Optimal First-line Treatment for Ovarian Cancer

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Ovarian cancer: survival rates

Bars indicate 95% CI

Ovarian Cancer not one disease

8704 patients from 7 Randomised trials

Mackay et al Int J Gyn Cancer 2010
Surgery

• How important is complete surgical debulking?
• What is the importance of specialised care and centralisation?
• Are patients disadvantaged by delaying primary surgery- ‘neoadjuvant chemotherapy’?
Role of surgical outcome as prognostic factor

Complete removal of visible tumour carries prognostic importance

“optimal debulking ≠ < 1 cm disease”

No residual disease v < 1 cm HR 2.20 (95% CI 1.90-2.54)

*Cochrane meta-analysis. Elattar et al 2011*

Du Bois et al Cancer 2009
Surgical specialisation?

Paulsen et al. Int J Gynecol Cancer 2006
Primary (Neoadjuvant) Chemotherapy

• Consider if radical debulking is not possible
• Is it safe to defer surgery by primary chemotherapy?

EORTC 55971

Stage IIIC–IV Randomize

718 patients enrolled

NACT

Chemotherapy

TC q3wks, 3 cycles

Chemotherapy:
Platinum-based (cisplatin >75 mg/m² or carboplatin AUC 5)
Plus taxane (paclitaxel 175 mg/m² 3 hours of docetaxel 75 mg/m²)

IDS

Chemotherapy

TC q 3 wks, 3 cycles

PDS

Chemotherapy

TC q3wks, 6 cycles

Neoadjuvant chemotherapy
EORTC 55971

Progression-free survival

Overall survival

Multivariate analysis for OS EORTC 55971

<table>
<thead>
<tr>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal debulking</td>
<td>0.0001</td>
</tr>
<tr>
<td>Histological type (nine categories)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Largest tumour size at randomization</td>
<td>0.0008</td>
</tr>
<tr>
<td>FIGO stage (IIIC vs. IC)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Country (14 categories)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Age</td>
<td>0.0020</td>
</tr>
<tr>
<td>WHO PS</td>
<td>NS</td>
</tr>
<tr>
<td>Differentiation grade</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment arm</td>
<td>NS</td>
</tr>
</tbody>
</table>

International Trials of neoadjuvant chemotherapy
Chemotherapy

- Cisplatin: 1977
- Carboplatin: 1985
- Cisplatin & paclitaxel: 1996
- Carboplatin & paclitaxel: 1998
2000-2009

Carboplatin/paclitaxel + third drug
Carboplatin/paclitaxel sequential doublets
No improvement in PFS

Maintenance chemotherapy
No improvement in PFS
1 trial with 12 cycles paclitaxel led to PFS but no OS

High dose chemotherapy
No improvement in PFS
Progression-free survival in first-line trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Pt. numbers</th>
<th>PFS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>ICON 2</td>
<td>1526</td>
<td>17, 15.5</td>
</tr>
<tr>
<td></td>
<td>ICON 3</td>
<td>2074</td>
<td>16, 17.3</td>
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<tr>
<td></td>
<td>ICON 5</td>
<td>4312</td>
<td>16, 16</td>
</tr>
<tr>
<td>2010</td>
<td>OVAR-7</td>
<td>1308</td>
<td>18.5, 18.2</td>
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<tr>
<td></td>
<td>OVAR-9</td>
<td>1742</td>
<td>19.3, 17.8</td>
</tr>
</tbody>
</table>
Moving Forward

- Intraperitoneal chemotherapy
- Dose-dense chemotherapy
- Molecular Targeted therapies
Intraperitoneal Therapy

GOG-172

Cisplatin 75 mg/m²
Paclitaxel 135 mg/m²

Day 1: IV Paclitaxel 135 mg/m²
Day 2: IP Cisplatin 100 mg/m²
Day 8: IP Paclitaxel 60 mg/m²

Intraperitoneal therapy

Treatment Hazard Ratios for Death Intraperitoneal vs Intravenous Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Rel Haz</th>
<th>Var(ln(HR))</th>
<th>IP regimen better</th>
<th>IV regimen better</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG/GOG–104 (1996)</td>
<td>0.760</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GONO (2000)</td>
<td>0.670</td>
<td>0.077</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG–114/SWOG (2001)</td>
<td>0.810</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan (2001)</td>
<td>1.130</td>
<td>0.064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC–55875 (2003)</td>
<td>0.820</td>
<td>0.054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG–172 (2005)</td>
<td>0.710</td>
<td>0.020</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( X^2 \) heterogeneity (5 d.f.) = 3.1, \( p=0.68 \)

- Is the observed effect real?
- Do carboplatin and cisplatin have an equivalent effect when given i.p.?
- What is the contribution of weekly paclitaxel?
Ongoing intraperitoneal therapy studies

GOG 252

Ovarian (epithelial), primary peritoneal, or fallopian tube cancer
Stage II–IV optimal
No prior anti-VEGF therapy
n=1250 (target)

Primary endpoint: PFS
Secondary endpoints: OS, QoL, safety

Arm I
- IV carboplatin AUC 6 q3w
- Weekly IV paclitaxel 80 mg/m²
- Bevacizumab 15 mg/kg q3w

Arm II
- IP carboplatin AUC 6 q3w
- Weekly IV paclitaxel 80 mg/m²
- Bevacizumab 15 mg/kg q3w

Arm III
- IP cisplatin 75 mg/m² d2
- IV paclitaxel 135 mg/m² d1
- IP paclitaxel 60 mg/m² d8
- Bevacizumab 15 mg/kg q3w

22 cycles
Epithelial ovarian cancer
Stages II–IV
Including bulky tumour

Randomization

- Dose dense–TCiv
  - Paclitaxel 80 mg/m² IV Day 1,8,15
  - Carboplatin AUC 6 IV Q21, 6–8 cycles

- Dose dense–TCip
  - Paclitaxel 80 mg/m² IV Day 1,8,15
  - Carboplatin AUC 6 IP Q21, 6–8 cycles

Primary endpoint: PFS
Secondary endpoints: OS, toxicity, QoL
Accrual goal: 746 patients / 511 events
Intrapertioneal therapy after interval debulking surgery

NCIC- OV21 & NCRI – GEICO[PETROC] - SWOG

Patients with EOC

3-4 cycles neoadjuvant chemotherapy

Initial surgery: ≤ 1 cm residual

3 cycles standard IV carboplatin/paclitaxel

3 cycles IP/IV platinum and paclitaxel
Phase II

First phase - 50 patients per arm, assessing PD rate at 9 months and tolerability

Part II will drop one of the ip arms

Endpoints: PFS and OS
Stage II-IV EOC/FTC/PPC n=637

1:1 randomisation

- Carboplatin AUC6 q3w
- Paclitaxel 180mg/m² q3w

- Carboplatin AUC6 q3w
- Paclitaxel 80mg/m² q1w

- 66% stage III
- 98% ECOG PS 0-2
- 89% primary debulking, 10% delayed debulking
- 55% residual disease >1cm
- 56% serous, 12% endometrioid, 11% clear cell, 5% mucinous

JGOG 3016

Katsumata et al; Lancet 2009
JOGG 3016- Outcome

Progression-free survival

Overall survival

Katsumata et al; Lancet 2009
JGOG treatment delivery

- Discontinuation due to toxicity
  113 vs 69
  - Haematological 60 vs 43%
  - Cycle delayed 76% vs 67%
- Dose intensity
  - Carboplatin
    (AUC/wk 1.54 vs 1.71)
  - Paclitaxel
    (mg/m²/wk 63 vs 52)

Katsumata et al; Lancet 2009
JGOG3016: Updated Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Deaths, n (%)</th>
<th>Median OS</th>
<th>5-yr survival</th>
<th>P value</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>139 (45)</td>
<td>not reached</td>
<td>58.7%</td>
<td>0.039</td>
<td>0.79</td>
<td>0.63-0.99</td>
</tr>
<tr>
<td>c-TC</td>
<td>319</td>
<td>168 (53)</td>
<td>62.2 mos.</td>
<td>51.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

median follow-up period: 6.4 years

Katsumata et al ASCO 2012
JGOG 3016 – NOVEL trial

OS: by residual disease

Katsumata et al ASCO 2012
GOG 262- Dose dense chemotherapy

Stage III suboptimal debulking
Stage IV ovarian cancer

Carboplatin AUC5 IV d1
Paclitaxel 175mg/m²
+/- Bev. 15mg/kg (#2-6) at investigator’s discretion*

1:1
n = 625
Closed Feb 2012

Bevacizumab 15mg/kg q21 x 16 at investigator’s discretion*

Carboplatin AUC5 IV d1
Paclitaxel 80 mg/m² IV d1, 8, 15
+/- Bev. 15mg/kg (#2-6) at investigator’s discretion*

* 85% of patients received bevacizumab
Diagnosis of Stage IC-IV EOC/PPC/FTC

Immediate Primary Surgery (IPS)

Randomise 1:1:1

Arm 1
6 cycles

Arm 2
6 cycles

Arm 3
6 cycles

Arm 1 (control)
Carboplatin AUC 5       q3w
Paclitaxel 175mg/m²     q3w

Arm 2
Carboplatin AUC 5       q3w
Paclitaxel 80mg/m²      q1w

Arm 3
Carboplatin AUC 2       q1w
Paclitaxel 80mg/m²      q1w

Delayed Primary Surgery (planned)

Randomise 1:1:1

Arm 1
3 cycles

Arm 2
3 cycles

Arm 3
3 cycles

Arm 1
3 cycles

Arm 2
3 cycles

Arm 3
3 cycles

Cycle 3 d15 omitted

Delayed Primary Surgery (planned)

1590 patients

Single trial with a pre-specified stratification for IPS vs. DPS
Anti-angiogenic therapy of ovarian cancer

- Increased expression of angiogenic cytokines and receptors
- Associated with development of ascites
- High expression associated with poor prognosis
Two front-line trials with similar but not identical designs

GOG-0218¹
- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV (Oct 05 – Jun 09)

ICON7²
- High-risk stage I–IIA (grade 3 or clear cell)
- Stage IIB–IV (Dec 06 - Feb 09)

GOG0218: Updated PFS

HR (Bev throughout vs Control) 0.77; 95% CI, 0.68 to 0.87

GOG0218: Updated OS

Bevacizumab throughout group HR: 0.885 (0.750 to 1.040)

ICON7: Updated progression-free survival by risk groups

ICON7: updated (interim) survival

C Updated Data, Overall Survival

D Updated Data, Overall Survival in Patients at High Risk for Progression

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Standard chemotherapy</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard chemotherapy</td>
<td>764 741 724 703 672 646 623 542 421 304 212 132 71 26</td>
<td>764 753 737 717 702 680 657 592 459 329 228 129 69 19</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>234 226 219 208 194 175 166 137 107 67 46 25 15 6</td>
<td>231 227 222 214 208 199 186 164 134 94 65 31 18 4</td>
</tr>
</tbody>
</table>

Questions

- Will survival benefit be confirmed in the ‘high risk’ subset of ICON 7
- How will this affect use?
  - bevacizumab not licensed in the USA for ovarian cancer
- What dose? 7.5 or 15 mg/kg
- For how long?
  - Boost study exploring extended use of maintenance bevacizumab
- Which group of patients?
  - First line; ‘platinum sensitive’ recurrence; ‘platinum-resistant’
- Who?
  - No predictive markers to select patients. Can healthcare providers accept an expensive treatment that is potentially given to all with no prior knowledge?
Anti-angiogenic agents

- VEGFR Tyrosine Kinase Inhibitors - small molecules
  - Oral
  - Not pure VEGFR antagonists
  - Different spectrum of s/e: hypertension; diarrhoea, mucositis

<table>
<thead>
<tr>
<th>TKI</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>VEGFR; PDGFR; c-kit; FGFR</td>
</tr>
<tr>
<td>BIBF 1120 (nintedanib)</td>
<td>VEGFR; PDGFR; FGFR</td>
</tr>
</tbody>
</table>

- Angiopoietin Antagonist
  - Angiopoietin 1 and 2 neutralising peptibody
  - Blocks interaction with tie-2 receptor
  - AMG 386 (trebananib)- intravenous weekly
AGO-OVAR 12 (LUME-Ovar 1): a first-line Phase III study

BIBF 1120 (Nintedanib) in combination with carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer

Advanced epithelial ovarian, fallopian tube or primary peritoneal cancer
N=1300

2:1 randomization

BIBF 1120 200 mg p.o. BID
PLUS
Paclitaxel 175 mg/m² + carboplatin AUC 5/6
Every 21 days for 6 courses

Placebo p.o. BID
PLUS
Paclitaxel 175 mg/m² + carboplatin AUC 5/6
Every 21 days for 6 courses

BIBF 1120/placebo monotherapy continued in patients who have not progressed until AEs, disease progression or for a maximum of 120 weeks after randomization
AGO-OVAR16/VEG110655: Study Design

- Phase III randomized, two-arm, placebo controlled, double-blind, multicentre, intergroup study
- N= 900 subjects (1:1). Pazopanib administered at 800 mg daily for 52 weeks (12 months) – extended to 104 weeks (24 months).

First-line Chemotherapy (allow ip, neoadj) → Screening Baseline → RANDOMIZE

If not PD → Treatment Period → Pazopanib (12->24 months)

Placebo (12->24 months) → Post-Treatment Period → Observation (to PD)

Efficacy and safety → Efficacy only → Survival only

Follow-up Period → Survival Follow-up (post-PD)
Ovarian, tubal or peritoneal cancer FIGO stage III-IV (n = 2000)

Randomisation 2:1

6 courses
Paclitaxel 175 mg/m² q3w
Carboplatin AUC 5 or 6 q3w
Trebananib 15mg/kg qw

Interval debulking allowed after 3 cycles

Maintenance Trebananib qw 18 months

Primary Endpoint: Progression-free survival

Secondary endpoints: Overall Survival, Quality of Life, Complications, PK

6 courses
Paclitaxel 175 mg/m² q3w
Carboplatin AUC 5 or 6 q3w
Placebo qw

Interval debulking allowed after 3 cycles

Maintenance Placebo qw 18 months

Stratification:
- AUC 5 or 6
- PDS or IDS
- Resid Tumour,
- IIIa-B vs IIIc-IV

Accrual 152/2000
Conclusions

- Survival of women with advanced ovarian cancer is increasing

- Management of recurrent disease contributes significantly towards this

- Areas contributing to improvements in outcome from first-line therapy:
  
  - Earlier diagnosis
  - Specialised centres - surgery and chemotherapy
  - Improvements first line treatment

- Over last 15 years little improvement in PFS from first line therapy with different combinations of cytotoxic therapy

- Early indications are that novel molecular targeted therapies and/or different dose scheduling may improve current outcome figures