Ovarian cancer: State of the Art in Primary Chemotherapy

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Stage Distribution at Diagnosis and Overall Survival (1999-2001)

Adapted from FIGO Annual Report 2006 Int J Gynecol Obstetr 95 Suppl 1 161
Prognosis, Cisplatin, Paclitaxel

5 Year Overall Survival (%)


0 10 20 30 40 50 60 70 80 90

Synthesis of CDDP
FDA Approval of CDDP
GOG111

IA IIIA IIIB IIIC IV

FIGO Annual Report 2006 Int J Gynecol Obstetr 95 Suppl 1 161
Progress in Fast Forward

- \( cDDP \approx CBDCA \)
  Mangioni JNCI 1989 81 1464

- \( \text{CAP}_{(50)} > CP_{(75)} \)
  A’Hern J Clin Oncol 1995 3 726-3

- \( cDDP_{(75)} + PTX > cDDP + C \)

- \( \text{CAP} \approx CBDCA! \)
  ICON2 Lancet 1998 352 1571

- \( cDDP_{(75)} + PTX \approx cDDP_{(100)} \)
  Muggia GOG 132 JCO 2000 18 106

- \( \text{CBDCA} \approx CBDCA + PTX! \)
  ICON3 Lancet 2002 360 505

- \( cDDP_{(75)} + PTX \approx CBDCA + PTX \)

In 2003, “no therapy has been proven superior to carboplatin + paclitaxel”

> is more efficacious than; \( \approx \), efficacy is not significantly different; C, cyclophosphamide; A, doxorubicin; P, cisplatin; cDDP, cisplatin; PTX, paclitaxel
Questions

◆ Stage III and IV
  • Are triplets or sequential doublets more efficacious than carboplatin+paclitaxel?
  • Does maintenance therapy improve the prognosis?
  • Does bevacizumab improve the prognosis?
  • Is intraperitoneal therapy superior to intravenous?
  • Preoperative or postoperative chemotherapy

◆ Early stages
  • Who needs chemotherapy?
  • For how long?

◆ What else do I need to know?
Triplets and Sequential Doublets

GOG0182-ICON5
FIGO III or IV
CP vs CPGem vs CPDox vs CT→CP vs CG→CP

Addition of a 3rd Substance
- Epirubicin or Doxorubicin
  - du Bois JCO 2006 24 1127; Avrantinos EJC 2008 44 2169
- Gemcitabine
  - Du Bois J Clin Oncol 2010 28 4162

WAS NOT EFFECTIVE

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Bookman JCO 2009 27 1419
Maintenance Chemotherapy after Clinical Remission

◆ GOG-178
„Platinum“+PTX → 3 vs 9 cycles PTX (q 4 wk)
Markman JCO 2003 21 2460; Gynecol Oncol 2009 114 195

◆ „After-6“
„Platinum“+PTX → 0 vs 6 cycles PTX (q 3 wk)
Pecorelli JCO 2009 27 4642

◆ AGO/GINECO and MITO-1
CBDCA+PTX → 0 vs. 4 cycles Topotecan
Pfisterer JNCI 2006 98 1036; de Placido JCO 2004 22 2635

No improvement of OS and PFS (except GOG-178)
“With a protocol-specified early termination boundary of $P=0.005$, these findings led the Southwest Oncology Group Data Safety Monitoring Committee to discontinue the trial.”

Markman JCO 2003 21 2460
Markman Gynecol Oncol 2009 114 195
Maintenance Chemotherapy after Clinical Remission

“With a protocol-specified early termination boundary of \( P = 0.005 \), these findings led the Southwest Oncology Group Data Safety Monitoring Committee to discontinue the trial.”

Markman JCO 2003 21 2460
Markman Gynecol Oncol 2009 114 195
...other promising areas of research...

- Modulation of drug efflux pumps, e.g.
  MDR1/Pgp: Valdospal
  Lhomme JCO 2008 26 2674

- Monoclonal antibody oregovomab
  Berek JCO 2009 27 418

- $^{90}$Y-muHMFG1 (radioimmununotherapy)
  Verheijen JCO 2006 24 571

- High dose chemotherapy
  Möbus JCO 2007 25 4187

...did not fulfill their promises...
The First Step Forward Since 1996

- Stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal carcinoma
- Carboplatin, AUC = 6 mg/ml*min + Paclitaxel 180 mg/m² q 3 weeks, x 6 vs.
  Carboplatin, AUC = 6 mg/ml*min + Paclitaxel 80 mg/m² q week, x 18
- The primary endpoint was progression-free survival. Analysis by ITT.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 (25-87)</td>
<td>62 (20%)</td>
<td>202 (65%)</td>
<td>48 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>54 (17%)</td>
<td>215 (67%)</td>
<td>50 (16%)</td>
</tr>
<tr>
<td>III</td>
<td>54 (17%)</td>
<td>215 (67%)</td>
<td>50 (16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>283 (91%)</td>
<td>287 (90%)</td>
</tr>
<tr>
<td>2</td>
<td>23 (7%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (2%)</td>
<td>12 (4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>260 (83%)</td>
<td>276 (87%)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>14 (4%)</td>
<td>18 (6%)</td>
</tr>
<tr>
<td>Primary peritoneal</td>
<td>38 (12%)</td>
<td>25 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology only</td>
<td>35 (11%)</td>
<td>35 (11%)</td>
</tr>
<tr>
<td>Primary debulking</td>
<td>277 (89%)</td>
<td>284 (89%)</td>
</tr>
<tr>
<td>Interval debulking</td>
<td>34 (11%)</td>
<td>29 (9%)</td>
</tr>
<tr>
<td>Secondary/second-look</td>
<td>38 (12%)</td>
<td>56 (18%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Residual disease</th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 cm</td>
<td>144 (46%)</td>
<td>145 (45%)</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>168 (54%)</td>
<td>174 (55%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous adenocarcinoma</td>
<td>173 (55%)</td>
<td>182 (57%)</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>38 (12%)</td>
<td>39 (12%)</td>
</tr>
<tr>
<td>Clear-cell carcinoma</td>
<td>31 (10%)</td>
<td>37 (12%)</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>23 (7%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Other types</td>
<td>47 (15%)</td>
<td>50 (16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological grade</th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>42 (13%)</td>
<td>40 (13%)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>60 (19%)</td>
<td>71 (22%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>79 (25%)</td>
<td>72 (23%)</td>
</tr>
<tr>
<td>Unknown/not applicable</td>
<td>131 (42%)</td>
<td>136 (43%)</td>
</tr>
</tbody>
</table>
The First Step Forward Since 1996

**Progression-free survival**

- HR 0.71 (95% CI 0.58–0.88); p=0.015

**Overall survival**

- HR 0.75 (95% CI 0.57–0.98); p=0.03

Katsumata Lancet 2009 374 1331

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The First Step Forward Since 1996

- Similar effect size in subgroups by
  - Residual disease
  - Stage
  - Location of primary
  - Age
  - Performance status

- No benefit in mucinous and clear cell cancers

### Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Dose-dense regimen group (n=312)</th>
<th>Conventional regimen group (n=314)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>286 (92%)</td>
<td>276 (88%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>136 (44%)</td>
<td>120 (38%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Anaemia</td>
<td>214 (69%)</td>
<td>137 (44%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>29 (9%)</td>
<td>29 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (10%)</td>
<td>36 (11%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (3%)</td>
<td>11 (4%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (3%)</td>
<td>8 (3%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (5%)</td>
<td>8 (3%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (1%)</td>
<td>5 (2%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Neuropathy (motor)</td>
<td>15 (5%)</td>
<td>12 (4%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Neuropathy (sensory)</td>
<td>21 (7%)</td>
<td>20 (6%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

*Table 3: Frequency of grade 3 or 4 adverse events*
Questions

◆ Stage III and IV
  • Are triplets or sequential doublets more efficacious than carboplatin+paclitaxel?
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  • Does bevacizumab improve the prognosis?
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◆ Early stages
  • Who needs chemotherapy?
  • For how long?

◆ What else do I need to know?
Bevacizumab – GOG-218

Front-line: Epithelial OV, PP or FT cancer
- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

n=1800 (planned)

Stratification variables:
- GOG performance status (PS)
- Stage/debulking status

Randomize 1:1:1

Arm I
- Carboplatin (C) AUC 6
- Paclitaxel (P) 175 mg/m²
- Placebo

Arm II
- Carboplatin (C) AUC 6
- Paclitaxel (P) 175 mg/m²
- BEV 15 mg/kg
- Placebo

Arm III
- Carboplatin (C) AUC 6
- Paclitaxel (P) 175 mg/m²
- BEV 15 mg/kg

Cytotoxic (6 cycles)  Maintenance (16 cycles)  15 months

J Clin Oncol 28:18s, 2010 (suppl; abstr LBA1)
Bevacizumab – GOG-218

GOG-0218: Investigator-Assessed PFS

<table>
<thead>
<tr>
<th>Arm I</th>
<th>Arm III</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>CP + BEV → BEV</td>
</tr>
<tr>
<td>(n=625)</td>
<td>(n=623)</td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>423 (67.7)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.3</td>
</tr>
<tr>
<td>Stratified analysis HR (95% CI)</td>
<td>0.717 (0.625–0.824)</td>
</tr>
<tr>
<td>One-sided p-value (log rank)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Proportion surviving progression free

Months since randomization

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J Clin Oncol 28:18s, 2010 (suppl; abstr LBA1)
Bevacizumab – GOG-218

GOG-0218: Overall Survival Analysis

At time of final PFS analysis

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Proportion alive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
</tbody>
</table>

**Arm I**
- CP (n=625)
- Patients with events, n (%) = 156 (25.0)
- Median, months = 39.3
- HR (95% CI) = 1.036 (0.827–1.297)
- One-sided p-value = 0.361

**Arm II**
- CP + BEV (n=625)
- Patients with events, n (%) = 150 (24.0)
- Median, months = 38.7
- HR (95% CI) = 0.915 (0.727–1.152)
- One-sided p-value = 0.252

**Arm III**
- CP + BEV → BEV (n=623)
- Patients with events, n (%) = 138
- Median, months = 39.7
- HR (95% CI) =
- One-sided p-value =

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J Clin Oncol 28:18s, 2010 (suppl; abstr LBA1)
Intraperitoneal Therapy Pharmacology 1
## Intraperitoneal Therapy Pharmacology 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ratio</th>
<th>Peritoneal cavity:Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Peak concentration</td>
</tr>
<tr>
<td>Cisplatin‡</td>
<td>20:1</td>
<td>12:1</td>
</tr>
<tr>
<td>tissue penetration ≈ 2mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel*</td>
<td>1000:1</td>
<td>1000:1</td>
</tr>
<tr>
<td>t ½ ≈ 72h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin‡</td>
<td>18:1</td>
<td></td>
</tr>
</tbody>
</table>

‡high absorption: systemic exposure equal to intravenous use

*in Cremophor EL: low absorption, systemic exposure lower than with i.v. use

adapted from Markman Lancet Oncology 2003 4 277
Markman et al. JCO 1992 10 1485
Mohamed F et al. Cancer Chemother Pharmacol 2003 52 405
IP Trials

**SWOG 8501/GOG 104**
- RR Death: 0.76*
  - Alberts DS et al. NEJM 1996 335 1950

**GOG 114**
- RR Death: 0.81
  - Markman M et al. JCO 2001 19 1001

**GOG 172**
- RR Death: 0.75*
  - Armstrong DK et al. NEJM 2006 354 24

* p<0.05
GOG 172

Intraperitoneal therapy

Intravenous therapy

P=0.03

Armstrong DK et al. NEJM 2006 354 24
GOG 172 Toxicity and Quality of Life

Table 2. Frequency of Grade 3 or 4 Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Intravenous-Therapy Group (N=210)</th>
<th>Intraperitoneal-Therapy Group (N=201)*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia‡</td>
<td>134 (64)</td>
<td>152 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count &lt;25,000/mm³</td>
<td>8 (4)</td>
<td>24 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Other hematologic event</td>
<td>190 (90)</td>
<td>188 (94)</td>
<td>0.87</td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>51 (24)</td>
<td>92 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal or genitourinary event</td>
<td>5 (2)</td>
<td>14 (7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulmonary event</td>
<td>5 (2)</td>
<td>7 (3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>10 (5)</td>
<td>19 (9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>18 (9)</td>
<td>39 (19)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cutaneous change</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Event involving lymphatic system</td>
<td>0</td>
<td>3 (1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (4)</td>
<td>19 (9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Infection</td>
<td>12 (6)</td>
<td>33 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (4)</td>
<td>36 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic event</td>
<td>15 (7)</td>
<td>55 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (1)</td>
<td>23 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatic event</td>
<td>1 (&lt;1)</td>
<td>6 (3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;1)</td>
<td>6 (3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Armstrong DK et al. NEJM 2006 354 34
Wenzel LB et al. JCO 2007 25 437
Preoperative chemotherapy

- Stage IIIC or IV epithelial ovarian carcinoma, fallopian-tube carcinoma, or primary peritoneal carcinoma
- Randomization¹
  - primary debulking surgery followed by platinum-based chemotherapy
  - neoadjuvant platinum-based chemotherapy followed by debulking surgery

¹Minimization to stratify for institution, method of biopsy (image-guided, laparoscopy, laparotomy, or fine-needle aspiration), tumor stage (IIIC or IV), and largest preoperative tumor size (excluding ovaries) (≤5 cm, >5 to 10 cm, >10 to 20 cm, or >20 cm)
Preoperative chemotherapy

A Intention-to-Treat Analysis

Non-inferior
HR = 0.8, p=0.01

Vergote NEJM 2010 363 943
Questions

◆ Stage III and IV
  • Are triplets or sequential doublets more efficacious than carboplatin+paclitaxel?
  • Does maintenance therapy improve the prognosis?
  • Does bevacizumab improve the prognosis?
  • Is intraperitoneal therapy superior to intravenous?
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◆ Early stages
  • Who needs chemotherapy?
  • For how long?

◆ What else do I need to know?
Adjuvant Therapy for Early Stage OC
Does it work?

**ICON 1**
- N=477, median age: 55
- 93% stage I
- Staging not defined
- 71% CBDCA
- Benefit only in G3 and IC cancers

(ASCO 2007)

**ACTION**
- N=448, median age: 55
- 92% stage I
- FIGO-recommended staging 37%!
- 4-6 cycles, “platinum-based”

Hazard ratio = 0.66 (0.45-0.79)
P=0.03

Hazard ratio = 0.69
P=0.10
Adjuvant Therapy for Early Stage OC
Does it work?

Inadequately Staged

Adequately Staged

HR = 0.68
95% CI, 0.52 to 0.89

Chemotherapy Better

HR = 0.91
95% CI, 0.51 to 1.61

Chemotherapy Better

No Chemotherapy Better

No Chemotherapy Better

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Tropé et al. JCO 2007 25 2909
Adjuvant Therapy for Early Stage OC
How many courses? GOG 157

All Patients
Serous Histology

CBDCA + PTX (q 3 weeks). 3 vs. 6 cycles

Bell Gynecol Oncol 2006 102 432
Chan Gynecol Oncol 2010 116 301
Toxicity → Efficacy

- Retrospective, observational
- N=255, 6 cycles CBDCA+PTX (q 3 weeks)
Summary

- Best guess in October 2010: Carboplatin + (weekly) PTX, 6 courses
- For all patients with stage IA/IB and grade 3
- For all patients with stage IC and higher
- No maintenance
- No bevacizumab (yet?)
- No i.p. therapy?
- Do not underdose!