OVARIAN CANCER: IP CHEMOTHERAPY

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OVARIAN CANCER

Intraperitoneal chemotherapy (IP) and Hyperthermic intraperitoneal chemotherapy (HIPEC) - Outline

Where we are
IP chemotherapy: rationale and pivotal trials
New data from old trials
New trials, more questions
IP chemotherapy: place in therapy
HIPEC: a different story
OVARIAN CANCER: STATE OF THE ART

- Tissue should be obtained for histopathologic diagnosis
- Staging should be performed according to FIGO guidelines, including lymph node sampling and peritoneal staging
- In early stages, adjuvant chemotherapy reduces the risk of relapse by 1/3
- In advanced stages, optimal surgical debulking (no macroscopic residual disease) is the most important determinant of survival
- Neoadjuvant chemoRx followed by debulking surgery is an acceptable option for patients unlikely to be optimally resected upfront
- In advanced stages, chemotherapy can induce an OR in 70-80% of the patients with 20-50% 5 y survivors
- Carboplatin/Paclitaxel is the standard chemotherapy regimen (recent introduction of Bevacizumab for «high risk» patients)
- Maintenance treatment with PARPi prolongs PFS in case of BRCAm HGSOC
### The Challenge of Going Beyond Carboplatin/Paclitaxel

#### Key trials worldwide

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Regimens compared</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 104</td>
<td>654</td>
<td>IV Cis/cyclo vs. IP Cis/IV cyclo</td>
<td>IP improved OS with less toxicity</td>
</tr>
<tr>
<td>GOG-0162</td>
<td>324</td>
<td>Cis + either 24 h or 96 h pac</td>
<td>Efficacy similar</td>
</tr>
<tr>
<td>AGO-GINECO</td>
<td>1,282</td>
<td>Carbo/pac vs. carbo/pac/epirubicin</td>
<td>No benefit of a third agent</td>
</tr>
<tr>
<td>MITO-1</td>
<td>273</td>
<td>Carbo/pac x6 ↔ topo x4 or surveillance</td>
<td>No PFS benefit with topo maintenance</td>
</tr>
<tr>
<td>GOG-0172</td>
<td>429</td>
<td>IV cis/IV pac vs. IP cis/IP pac</td>
<td>IP improved OS, worse toxicity and QoL</td>
</tr>
<tr>
<td>GCIG</td>
<td>887</td>
<td>Carbo/pac vs. carbo/pac/epirubicin</td>
<td>No benefit of a third agent</td>
</tr>
<tr>
<td>AGO-GINECO</td>
<td>1,308</td>
<td>Carbo/pac ↔ topo x4 or surveillance</td>
<td>No benefit of topo maintenance</td>
</tr>
<tr>
<td>GOG-0178</td>
<td>277</td>
<td>Cis/pac ↔ pac x3 vs. x12 cycles in patients in CR</td>
<td>PFS improved/no OS difference</td>
</tr>
<tr>
<td>After Six</td>
<td>200</td>
<td>Carbo/pac x6 ↔ pac x 6 vs. surveillance in pts in CR</td>
<td>No benefit with pac maintenance</td>
</tr>
<tr>
<td>GOG-0182</td>
<td>4,312</td>
<td>Carbo/pac vs. carbo/pac/gem vs. carbo/pac/topo vs. carbo/pac/PLD</td>
<td>No benefit of a third agent</td>
</tr>
<tr>
<td>OV16</td>
<td>819</td>
<td>Carbo/pac x8 vs. cis/topo x4 ↔ carbo/pac x4</td>
<td>Efficacy similar; better tolerability with carbo/pac</td>
</tr>
<tr>
<td>AGO-OVAR9</td>
<td>1,742</td>
<td>Carbo/pac vs. carbo/pac/gem</td>
<td>No benefit of a third agent</td>
</tr>
<tr>
<td>GOG 218</td>
<td>1,873</td>
<td>Carbo/Pac vs. carbo/pac/bev vs. carbo/pac/beva→beva</td>
<td>PFS improved with beva→beva</td>
</tr>
<tr>
<td>ICON 7</td>
<td>1,528</td>
<td>Carbo/pac/bev vs. carbo/pac/beva 7.5→beva 7.5</td>
<td>PFS improved with beva→beva</td>
</tr>
<tr>
<td>JGOG 3016</td>
<td>637</td>
<td>Carbo/pac vs. carbo/pac DD</td>
<td>PFS &amp; OS improved with DD</td>
</tr>
<tr>
<td>MITO-7</td>
<td>810</td>
<td>Carbo/pac vs. carbo/pac DD</td>
<td>No difference in PFS/OS; DD more tolerable</td>
</tr>
</tbody>
</table>
OVARIAN CANCER

IP chemotherapy and HIPEC - Outline

Where we are
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HIPEC: a different story
ROOM FOR IMPROVEMENT: INTRAPERITONEAL THERAPY

Rationale

Major route of tumour spread in peritoneal cavity
High IP concentration of drug
Longer half – life in peritoneal cavity
Prolonged systemic exposure of residual peritoneal tumour to ↑ drug concentration

Limitations

Poor penetration of bulk tumour
Exposure of extra-peritoneal disease to IP drugs

Target population

• Optimal stage disease
• Minimal residual ≤1cm
• No residual (R0)
**Methods**
Multicentre RCT
06/1986-07/1992

**Participants**
Stage III
Residual disease <2cm
PS 0-2
N° 654 (546 eligible)

**Interventions**
Arm 1:
IV Cyclophosphamide (600 mg/sqm) + IV cisplatin (100 mg/sqm) q 3 weeks for a total of 6 cycles.
Arm 2:
IV cyclophosphamide 600 mg/sqm + IP cisplatin (100 mg/sqm) q 3 weeks for a total of 6 cycles.

**Outcomes**
Overall Survival
Pathological CR

<table>
<thead>
<tr>
<th></th>
<th>IP</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path CR</td>
<td>47%</td>
<td>36%</td>
</tr>
<tr>
<td>Survival</td>
<td>49 Mo</td>
<td>41 Mo</td>
</tr>
</tbody>
</table>

SURVIVAL BENEFIT
LESS TOXICITY:
  • G3-4 Ototoxicity
  • G2-4 Haematologic toxicity and neuromuscular events

PRO

CON

NO PACLITAXEL
EFFECT OF TREATMENT NOT INFLUENCED BY RESIDUAL DISEASE (no benefit in smaller residual tumour)

Methods
Multicentre RCT
08/1992-0471995

Participants
Stage III
Residual disease ≤1cm
PS <3
N° 523 (462 evaluable)

Interventions
Arm 1: IV paclitaxel (135 mg/sqm) over 24 h at day 1 + IV cisplatin (75 mg/sqm) at day 2, every 3 weeks for a total of 6 cycles.
Arm 2: IV carboplatin (AUC 9) for two courses q 28 days, followed 4 weeks later by IV paclitaxel (135 mg/sqm) over 24 h at day 1 + IP cisplatin (100 mg/sqm) at day 2, q 3 weeks for a total of 6 cycles.

Outcomes
Overall Survival
Pathological CR

<table>
<thead>
<tr>
<th></th>
<th>Carbo/Taxol</th>
<th>Taxol</th>
<th>IV Cisplatin</th>
<th>IV Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>27.6 mos</td>
<td>22.5 mos</td>
<td>P=0.01</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>63.2 mos</td>
<td>52.5 mos</td>
<td>P=0.05</td>
<td></td>
</tr>
</tbody>
</table>

**IMPROVED OUTCOMES:**
- PFS significant;
- OS borderline (p 0.05)

**MORE G3-G4 TOXICITY** (Leukopenia, Thrombocytopenia, GI, Neuropathy)
- Carbo AUC9 (confounding factor, toxicity)

**Methods**
Multicentre RCT
04/1989-12/1996

**Participants**
Stage II-IV
Residual disease <2cm
PS 0-2
N° 113 (100 eligible)

**Interventions**
Arm 1: IV Epidox (60 mg/sqm) + IV CTX (600 mg/sqm) + IV cisplatin (50 mg/sqm) q 4 weeks for a total of 6 cycles.
Arm 2: IV Epidox (60 mg/sqm) + IV CTX (600 mg/sqm) + IP cisplatin (50 mg/sqm) q 4 weeks for a total of 6 cycles.

**Outcomes**
Overall Survival
Disease Free Survival

<table>
<thead>
<tr>
<th></th>
<th>IP Cisplatin</th>
<th>IV Cisplatin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>42 mo</td>
<td>25 mo</td>
<td>0.13</td>
</tr>
<tr>
<td>OS</td>
<td>67</td>
<td>51</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Reprinted from Gynecologic Oncology 76(2), Gadducci A, et al., Intraperitoneal versus Intravenous Cisplatin in Combination with Intravenous Cyclophosphamide and Epidoxorubicin in Optimally Cytoreduced Advanced Epithelial Ovarian Cancer: A Randomized Trial of the Gruppo Oncologico NordOvest, 157–6, Copyright 2000, with permission from Elsevier
GONO

- LESS G2-4 NEUROTOXICITY
- IMPROVED OUTCOMES (not significant)

PRO

CON

- ANTHRA NO LONGER STANDARD
- NO PACLITAXEL
- LOW STATISTICAL POWER

**Methods**
Multicentre RCT
03/1998-01/2001

**Participants**
Stage III
Residual disease < 1cm
PS 0-2
N° 415

**Interventions**
Arm 1:
IV Paclitaxel (135 mg/sqm) d1 + IV cisplatin (75 mg/sqm) d2
q 3 weeks for 6 courses
Arm 2:
IV Paclitaxel (135 mg/sqm) d1 + IP cisplatin (100mg/sqm)d2 + IP Paclitaxel (60 mg/sqm) d8 q 3 weeks for 6 courses

**Outcomes**
Overall Survival
Disease Free Survival

<table>
<thead>
<tr>
<th>IP Cisplatin mo</th>
<th>IV Cisplatin mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS 23.8 mo</td>
<td>18.3 mo</td>
</tr>
<tr>
<td>OS 65.6</td>
<td>49.7</td>
</tr>
</tbody>
</table>

PFS = 0.05
OS = 0.03

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GOG 172

- IMPROVED OUTCOMES (PFS & OS)
- 25% RR of DEATH

- PRO
- CON

- POOR TOLERABILITY (42% of IP treatments completed)
- COMPLEX SCHEDULE
- DIFFERENT CHEMO DOSES

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LONG-TERM SURVIVAL ADVANTAGE AND PROGNOSTIC FACTORS

Associated with intraperitoneal chemotherapy treatment in advanced OC: A GOG Study

Retrospective analysis on 876 pts with a median f.u. of 10.7 years from GOG 114 and 172. Cox proportional hazards regression models were used for statistical analyses

IP therapy enhanced mOS from 51.4 to 61.8 months. Survival improved with increasing number of IP cycles.

Tewari D, et al., J Clin Oncol 2015; 33:1460-1466. Reprinted with permission. ©2015 American Society of Clinical Oncology. All rights reserved.
HAZARD RATIOS

For progression or death
Intraperitoneal vs. intravenous therapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio IV, Fixed, 95% CI</th>
<th>Hazard ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadducci 2000</td>
<td>-0.3509</td>
<td>0.2367</td>
<td>4.7%</td>
<td>0.70 [0.44, 1.12]</td>
<td></td>
</tr>
<tr>
<td>GOG 172</td>
<td>-0.2231</td>
<td>0.1138</td>
<td>20.3%</td>
<td>0.80 [0.64, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Markman 2001</td>
<td>-0.2485</td>
<td>0.0902</td>
<td>32.3%</td>
<td>0.78 [0.65, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Yen 2009</td>
<td>-0.274</td>
<td>0.08</td>
<td>41.1%</td>
<td>0.76 [0.65, 0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>98.4%</strong></td>
<td><strong>0.77 [0.70, 0.85]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.30, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 5.01 (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio IV, Fixed, 95% CI</th>
<th>Hazard ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberts 1996</td>
<td>-0.2744</td>
<td>0.1157</td>
<td>23.9%</td>
<td>0.76 [0.61, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Gadducci 2000</td>
<td>-0.4025</td>
<td>0.2776</td>
<td>4.2%</td>
<td>0.67 [0.39, 1.15]</td>
<td></td>
</tr>
<tr>
<td>GOG 172</td>
<td>-0.2877</td>
<td>0.1312</td>
<td>18.6%</td>
<td>0.75 [0.58, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Markman 2001</td>
<td>-0.2107</td>
<td>0.1099</td>
<td>26.5%</td>
<td>0.81 [0.66, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Yen 2001</td>
<td>0.1222</td>
<td>0.253</td>
<td>5.0%</td>
<td>1.13 [0.69, 1.86]</td>
<td></td>
</tr>
<tr>
<td>Yen 2009</td>
<td>-0.163</td>
<td>0.13</td>
<td>18.9%</td>
<td>0.85 [0.66, 1.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>97.1%</strong></td>
<td><strong>0.80 [0.72, 0.90]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.95, df = 5 (P = 0.71); I² = 0%
Test for overall effect: Z = 3.88 (P = 0.0001)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative effect (95% CI)</th>
<th>Patients &amp; trials</th>
<th>Quality of evidence (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1.64 (1.13-2.38)</td>
<td>1797 women (5 trials)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.32 (1.06-5.07)</td>
<td>1171 women (3 trials)</td>
<td>++++ high</td>
</tr>
<tr>
<td>gastrointestinal AEs</td>
<td>1.71 (1.28-2.26)</td>
<td>1339 women (5 trials)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Metabolic AEs</td>
<td>4.45 (2.72-7.26)</td>
<td>873 women (2 trials)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Infections*</td>
<td>3.34 (2.06-5.43)</td>
<td>1171 women (3 trials)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Pain*</td>
<td>7.47 (4.41-12.67)</td>
<td>1235 women (3 trials)</td>
<td>++++ high</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>0.67 (0.46-0.99)</td>
<td>1009 women (3 trials)</td>
<td>++++ high</td>
</tr>
</tbody>
</table>

*Catheter-related


Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer
OVARIAN CANCER

IP chemotherapy and HIPEC - Outline

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NEW TRIALS INVESTIGATING INTRAPERITONEAL THERAPY

For ovarian cancer with carboplatin

GOG252
NCIC CTG OV21
JGOG 3019
GOG 252: SCHEMA

GOG 252: Schema

Eligibility

- Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal
- Resected to optimal: less than or equal to 1 cm visible tumor by surgeon report
- Exploratory: suboptimal (7%) and Stage IV (5%)

Phase A: Cycles 1-6*

- Arm 1
  - Paclitaxel 80 mg/m² IV over 1 hour days 1, 8, and 15
  - Carboplatin AUC 6 IV on day 1
  - Bevacizumab 15 mg/kg IV on day 1 beginning on cycle 2

- Arm 2
  - Paclitaxel 80 mg/m² IV over 1 hour days 1, 8, and 15
  - Carboplatin AUC 6 IP on day 1
  - Bevacizumab 15 mg/kg IV on day 1 beginning on cycle 2

- Arm 3
  - Paclitaxel 135 mg/m² IV over 3 hours day 1
  - Cisplatin 75 mg/m² IP on day 2
  - Paclitaxel 60 mg/m² IP on day 8
  - Bevacizumab 15 mg/kg IV on day 1 beginning on cycle 2

Phase B: Cycles 7-22*

- Bevacizumab 15 mg/kg IV on day 1 for cycles 7-22
## GOG 252 TOXICITY

<table>
<thead>
<tr>
<th>Event</th>
<th>IV carbo</th>
<th>IP carbo</th>
<th>IP cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; G3 %</td>
<td>&gt; G3 %</td>
<td>&gt; G3 %</td>
</tr>
<tr>
<td>FN</td>
<td>2.5</td>
<td>2.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Platelets</td>
<td>17.6</td>
<td>15.1</td>
<td>6.1</td>
</tr>
<tr>
<td>HTN</td>
<td>11.9</td>
<td>13.8</td>
<td>20.5</td>
</tr>
<tr>
<td>N&amp;V</td>
<td>5.1</td>
<td>4.7</td>
<td>11.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>G2 %</th>
<th>&gt; G3 %</th>
<th>G2 %</th>
<th>&gt; G3 %</th>
<th>G2 %</th>
<th>&gt; G3 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>24.1</td>
<td>5.7</td>
<td>22.6</td>
<td>4.5</td>
<td>21.3</td>
<td>5.5</td>
</tr>
</tbody>
</table>

All arms: excessive toxicity & neurotoxicity similarly high. IP cisplatin enhances bevacizumab – related HTN

Modified from Joan L Walker, 2016 ASCO Annual Meeting
### GOG 252 ASSIGNED TREATMENT COMPLETION

<table>
<thead>
<tr>
<th>Arm</th>
<th>At least 6 cycles of platinum</th>
<th>At least 6 cycles of taxane</th>
<th># Bev cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: IV Carbo</td>
<td>90%</td>
<td>87%</td>
<td>20</td>
</tr>
<tr>
<td>Arm 2: IP Carb</td>
<td>90%</td>
<td>88%</td>
<td>19</td>
</tr>
<tr>
<td>Arm 3: IP Cisp</td>
<td>84%</td>
<td>87%</td>
<td>17</td>
</tr>
</tbody>
</table>

Cross-over to IV Arm occurred in 16% allocated to IP Carbo and 28% to IP Cisplatin. Twice as many patients stopped protocol directed Beva prior to completion of Cycle 6 on the arm 3 IP Cisplatin (30% vs. 15%)
WHY DID GOG 252 FAIL TO CONFIRM SUPERIORITY OF IP CHEMO?

- Suboptimal compliance and cross-over
- CT scan every 6 mos to evaluate PFS
- Lower doses of ip Cisplatin
- Role of bevacizumab
- Too early for Overall Survival
- No Standard Arm
- PFS shorter than predicted
OV21/PETROC: SCHEMA (2 STAGE STUDY)

Eligibility
- EOC, fallopian tube or primary peritoneal cancer
- Clinical FIGO stage IIB-IV at diagnosis
- Neoadjuvant platinum-based chemotherapy
- Resected to optimal <1cm

Stratification variables:
- Cooperative group
- Residual disease: Macroscopic vs. microscopic
- Reason for NACT: Non-resectable disease vs. other
- Timing of IP catheter insertion: Intra-operative vs. postoperative

**Eligibility**

*Presented by Helen J MacKay at 2016 ASCO Annual Meeting*

*AUC 5 (measured GFR)/AUC 6 (calculated GFR)
OV21/PETROC: RESULTS

**PD rate at 9 months following randomisation (per protocol)**

<table>
<thead>
<tr>
<th>Arm</th>
<th>9 month PD rate</th>
<th>P value stratified</th>
<th>P value unstratified</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 IV</td>
<td>42.2 %</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>3 IP</td>
<td>23.3 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OV21/PETROC: Progression-free survival***

- **Arm 1 (IV)**: N = 101, Median PFS* (Mo) = 11.3, HR, 95% CI = 0.82, 0.57-1.17, P=value = 0.27
- **Arm 3 (IP)**: N = 102, Median PFS* (Mo) = 12.5

**OV21/PETROC: Overall survival***

- **Arm 1 (IV)**: N = 101, Median OS* (Mo) = 38.1, HR, 95% CI = 0.80, 0.47-1.35, P=value = 0.40
- **Arm 3 (IP)**: N = 102, Median OS* (Mo) = 59.3

*PFS and OS are defined as the time from randomisation to disease progression

Presented by Helen J MacKay at 2016 ASCO Annual Meeting
Multicentre randomised controlled trial

Study duration: June 2010 for 3 years or until completed accrual (746 evaluable)

Planned follow-up: 3 years

**Epithelial Cancer**
- Ovarian
- Peritoneal
- Fallopian Tube

**Stages** II-IV
- Optimal (<1cm)
- Suboptimal (>1cm)

**Treatment Arms**

1. **IV Paclitaxel** 80 mg/m² qw x 6
2. **IP Carboplatin** AUC 6 q3w
3. **IV Bevacizumab** 15 mg/kg (optional)

**Bevacizumab** q 3wk (if chosen) maintenance to progression

- **Primary endpoint:** PFS
- **Secondary:** OS, QoL, costs
OVARIAN CANCER:
SUMMARY OF IP TRIALS

Positive Trials
- GOG 104
- GOG 114
- GONO
- GOG 172
- OV21

Negative Trials
- GOG 252
OVARIAN CANCER

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OVARIAN CANCER: DOES HISTOLOGY MATTER?
DIFFERENT HISTOLOGY – DIFFERENT BIOLOGY

Reprinted from human Pathol 2011, Kurman and Shih, Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—Shifting the paradigm; 42(7):918-31, Copyright 2011, with permission from Elsevier
ADVANCED OVARIAN CANCER

BRCA1 expression and IP chemotherapy

392 patients from GOG 172
189 with aberrant BRCA1 expression

BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. this work is licensed under the Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License.
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PROGNOSTIC FACTORS FOR STAGE III EPITHELIAL OVARIAN CANCER

Treated with intraperitoneal chemotherapy: A Gynaecologic Oncology Group study

Progression free (PFS) and overall survival (OS) curves for patients randomised to intraperitoneal chemotherapy stratified by residual disease following primary cytoreductive surgery. Median PFS and OS for patients with microscopic residual disease were...

IP CHEMOTHERAPY FOR OVARIAN CANCER
A risk-benefit balance
**TREATMENT ALGORITHM FOR STAGE III-IV EOC**

- Optimal debulking surgery performed in a highly variable, centre-dependent, % of patients (from 20 to 80%)
- Increasing proportion of patients treated with NACT
- Bevacizumab administered mainly to «high-risk» patients with macroscopic RD

**TREATMENT ALGORITHM FOR STAGE III-IV EOC**

- **NACT**
  - Cb Pac +/- Beva x 3-4 courses
- **IDS**
  - Cb Pac up to 6 courses
  - Beva up to 22 courses

- **PDS**
  - **Optimally debulked**
    - Cb Pac x 6 courses
    - +/- Beva x 22 courses
  - **Sub-optimally debulked**
    - Cb ip + Pac x 6 courses
    - Cb Pac x 6 courses
    - +/- Beva x 22 courses
HIPEC: RATIONALE

- **Delay** of IP therapy

- **LIMITED ACCESS** of IP fluid to tumour locations

- Theoretical benefit of **IP infusion immediately after surgery**

HIPEC (hyperthermic IP chemotherapy)

- Combined heat (T 41-42°C) + chemotherapy drugs
  - Cytotoxicity (linear increase: cisplatin)
  - Peritoneal tumour penetration
- Intraoperative chemoperfusion: No adhesion barriers
- Controlled application of anesthesia

**Therapeutic synergism**
A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer

Luis M. Chiva *, Antonio Gonzalez-Martin

MD Anderson Cancer Center Madrid, Spain

PUBMED search: “HIPEC” and “ovarian cancer”
143 publications from 2008 to May 2014

Articles focus on “HIPEC and ovarian cancer”
(mixed series with other tumours were discarded)
22 publications 1450 patients

<table>
<thead>
<tr>
<th></th>
<th>Primary debulking HIPEC</th>
<th>Recurrent sensitive HIPEC</th>
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</thead>
<tbody>
<tr>
<td>mOS m.</td>
<td>37.3</td>
<td>36.5</td>
</tr>
<tr>
<td>mDFS m.</td>
<td>14.4</td>
<td>20.2</td>
</tr>
<tr>
<td>5y OS %</td>
<td>40</td>
<td>NR</td>
</tr>
<tr>
<td>Severe morbidity %</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

Primary setting 493 patients
11 studies, 248 patients
HIPEC at primary debulking with data either on OS-DFS

Recurrent setting 957 patients
8 studies, 499 patients
HIPEC at secondary debulking with data on either OS-DFS & PLATINUM INT

Ongoing trials for ovarian, fallopian and peritoneal cancers

<table>
<thead>
<tr>
<th>Trial phase</th>
<th>Cancer type</th>
<th>Treatment arm</th>
<th>Control arm</th>
<th>Sponsor/country</th>
<th>Primary outcome</th>
<th>ECD</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Ovarian</td>
<td>CyRS + HIPEC</td>
<td>CyRS</td>
<td>The Netherlands Cancer Institute, The Netherlands</td>
<td>RFS</td>
<td>2015</td>
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<tr>
<td>II</td>
<td>Ovarian, fallopian, and peritoneal</td>
<td>CyRS + HIPEC + AC</td>
<td>CyRS + AC</td>
<td>Mercy Medical Center, USA</td>
<td>Post-operative complication rates</td>
<td>2016</td>
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<tr>
<td>III</td>
<td>Ovarian*</td>
<td>Surgery + HIPEC</td>
<td>Surgery</td>
<td>UNICANCER, France</td>
<td>OS</td>
<td>2018</td>
</tr>
<tr>
<td>III</td>
<td>Ovarian*</td>
<td>Surgery + HIPEC</td>
<td>Surgery</td>
<td>Catholic University of the Sacred Heart, Italy</td>
<td>PFS</td>
<td>2018</td>
</tr>
<tr>
<td>III</td>
<td>Ovarian</td>
<td>CyRS + HIPEC</td>
<td>CyRS</td>
<td>A.O. Ospedale Papa Giovanni XXIII, Italy</td>
<td>DFS</td>
<td>2018</td>
</tr>
</tbody>
</table>

*Recurrent ovarian cancer. No peritoneal carcinomatosis. ECD, estimated completion date; CyRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; RFS, recurrence free survival; AC, adjuvant chemotherapy; OS, overall survival; PFS, progression free survival; DFS, disease free survival.

HIPEC FOR EOC

- HIPEC cannot be considered a standard treatment and should not be offered outside of clinical trials (Chiva L, et al., Gynecol Oncol 2015)
- HIPEC is not recommended and should be rejected outside of prospective controlled trials (Harter P, et al., AGO, NOGGO, AGO Austria, AGO Switzerland statement 2016)
- No role for HIPEC outside of clinical trials (Mackay H, ASCO discussant 2016)
THANK YOU!