PRO: HIPEC improves survival in AOC

Gabe Sonke, medical oncologist
Netherlands Cancer Institute
• Institutional research support from AstraZeneca, Merck, Novartis, and Roche
Friday 22nd February
12:35
Palau de la Música

Belgium

Netherlands

Does HIPEC improve survival in AOC?
12th International Symposium Advanced Ovarian Cancer
Why consider HIPEC in ovarian cancer?

- Far too many women die from recurrent disease
- Peritoneal recurrences are common (even after complete resection)
- HIPEC increases peritoneal exposure to cisplatin
- Hyperthermia induces homologous recombination deficiency
Patients were ineligible for primary cytoreductive surgery (CRS) because of extent of disease.

Follow-up visits were performed every 3 months for the first 2 years, then every 6 months thereafter.

Tumor assessments with CT scans were performed 6, 12, and 24 months after the last chemotherapy.

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used for grading toxicity.

van Driel et al. NEJM 2018
OVHIPEC study

Surgical findings

• Differences
  – longer OR time (146 min, per protocol)
  – longer ICU stay (1 day, per protocol)

• No difference in
  – complete resections (68%)
  – optimal resections (30%)
  – bowel resections
  – quality of life
  – adverse events
  – days in hospital
  – time to restart chemotherapy
  – chemotherapy completion rate
OVHIEPC study

Results

van Driel et al. NEJM 2018
## OVHIPEC study

### Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Surgery</th>
<th>Surgery plus HIPEC</th>
<th>Hazard Ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>43/45</td>
<td>34/43</td>
<td>0.63 (0.35–1.15)</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>67/78</td>
<td>65/79</td>
<td>0.72 (0.46–1.12)</td>
</tr>
<tr>
<td><strong>Histologic type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade serous</td>
<td>96/107</td>
<td>91/112</td>
<td>0.69 (0.48–1.02)</td>
</tr>
<tr>
<td>Other</td>
<td>14/15</td>
<td>7/9</td>
<td>0.56 (0.17–1.86)</td>
</tr>
<tr>
<td><strong>Previous surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100/111</td>
<td>90/110</td>
<td>0.71 (0.49–1.03)</td>
</tr>
<tr>
<td>Yes</td>
<td>10/12</td>
<td>9/12</td>
<td>0.47 (0.14–1.61)</td>
</tr>
<tr>
<td><strong>No. of involved regions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>73/83</td>
<td>62/83</td>
<td>0.64 (0.41–1.01)</td>
</tr>
<tr>
<td>6–8</td>
<td>37/40</td>
<td>37/39</td>
<td>0.66 (0.35–1.23)</td>
</tr>
<tr>
<td><strong>Laparoscopy before surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>95/105</td>
<td>86/103</td>
<td>0.69 (0.47–1.02)</td>
</tr>
<tr>
<td>Yes</td>
<td>15/18</td>
<td>13/19</td>
<td>0.61 (0.23–1.63)</td>
</tr>
</tbody>
</table>

van Driel et al. NEJM 2018
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

TO THE EDITOR:

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Essen, Germany

Is there a role for HIPEC in ovarian cancer?

Philipp Harter1,2, S. Mahner3, Ignace Vergote4, Luis Chiva5, Antonio Gonzalez-Martin6, Christina Fotopoulou2,7

HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer?

C. Fotopoulou1,2,3,4, J. Sehouli2,3,4, S. Mahner5,6, P. Harter4, E. Van Nieuwenhuysen7,8, A. Gonzalez-Martín9,10, I. Vergote10,11 & A. Du Bois5,6

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Issues raised by Vergote et al.

1. Study took long to accrue
2. Design of the study and endpoints
3. Study addresses only a small population of EOC patients
4. Heterogeneity of the results
5. Underreported toxicity
6. Korean study

Study took long to accrue

Only an average of 3.5 patients per year per center were recruited

Large difficulties [...] in recruitment of the trial may be interpreted as surrogate marker for the quality of the study and the presence of strong selection bias.

- Slow accrual due to limited funding (no pharmaceutical incentive)
- Individual hospitals had to pay for procedures

- I am not aware of any association between duration and quality
- I am not aware of any association between duration and strong selection bias

Design: AGO DESKTOP III
(ENGOT-ov20; NCT01166737)

Pts. with:
- 1st relapse
- PSROC
- AGO Score +ve

R
n = 408

Cytoreductive Surgery with max. effort for complete resection

Platinum-based Combination therapy strongly recommended

No OP

Immediate Platinum-based Combination therapy strongly recommended

- 80 centres in 12 countries
- Recruitment 9/2010 - 3/2015
- 407 of 409 pts evaluated (2 screening failures)

OP Allowed 3rd line
Design of the study and endpoints

The primary end point should have been overall survival, in which case the trial would have been larger and reliable enough to exclude significant bias

• PFS advocated at the 3rd Ovarian Cancer Consensus Meeting
• a small study may lack the power to detect an OS difference
• however, since we observed a clear OS benefit, this arguments fails

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018; du Bois et al. 3rd ovarian cancer consensus meeting
AGO DESKTOP III: Outcome 2 (PFS, ITT population)
(AGO-OVAR OP.4; ENGOT-ov20; NCT01166737)

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>No surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>19.6 mos</td>
<td>14.0 mos</td>
</tr>
<tr>
<td>Δ median PFS</td>
<td>5.6 mos</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.66 (0.52 – 0.83)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

296 (73%) PFS events
1. **Complete cytoreductive surgery followed by systemic treatment offers benefits regarding PFS and TFST in selected patients with first recurrent OC; an OS benefit has not been proven as data are not mature yet.**

   Patients eligible for cytoreductive surgery should be informed about this option.  

   **Level 1 A**

1.1 **Patient selection may consider the following predictors for complete resection**
   a. TFI platinum of 6+ months
   b. The AGO Score (good performance status, complete resection at 1st surgery, absence of large volume ascites) (Level III A)
   c. Imaging without signs of probably irresectable lesions
   d. contraindications to surgery (e.g. co-morbidities, prior serious complications)

1.2 **Centre selection may consider the following factors**
   a. available ressources and infrastructure
   b. established multidisciplinary cooperation pre-, intra-, and post-operatively
   c. Experience and volume of 2nd cytoreductive surgery with a track record of achieving a complete resection in the majority of these procedures

2. **Cytoreductive surgery in second or later recurrence may provide benefit in highly selected patients and specialized centres.**

   **Level V A**
Study addresses only a small population of EOC patients

The ‘super-selection’ of patients in this trial [...] affects a minority (<10%) of the entire patient population

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced ovarian cancer</td>
<td>1000</td>
</tr>
<tr>
<td>- stage IV</td>
<td>300</td>
</tr>
<tr>
<td>- frail / elderly</td>
<td>100</td>
</tr>
<tr>
<td>Leaves</td>
<td>600</td>
</tr>
<tr>
<td>- complete primary surgery possible (?)</td>
<td>500</td>
</tr>
<tr>
<td>Eligible for HIPEC</td>
<td>100</td>
</tr>
</tbody>
</table>

Even we only involve 10%, we normally embrace the improved outcome

Let us be consistent in the use of scientific arguments!
Heterogeneity of the results

There is an imbalance of HGSOC and non-HGSOC in the two arms despite randomization

- High-grade serous: 107 vs 112
- Randomization ensures equal prognosis of all factors combined

Heterogeneity of the results

A strong correlation between large centres showing the least effect and small centres driving the trial into positivity

• Tests for interaction were all non-significant
Significant underreported perioperative and long term toxicity, make the interpretation and broad acceptance of the trial even more challenging.

van Driel et al. NEJM 2018; Alyami et al. Int J Hyperth 2017
**Korean Study**

*No overall effect for HIPEC in interim analysis*

<table>
<thead>
<tr>
<th></th>
<th>Van Driel et al.</th>
<th>Lim et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>245</td>
<td>185</td>
</tr>
<tr>
<td>Stage</td>
<td>III</td>
<td>III and IV</td>
</tr>
<tr>
<td>Surgery</td>
<td>IDS</td>
<td>PDS and IDS</td>
</tr>
<tr>
<td>Population</td>
<td>European</td>
<td>Asian</td>
</tr>
<tr>
<td>Cisplatinum</td>
<td>100 mg/m2</td>
<td>75 mg/m2</td>
</tr>
<tr>
<td>Trial completed</td>
<td>Yes</td>
<td>no</td>
</tr>
<tr>
<td>Results published</td>
<td>Yes</td>
<td>Abstract only 2017</td>
</tr>
<tr>
<td>HR neo-adjuvant</td>
<td>0.66 (0.50 - 0.87)</td>
<td>0.29 (0.08 - 1.00)</td>
</tr>
</tbody>
</table>
What causes the reluctance to embrace HIPEC?

1. Study took long to accrue
2. Design of the study and endpoints
3. Study addresses a small population of EOC patients
4. Heterogeneity of the results
5. Underreported toxicity
6. Korean study

7. *We must question ourselves whether the resources [...] are worth investing in broadly implementing HIPEC facilities [...] or rather to perform maximal effort cytoreductive surgery and maintenance regimens* 

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIPEC</td>
<td>€ 15.700</td>
</tr>
<tr>
<td>1 year bevacizumab</td>
<td>€ 66.300</td>
</tr>
<tr>
<td>1 year parp inhibition</td>
<td>€ 64.000</td>
</tr>
</tbody>
</table>

Patients eligible for interval cytoreductive surgery should be offered this option

- Approval by health technology assessors (full reimbursement)
- Centralisation: 10 centers will perform OVHIPEC
- Results monitored in nationwide clinical audit
- New study in primary debulking setting
OVHIPEC-2 study

Design

- Patients eligible for primary cytoreductive surgery (CRS)
- ENGOT/GCIG study
- Trial groups from Ireland, Australia, NSGO, Netherlands, UK, France, Italy
- Funding from the Dutch Cancer Society and the Dutch government

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