UPDATE ON NEW TREATMENT OPTIONS IN RECURRENT OVARIAN CANCER

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Barcelona
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OVARIAN CANCER – the typical patient

DIAGNOSIS 1\textsuperscript{st} relapse death
0 12 24 36 48 60

SURGERY
chemo

<table>
<thead>
<tr>
<th>chemo 1</th>
<th>chemo 2</th>
<th>chemo 3</th>
<th>chemo 4</th>
<th>chemo 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>carboplatin ± paclitaxel</td>
<td>carboplatin-based</td>
<td>carboplatin-based</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thus: for typical patient, duration of survival after 1\textsuperscript{st} relapse exceeds initial time to relapse

options include:
repeat paclitaxel (weekly), Liposomal doxorubicin, topotecan, etoposide, potentially Phase I trial
ROLE OF WEEKLY PACLITAXEL IN OVARIAN CANCER

Japanese Gynae Oncol Group Trial, reported at ASCO 2008

FIRST LINE
Stage II – IV
OVARIAN CANCER
(incl. primary peritoneal fallopian tube)

Randomise

Paclitaxel 180 mg/m² day 1  q 3w
Carboplatin AUC 6  day 1  6 – 9 cycles

Paclitaxel 80 mg/m² days 1,8,15  q 3w
Carboplatin AUC 6  day 1  6 – 9 cycles

Primary end-point: PFS
Total accrual: 632 pts

WEEKLY PACLITAXEL IN FIRST-LINE THERAPY - CONCLUSIONS

<table>
<thead>
<tr>
<th></th>
<th>Conventional paclitaxel/carbo (n = 319)</th>
<th>Weekly paclitaxel/carbo (n = 312)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurable response CR/PR</td>
<td>54%</td>
<td>56%</td>
<td>0.72</td>
</tr>
<tr>
<td>Median PFS</td>
<td>17.2 m</td>
<td>28.0 m</td>
<td>0.0015</td>
</tr>
<tr>
<td>2 yr survival</td>
<td>77.7%</td>
<td>83.6%</td>
<td>0.049</td>
</tr>
<tr>
<td>Received ≥6 cycles</td>
<td>72%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Discontinued protocol therapy (9 cycles) because of toxicity</td>
<td>22%</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

- Well conducted, well-balanced (55% optimal debulk), sizeable trial with sufficient follow-up
- Intriguing evidence to indicate significant improvement in PFS, albeit with some increase in (myelo)toxicity, G3/4 anaemia 44% vs 69% (p < 0.001)
- Size of benefit, i.e. 17 m → 28 m, requires urgent confirmation in another first-line trial
WEEKLY PACLITAXEL FOR OVARIAN CANCER – KEY ISSUES FOR 2010 ONWARDS

• can results in Japanese trial be confirmed in large scale randomized first line trials?
  • confirmatory trials planned by GOG/ICON-8
• is weekly paclitaxel an alternative form of “antiangiogenic” therapy?
  • new randomized trials will compare with bevacizumab
• in recurrent ovarian cancer, response rate is ~50% but response duration is short (Linch et al, 2008); can efficacy of weekly paclitaxel be improved by addition of novel targeted agents?
  • randomized trials planned/underway include a SRC-inhibitor and IGFR inhibitor

NEW TREATMENT OPTIONS IN RECURRENT OVARIAN CANCER

• “molecular targeted” agents
  - monoclonal antibodies
  - small molecules
• novel cytotoxics

Major issues:
• can we select those patients who will benefit most?
• is a single agent, or combination approach preferable?
RATIONAL TARGETS IN OVARIAN CANCER

• VEGF receptor and ligand
• PI3K/AKT pathway
• alpha folate receptor
• and the dysfunctional BRCA gene!

TARGETING VEGF IN OVARIAN CANCER
– WILL THIS BE ITS FINEST HOUR?

• VEGF family plays key role in biology of healthy ovary and of ovarian cancer

• anti-VEGF strategy effective in appropriate preclinical models

• in ovarian cancer single agent treatment (with bevacizumab) more effective than in any other solid tumour except renal

**BEVACIZUMAB IN OVARIAN CANCER**

Two single agent Phase II trials with bevacizumab 15 mg/kg i.v. q3 weekly

<table>
<thead>
<tr>
<th>STUDY</th>
<th>no</th>
<th>Resp %</th>
<th>PFS at 6 m</th>
<th>Prior treatment</th>
<th>Bowel perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 170D</td>
<td>63</td>
<td>18% PR</td>
<td>39%</td>
<td>42% plat. sensitive (up to 2 prior treatments)</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td>55% SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannestra</td>
<td>44*</td>
<td>16% PR</td>
<td>27%</td>
<td>All plat. refractory or resistant (up to 3 prior regimens)</td>
<td>5</td>
</tr>
<tr>
<td>et al, 2006</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Study stopped early because of bowel perforations (1 fatal)
  • is this related to bowel tumour involvement (obstruction and bowel wall thickening)?

**RANDOMIZED TRIALS OF BEVACIZUMAB IN OVARIAN CANCER**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>CHEMO</th>
<th>BEVACIZUMAB</th>
<th>No. of PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST LINE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG (218)</td>
<td>Paclitaxel Carboplatin</td>
<td>Concurrent and maintenance 15 mg/kg q3w (3 arm placebo)</td>
<td>1800</td>
</tr>
<tr>
<td>GCIG (ICON7)</td>
<td>Paclitaxel Carboplatin</td>
<td>Concurrent only 7.5 mg/kg q3w (2 arm)</td>
<td>1500</td>
</tr>
<tr>
<td>SECOND LINE – PLATINUM SENSITIVE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG (213)</td>
<td>Paclitaxel Carboplatin</td>
<td>Concurrent and maintenance (2 arm) 15 mg/kg q3w</td>
<td>1600</td>
</tr>
<tr>
<td>OCEANS</td>
<td>Gemcitabine Carboplatin</td>
<td>Concurrent (2 arm) 15 mg/kg q3w</td>
<td>200</td>
</tr>
</tbody>
</table>
BEVACIZUMAB IN OVARIAN CANCER

Current position:
- established single agent activity in recurrent disease
- well tolerated; (higher) risk of GI perforation will probably be reduced by careful patient selection
- results of first-line combination studies (with paclitaxel/carboplatin) expected in 2010, involving concurrent and maintenance treatment
- other combinations now being explored with chemotherapy or other targeted agents

SMALL MOLECULE ANTI-ANGIOGENIC APPROACH TO OVARIAN CANCER

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Target</th>
<th>No of eval pts</th>
<th>Dose</th>
<th>Response: clinical benefit (PR/SD &gt;3 m) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cediranib</td>
<td>VEGFR 1-3 PDGFR</td>
<td>72 (2 trials)</td>
<td>30-45 mg o.d.</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR PDGFR</td>
<td>17</td>
<td>37.5 mg o.d.</td>
<td>12 (70%)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR 1-3 PDGFR</td>
<td>36</td>
<td>800 mg o.d.</td>
<td>13 (36%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR 1-3 PDGFR RAF</td>
<td>59</td>
<td>400 mg b.d.</td>
<td>22 (37%)</td>
</tr>
</tbody>
</table>

Randomized trials planned or underway in first and second line, inc. ICON-6 - also including Vargatef (BIBF 1120)
RANDOMIZED TRIAL FOR PLATINUM-SENSITIVE RELAPSED OVARIAN CANCER

ICON-6: Can VEGFR inhibitor Cediranib improve survival?

Platinum sensitive relapse, >6 m interval, one prior treatment

Randomize

(paclitaxel)-carboplatin x 6 and concurrent placebo

(paclitaxel)-carboplatin x 6 and concurrent Cediranib 20 mg daily, then “maintenance” placebo for 18 m, or until PD

(paclitaxel)-carboplatin x 6 and concurrent Cediranib 20 mg daily, then “maintenance” Cediranib for 18 m, or until PD

n = 2000 pts
Primary outcome: OS (hazard ratio 0.75)

A MAINTENANCE ANTI-ANGIOGENIC APPROACH TO OVARIAN CANCER

Randomized Phase II trial of BIBF 1120 (VEGFR, PDGFR, FGFR inhibitor)

Relapsed ovarian cancer, responded to 2nd/3rd/4th line chemo, which had been started <12 m from previous chemo

Randomize

BIBF 1120 250 mg bd for up to 36 w placebo

Completed 36 w PFS at 36 w

<table>
<thead>
<tr>
<th></th>
<th>n = 43</th>
<th>n = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>15.6%</td>
<td>(3.6-27.3)</td>
</tr>
<tr>
<td>0</td>
<td>2.0%</td>
<td>(0-8.4)</td>
</tr>
</tbody>
</table>

G 3/4 adverse events: 61% vs 28% with frequent elevated transaminases on BIBF 1120 (43%) but only 2 pts discontinued

Conclusion: BIBF 1120 could delay disease progression in previously responding ovarian cancer patients

ASCO 2009
PI3 KINASE/AKT PATHWAY and OVARIAN CANCER

- key to normal cellular functions including glucose metabolism
- in cancer cells, it promotes growth factor-mediated cell survival and blocks apoptosis
- PIK3CA (gene encoding P110α – key catalytic subunit) is amplified in 40% of ovarian cancer (Shayesteh et al, 1999) and mutations also present (Campbell et al, 2004)

PI3 KINASE/AKT PATHWAY and OVARIAN CANCER

PI3K/AKT
- plays an important role in drug resistance to both paclitaxel (Asselin et al, 2001) and platinum (Mabucci et al, 2002) through negative effect on apoptosis
- inhibitors can reverse resistance to both agents, particularly in models with increased pathway activity

What’s in the clinic? - Several agents, mostly Phase I

- Range of small mol. wt. inhibitors incl. new structures
- Occasional responses (mainly CA125) noted in ongoing Phase I trials
- Combination studies planned or underway, and patient selection strategies under discussion

- PI3 KINASE
- PKB/AKT
- mTOR
- New TORC 1/2 inhibitor
- HSP90 inhibitors
ARE THERE OTHER NOVEL TARGETS? ONE POSSIBLE: THE ALPHA FOLATE RECEPTOR

Alpha folate receptor:
- cell-membrane linked high affinity folate transporter
- acts by receptor-mediated endocytosis
- restricted expression in normal tissue (placenta, kidney, choroid plexus)
- overexpressed in various epithelial tumours, particularly ovary
- potential to target new cytotoxics, e.g. TS inhibitor, ONX 0801

% tumours overexpressing

<table>
<thead>
<tr>
<th>Tissue</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>92%</td>
</tr>
<tr>
<td>Uterus</td>
<td>91%</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>70%</td>
</tr>
<tr>
<td>Kidney</td>
<td>50%</td>
</tr>
<tr>
<td>Stomach</td>
<td>38%</td>
</tr>
<tr>
<td>Lung</td>
<td>33%</td>
</tr>
<tr>
<td>Colon</td>
<td>22%</td>
</tr>
<tr>
<td>Choroid plexus</td>
<td>80% (epend)</td>
</tr>
<tr>
<td>Brain</td>
<td>80%  (mets)</td>
</tr>
</tbody>
</table>

α-FR overexpression in fresh clinical tumour material as measured by IHC (adapted from Garin-Chesa1993; Weltman 1992; Bueno 2001)

THE ALPHA FOLATE RECEPTOR (FR) and OVARIAN CANCER – A THERAPEUTIC ANTIBODY APPROACH

• Farletuzumab
  - humanized MoA against FR with experimental anti-tumour activity in resistant models, particularly in combination with chemo
  - in Phase I trial, significant tumour uptake seen using radiolabelled MoA
  - in Phase II trial of 44 platinum-sensitive relapsed pts treated with paclitaxel-carbo plus farletuzumab:
    • 70% RECIST response/89% CA125 response
    • in 9 pts (21%) second PFS was longer than first (Armstrong et al, ECCO 2009)
  - randomized trials planned in both platinum sensitive and resistant disease
## NOVEL CYTOTOXICS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TARGET</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabectedin (ET743)</td>
<td>minor groove of DNA</td>
<td>active in platinum-resistant models</td>
</tr>
<tr>
<td>Patupilone (epothilone EPO906)</td>
<td>microtubule</td>
<td>active in taxane-resistant models</td>
</tr>
</tbody>
</table>

## NOVEL CYTOTOXICS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACTIVITY</th>
<th>COMPLETED TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabectedin</td>
<td>25/78 (32%) PR in plat. sensitive pts, but only 4/92 (4%) in plat. resistant pts</td>
<td>Randomized Phase III trial of trabectedin/liposomal doxorubicin vs. liposomal doxorubicin - positive results for PFS and OS in 6-12 m group</td>
</tr>
<tr>
<td>Patupilone</td>
<td>8/33 (24%) PR in plat. resistant pts, with q3 w dosing</td>
<td>Randomized Phase III trial vs. liposomal doxorubicin in resistant pts - Results expected to be presented at ASCO 2010 (n = 810)</td>
</tr>
</tbody>
</table>
PARP INHIBITION and TUMOUR-SELECTIVE SYNTHETIC LETHALITY

DNA damage (SSBs)

DNA replication (accumulation of DNA DSBs)

Normal cell
HR-mediated DNA repair
Cell survival
HR-deficient tumor cell (e.g. BRCA 1/2−)
Impaired HR-mediated DNA repair
Cell death

Tumor-selective cytotoxicity

DSB, double-strand break; HR, homologous recombination
SSB, single-strand break


OLAPARIB
A novel, orally active PARP inhibitor

- A Phase I trial identified olaparib (AZD2281; KU-0059436) 400 mg bid as the maximum tolerated dose with a 50% (23/46 pts) combined response rate (RECIST and CA125) in BRCA-mutated ovarian cancer

- Most common toxicities: CTCAE grade 1 and 2 nausea and fatigue

- Significant PARP inhibition and tumor response at olaparib doses 100–400 mg bid

INTERNATIONAL PHASE II TRIAL of OLAPARIB in ASSOCIATED OVARIAN CANCER

57 pts (BRCA 1 39; BRCA 2 18) received either 400 mg b.d. or 100 mg b.d. in 2 sequential cohorts – (med. 3 prior CT)

<table>
<thead>
<tr>
<th>33 pts at 400 mg b.d.</th>
<th>RECIST response</th>
<th>Clinical benefit (inc. CA125 response)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 (66%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24 pts at 100 mg b.d.</th>
<th>RECIST response</th>
<th>Clinical benefit (inc. CA125 response)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 (13%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (42%)</td>
</tr>
</tbody>
</table>

Conclusion:
- level of efficacy confirmed, med. response duration 9.5 m
- favourable toxicity profile confirmed
- 400 mg b.d. appears to be more active than 100 mg b.d.
- recently completed randomized trial (vs. liposomal doxorubicin) will compare 400 mg b.d. + 200 mg b.d. doses
  (Audeh et al, ASCO, 2009)

POTENTIAL of PARP INHIBITOR (SINGLE AGENT) in SPORADIC OVARIAN CANCER

Question: What proportion of ovarian cancer patients will have BRCA1/2 dysfunction, either due to mutation of either gene or for other reasons, e.g. methylation of this or related genes?

Answer: • approx 15% of sporadic ovarian cancers have mutation of either gene; in serous histological subtypes, proportion is 18%
• approx 15-20% more cases have BRCA dysfunction, through methylation, etc.
• approx 10% have FANCF methylation

Therefore: potentially half the cases of serous ovarian ca could benefit from targeted single agent treatment - how can these be identified?
FURTHER DEVELOPMENT OF OLAPARIB – A MAINTENANCE TRIAL

Patients with serous ovarian cancer, responding to 2\textsuperscript{nd} or 3\textsuperscript{rd} line platinum-based chemo, with CR/PR (penultimate treatment-free interval >6 m)

- BRCA mutation not necessary

RANDOMISE

olaparib 400 mg bd until disease progression

placebo until disease progression

n = 250
end point: PFS
- recruitment now underway

PATIENT SELECTION FOR SINGLE AGENT TREATMENT WITH OLAPARIB

Predictive biomarker:

- immunohistochemistry, with BRCA 1/2 antibodies
- functional (ex vivo) test for loss of HR (RAD 51 foci-formation)
- molecular signature (gene array)

and/or: background of

- repeated response to platinum-based chemo
- prolonged survival (>5 yrs)
- serous histology
KEY ISSUES FOR FUTURE DEVELOPMENTS of PARP INHIBITORS

- Is a single agent or combination approach preferable?
- Single agent treatment utilises tumour selective synthetic lethality, with no issues of additional toxicity
- Combination with DNA-damaging chemotherapy, e.g. temozolamide or platinum, reverses resistance in experimental models
- But: clinically, myelotoxicity is usually enhanced by chemo/PARPi combination, and optimal duration of PARPi not yet defined
  - Exception: randomized trial in triple negative breast cancer with OSI-201
- Randomized trials in ovarian cancer (at least 4 now planned) will need careful interpretation

PARP INHIBITORS IN OVARIAN CANCER

Summary:
- Compelling clinical data with Olaparib indicate efficacy in BRCA-related cancer
- Potential role of single agent therapy in sporadic ovarian cancer (and TNBC) requires urgent assessment
- In this context, tests for “BRCaeness” (HR loss) need rapid development
- Combination approach merits further study, but regimens require careful consideration of dose/schedule of both chemo and PARPi, with appropriate patient selection
- Tumour selective synthetic lethality represents an important step forward in cancer treatment
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