking the effect of IP (see GOG-262)?
• Dose dense paclitaxel in the control arm has improved the performance of control arm?
• Different dose of cisplatin (75 mg/m² instead of 100 mg/m²)?
• Were “optimal < 1cm” patients in GOG-252 (presented in 2016) the same as in GOG-172 (published 2006)?

STILL, GOG-252 IS THE LARGEST AND BEST PLANNED RANDOMIZED IP STUDY, AND IS NEGATIVE!
HIPEC
Systematic Review HIPEC in Ovarian Cancer

PubMed search: “HIPEC” AND “Ovarian Cancer”
143 Publications
From 2008 to May 2014

Articles focus on “HIPEC AND Ovarian Cancer”
(Mixed series with other tumors were discarded)
22 Publications 1450 Patients

Primary setting 493 Patients
Recurrent setting 957 Patients

11 Studies
248 Patients
HIPEC at PRIMARY DEBULKING
With data either on OS-DFS

8 Studies
499 Patients
HIPEC at SECONDARY DEBULKING
With data either OS-DFS & Platinum Int.

This review has failed to show a clear survival benefit that justifies the use this technique as a standard daily practice. Therefore, it is our perspective that the currently available data regarding this approach is fractionated and very difficult to interpret. Thus, we believe that, based on the available information, neither gynecologic oncologists nor oncologic surgeons should offer this therapeutic approach to patients except in the context of a clinic ...
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer


- N = 245 pts
- N = 8 sites
- FIGO III only
- NACT 3 x Carbo/Pac
- At least SD

Standard Arm
No HIPEC

Experimental Arm
HIPEC Cisplatin 100 mg/m2 / 90 min

3 x Carboplatin / Paclitaxel IV
How could one dare questioning the NEW ENGLAND JOURNAL OF MEDICINE?

Ovarian Cancer Treatment — Are We Getting Warmer?

David R. Spriggs, M.D., and Oliver Zivanovic, M.D.

In conclusion, this randomized trial is a very important first step but should not drive changes in practice yet. Primary cytoreductive surgery for...
Sample size calculation

- “...estimated that...median PFS in the conventional...arm will be about 18 months.
- An increase in median PFS of at least 50% would be considered necessary” (18-> 24 months)
- “That means that 140 patients should be enrolled in each group” (n=280)
- Amendment 2012: total sample size 240 - why? TOO LOW ACCRUAL

Recruitment

- The study will start in 6 institutes, each treating between 10 and 50 eligible patients yearly. Other institutes will be invited to participate.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>6</td>
</tr>
<tr>
<td>2008</td>
<td>12</td>
</tr>
<tr>
<td>2009</td>
<td>21</td>
</tr>
<tr>
<td>2010</td>
<td>32</td>
</tr>
<tr>
<td>2011</td>
<td>44</td>
</tr>
<tr>
<td>2012</td>
<td>41</td>
</tr>
<tr>
<td>2013</td>
<td>28</td>
</tr>
<tr>
<td>2014</td>
<td>28</td>
</tr>
<tr>
<td>2015</td>
<td>25</td>
</tr>
<tr>
<td>2016</td>
<td>8</td>
</tr>
</tbody>
</table>
Patients who had received three cycles of neoadjuvant chemotherapy with carboplatin...and paclitaxel...could be registered in the trial before the interval cytoreductive surgery took place.

Protocol 2006: Before 1st cycle

NEJM: After 3 cycles NACT

7.3.1. Before start treatment
• When patients are eligible, following investigations should be performed within 14 days prior to registration (before 1st chemotherapy or before interval debulking):
  • If registration takes place before 1st cycle of chemotherapy, the baseline sample for proteomics studies and PBMC isolation should be obtained within 2 weeks before start chemotherapy.

Knowing whether the patient will get HIPEC or not, before or at the start of surgery might influence the surgeon and induce bias.
Van Driel - HIPEC - Comments (3)

Small study leading to possible bias: \( n = 245 \) – only 15 death events difference!

- **Selection of patients**
  - "Not suitable" for PDS - **no criteria defined** and NACT could be started in another hospital
  - Recruitment period 9 years = 3 pts/center/year - hyperselection

- **Selection of sites / surgeons**
  - Only "qualification criteria": HIPEC equipment available
  - No information about surgeons’ qualifications
Van Driel – HIPEC – Comments (3)
Small study leading to possible bias: n = 245 – only 15 death events difference!

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgery (N=123)</th>
<th>Surgery plus HIPEC (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (IQR) — yr</td>
<td>63 (56–66)</td>
<td>61 (55–66)</td>
</tr>
<tr>
<td>Tumor histologic type — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade serous</td>
<td>107 (87)</td>
<td>112 (92)</td>
</tr>
<tr>
<td>High-grade endometrioid</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>4 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Clear-cell carcinoma</td>
<td>5 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Low-grade serous</td>
<td>2 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Low-grade endometrioid</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Metastasis of gastrointestinal tumor</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

13 unfavourable non-HGSOC Versus 3!!!
Van Driel – HIPEC – Comments (3)

Small study leading to possible bias: n = 245 – only 15 death events difference!

Hazard ratios (HR) and recruitment numbers per centre
of note; 2 further centres recruiting only one patient each (Antwerp and CMSE) not included
<table>
<thead>
<tr>
<th>Adverse Events any Grade %</th>
<th>NONHIPEC</th>
<th>HIPEC</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>11</td>
<td>18</td>
<td>+ 63 %</td>
</tr>
<tr>
<td>Ileus</td>
<td>3</td>
<td>8</td>
<td>+ 166 %</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>33</td>
<td>+ 44 %</td>
</tr>
<tr>
<td>Thrombembolic event</td>
<td>2</td>
<td>6</td>
<td>+ 200 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>37</td>
<td>+ 23 %</td>
</tr>
<tr>
<td>Alopecia</td>
<td>16</td>
<td>19</td>
<td>????</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>14</td>
<td>+ 56 %</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
<td>12</td>
<td>+ 50 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical details</th>
<th>NONHIPEC</th>
<th>HIPEC</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel Resection with Stoma (% of pts. with any bowel resection)</td>
<td>43</td>
<td>72</td>
<td>+ 29 %</td>
</tr>
<tr>
<td>Median duration of Surgery [min.]</td>
<td>192</td>
<td>338</td>
<td>+ 146</td>
</tr>
</tbody>
</table>

... and not any data about surgical complications (e.g. Clavien-Dindo), no data on patient reported outcome (PRO)
## Van Driel – HIPEC – Comments (5)

Is the OS and PFS comparable to other trials?

<table>
<thead>
<tr>
<th>European (mainly) studies</th>
<th>PFS Median, mos</th>
<th>OS Median, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGO-OVAR 3</td>
<td>17.2</td>
<td>42.3</td>
</tr>
<tr>
<td>AGO-OVAR 5</td>
<td>17.9</td>
<td>41.1</td>
</tr>
<tr>
<td>AGO-OVAR 7</td>
<td>18.8</td>
<td>49.1</td>
</tr>
<tr>
<td>AGO-OVAR 9</td>
<td>20.5</td>
<td>53.2</td>
</tr>
<tr>
<td>AGO-LION</td>
<td>25.5</td>
<td>69.2</td>
</tr>
<tr>
<td>EORTC NACT</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>CHORUS NACT</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>ENGOT-ov2/Trinova 3</td>
<td>16</td>
<td>46</td>
</tr>
<tr>
<td>Dutch NACT- control arm- non-HIPEC*</td>
<td>11 + 3</td>
<td>34 + 3</td>
</tr>
<tr>
<td>Dutch NACT HIPEC*</td>
<td>14 + 3</td>
<td>45 + 3</td>
</tr>
</tbody>
</table>

- **HYPERSELECTED:** only stage FIGO III (no FIGO IV), only R < 1cm and 68% R0 !!!
- In the EORTC trial the R0 rate at IDS in Holland was only 28%! 
Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer.

Myong Cheol Lim, et al, Korea

184 patients
EOC III and IV
PDS and IDS
Residual tumor <1cm
July 2010 - January 2016.

HIPEC, cisplatin 75 mg/m²
- 92 patients

Standard (no HIPEC),
- 92 patients

Balanced groups for:
- Age
- BMI
- PS
- Stage,
- Histology
- CA125
- NACT
### OTHER RANDOMIZED STUDY ON HIPEC IN OVARIAN CANCER-
The Korean Study

<table>
<thead>
<tr>
<th></th>
<th>HIPEC</th>
<th>NONHIPEC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHOLE GROUP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year PFS</td>
<td>43.2%</td>
<td>43.5%</td>
<td>.569</td>
</tr>
<tr>
<td>5-year PFS</td>
<td>20.9%</td>
<td>16.0%</td>
<td>.569</td>
</tr>
<tr>
<td>5-year OS</td>
<td>51.0%</td>
<td>49.4%</td>
<td>.574</td>
</tr>
<tr>
<td><strong>NEoadjuvant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>20 m</td>
<td>19 m</td>
<td>.137</td>
</tr>
<tr>
<td>OS</td>
<td>54 m</td>
<td>51 m</td>
<td>.407</td>
</tr>
</tbody>
</table>

Control arm IDS: PFS 19 and OS 51 months (from start of NACT)!
HIPEC does not show any benefit!

HIPEC was introduced in COLON CANCER but also failed!!!

**PRODIGE 7: Randomized Phase III Trial of HIPEC for Colorectal Peritoneal Carcinomatosis**

HIPEC failed to show a benefit in PFS and OS in COLON CANCER

But morbidity is higher!

<table>
<thead>
<tr>
<th>60-day morbidity</th>
<th>HIPEC</th>
<th>Non-HIPEC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Complications</td>
<td>3-4-5</td>
<td>32 24.1</td>
<td>18 13.6</td>
</tr>
</tbody>
</table>

Adjuvant HIPEC in patients with colon cancer at high risk of peritoneal metastases: Primary outcome of the COLOPEC multicenter randomized trial (abstract 482)

Pieter Tanis, on behalf of the COLOPEC trial study group

Department of Surgery, Amsterdam UMC, University of Amsterdam, the Netherlands
Primary endpoint COLOPEC study: peritoneal metastasis free survival

Presented by: Pieter J Tanis

At risk control arm
At risk experimental arm

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>PMFS Control arm</th>
<th>PMFS Experimental arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>99</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>18</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>

18 months PMFS 81% vs 76%
HR 0.86 (0.51-1.54)
1st ESGO-ESMO Consensus Conference on Ovarian Cancer (May 2018)
# Advanced Stage

*Is there a place for intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy?*

<table>
<thead>
<tr>
<th>Summary of Recommendations</th>
<th>LoE</th>
<th>GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraperitoneal chemotherapy is not a standard of care as first-line treatment</td>
<td>I</td>
<td>A</td>
<td>Yes: 95% (38 voters) Abstain: 5% (2 voters)</td>
</tr>
<tr>
<td>Hyperthermic intraperitoneal chemotherapy is not a standard of care as first-line treatment</td>
<td>II</td>
<td>A</td>
<td>Yes: 95% (38 voters) Abstain: 5% (2 voters)</td>
</tr>
</tbody>
</table>

Conclusions- HIPEC

1. There are no adequate randomized data for the use of HIPEC in relapsed OC!
2. Data about HIPEC in first line ovarian cancer are not convincing, and do not change the standard of care, which remains IV chemotherapy in all patients
3. There is significant toxicity with HIPEC
4. Further use of HIPEC should be limited to prospective trials
5. These trials should be large enough AND avoid bias
   (OVIHIPEC-2 should take considerations of other GCIG/ENGOT groups into account: double blind? hyperthermia and iv chemotherapy,..?)