Developments in Targeted Therapy for Ovarian Cancer – 2 examples

Vergote et al. AMG 386 and carboplatin /paclitaxel
Liu et al. MM121 and weekly paclitaxel

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London

Vienna
September 2012
progress in the management of ovarian cancer: evolution over 40 years

five year survival

15% → 30% → 40% → ?50%?

key advances in chemotherapy

1970

first use of cisplatin

1980

first use of carboplatin

1990

first use of paclitaxel

2000

first reports of bevacizumab

first use of oral PARPi

2010

positive evidence for weekly paclitaxel in first line

in 2012, what is the potential role for molecular targeted therapy?
bevacizumab in ovarian cancer

positive randomised trials in first/second line and in recurrent disease
(GOG 218, ICON 7, OCEANS, AURELIA)

what will the limitations be (apart from cost)?
• Undue risk of bowel perforation in some patients
• other toxicities, i.e. hypertension, etc.
• resistance to VEGF-targeted therapy

how might these be addressed?
• Alternative approaches include
  • AMG 386
  • VEGFR targeted TKIs
  • Combination approaches, including vascular disrupting agents
AMG - 386 (trebananib)

A peptide-Fc fusion protein (peptibody), which prevents angiopoietin 1 and 2 interacting with Tie 2 receptors, thus inhibiting vascular maturation and reducing impact of VEGF stimulation.

in single agent Phase I trial, iv weekly treatment is well tolerated; hypertension, proteinuria, thrombosis not seen but peripheral oedema noted. DCE MRI confirms significant vascular effect; one response noted in ovarian cancer patients in combination with weekly paclitaxel, randomised placebo-controlled study in relapsed disease indicated that higher dose of 10mg/kg was most effective

is there a role in first line therapy? is higher dose (15mg/kg feasible?)

<table>
<thead>
<tr>
<th>AMG 386 with weekly paclitaxel in relapsed ovarian cancer</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Weekly paclitaxel</td>
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<tr>
<td>n = 53</td>
</tr>
<tr>
<td>Median PFS</td>
</tr>
<tr>
<td>RECIST response</td>
</tr>
<tr>
<td>CA125 response</td>
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<td>HR = 0.76 for A + B versus C</td>
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questions:

can AMG 386 15mg/kg iv weekly be given safely to patients as first-line treatment with paclitaxel/carboplatin q 3 weekly including those scheduled for interval surgery?

is AMG 386 15mg/kg iv weekly feasible as maintenance therapy for up to 18 months?

updated analysis from ASCO 2012 on 27 patients
AMG 386 plus paclitaxel-carboplatin as first-line therapy

Results:

a) in combination concurrently with chemo (n = 27)
   • no DLTs
   • main toxicity not attributable to chemo is oedema, in 11 cases (40%) mainly peripheral. Other G1-G2 toxicities include diarrhoea, nausea, fatigue in approximately 40%
   • no PK interaction between AMG 386 and paclitaxel / carboplatin
   • no major difference in patients undergoing interval (n=13) or primary (n=14) surgery

b) as maintenance therapy following chemo (n=13)
   • No additional toxicity to date, main side effect is localised oedema.

Conclusion:
First line treatment using AMG 386 dose of 15mg/kg is safe, for use within a randomised trial
AMG 386 plus paclitaxel-carboplatin as first-line therapy

**issues:** how does this compare with bevacizumab?

**advantages:**
- no hypertension/proteinuria/bowel perforations/thrombo-embolic events
- no restriction on interval surgery

**disadvantages:**
- peripheral oedema, presumably mechanism related (Ang 1,2 blockade)
- weekly therapy

**key question:**
- could AMG 386 potentially replace bevacizumab on grounds of efficacy as well as toxicity profile in first-line therapy?

**TRINOVA-3:** first line placebo-controlled trial (n=2000)
- paclitaxel/carbo ± AMG 386 q w during chemo and maintenance until PD
- primary end point: PFS.
Other questions:

• Is a combination approach, eg. AMG386/bevacizumab justified?
  – In vivo data support combined Ang 1/2 inhibition and VEGF inhibition

But note: AMG 386 ± sorafenib in renal cancer showed no benefit in randomised trial (n= 152)

• Are dual Ang or Tie 2 / VEGF inhibitors preferable?
  – Examples include CVX-241, CEP 11981 and several multi-targeted TKIs

• Is AMG-386 active in patients progressing after bevacizumab?
  – Pre-clinical data indicate potential role, through Ang 1/Tie 2, but clinical data lacking.
  – What key factors underlie clinical resistance to antiangiogenic therapy?
resistance to anti-angiogenic therapy

a) acquired resistance
   - activation/upregulation of alternative pro-angiogenic signalling, e.g. Ang 1/2
   - recruitment of bone-marrow derived pro-angiogenic cells
   - increased pericyte coverage of tumour vasculature, obviating need for VEGF signalling.

b) intrinsic (pre-existing) resistance
   - multiple pre-existing redundant pro-angiogenic signals
   - pre-existing inflammatory cell-mediated vascular protection
   - invasive co-option of normal vessels.

can resistance be addressed through inhibition of signalling through Tie 2 receptors (AMG 386)?
progress in the management of ovarian cancer: evolution over 40 years

Key advances in chemotherapy

- First use of cisplatin
- First use of carboplatin
- First use of paclitaxel
- First reports of bevacizumab
- First use of oral PARPi
- Positive evidence for weekly paclitaxel in first line

Five year survival

- 1970: 15%
- 1980: 30%
- 1990: 40%
- 2000: ??50%?
- 2010: ??

In 2012, what is the potential role for molecular targeted therapy?
issues: Will this prove superior to q 3 weekly schedule at all stages of ovarian cancer?

**in first line:**

JGOG trial (631 patients) demonstrated superiority over q3w schedule (median PFS 28m vs 17.5m), but results from confirmatory studies needed before adoption as new standard of care.

Katasumata et al. Lancet 2009

**in recurrent disease:**

weekly paclitaxel should now be a standard line of treatment for most patients (response rate up to 50%) however: response duration is short (often < 6m)


how can we do better?

• addition of other active agents, eg. Bevacizumab (AURELIA), AMG-386
• circumvention of resistance to paclitaxel
weekly paclitaxel in ovarian cancer

how do cells acquire resistance to therapy?

– through alterations in:
  • transport (MDR – p glycoprotein)
  • target (β tubulin mutations)
  • signalling pathways (apoptosis / survival)

– modulation strategies should ideally be based on translational / clinical data indicating most likely underlying mechanism (s) of resistance.

– more of these data needed.
Rationale for targeting signalling pathways

Negative clinical trials to date, focusing on other approaches (MDR → valsapodar; tubulin mutations → epothilones)

Multiple pre-clinical studies indicating potential for modulation through pathway-specific inhibitors, particularly targeting P13K/AKT/MTOR pathway

Predictive biomarker: p-S6K/S6K ratio is a downstream readout of activation of the PI3 kinase pathway

Preliminary clinical data, correlating activity of P13K/AKT pathway in tumour cells from ascites with acquired drug resistance.

Carden et al, Mol Canc Ther 2012
<table>
<thead>
<tr>
<th>target</th>
<th>drug</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>folate receptor</td>
<td>farletuzumab</td>
<td>randomised trial in platinum resistant patients discontinued following futility analysis n= &gt;400</td>
</tr>
<tr>
<td>Src protein</td>
<td>saracatinib</td>
<td>randomised trial in platinum resistant patients complete - analysis awaited n= 102</td>
</tr>
<tr>
<td>IGF-R</td>
<td>OSI – 906</td>
<td>randomised trial in platinum resistant patients – ongoing</td>
</tr>
<tr>
<td>Erb B family – Erb B3</td>
<td>MM-121</td>
<td>feasibility study n=38</td>
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# ErbB family of receptors in ovarian cancer

<table>
<thead>
<tr>
<th>receptor</th>
<th>ligand</th>
<th>frequency</th>
<th>therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR (Her 1)</td>
<td>EGF/TGFα/amphiregulin</td>
<td>amplification - 4-22% activating mutations - &lt; 4%</td>
<td>minimal efficacy for gefitinib, erlotinib (maintenance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>high-expression - up to 62%</td>
<td></td>
</tr>
<tr>
<td>ErbB2 (Her 2)</td>
<td>none</td>
<td>amplification 9% (partic. mucinous)</td>
<td>minimal efficacy for Herceptin</td>
</tr>
<tr>
<td>ErbB3 (Her 3)</td>
<td>heregulin 1/2</td>
<td>high-expression in 53%</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>amplification also noted(^2)</td>
<td></td>
</tr>
<tr>
<td>ErbB4</td>
<td>heregulin 1/2</td>
<td>expression (IHC) in &gt;80%</td>
<td>_</td>
</tr>
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1. Tanner et al. JCO 24 4317-4323 2006
ErbB signalling and potential role for MM-121 in ovarian cancer

ErbB3 as heterodimer with ErbB2, plays a key role in cancer cell survival signalling, through MAPK and Akt pathways

ErbB3 activation through autocrine loop, natural ligand is heregulin (HRG)

ErbB3 over-expression linked to decreased survival.

ErbB3 associated with resistance to chemotherapy, including taxanes

effects of ErbB3 signalling may be reversed by MM-121

MM 121 is fully human IgG2 antibody, recognises ErbB3 and blocks HRG signalling

Paclitaxel: 40 mg/kg q7d
MM-121: 600 μg/kg q3d
MM-121 – clinical data

phase 1 single agent trial (Dealinger et al, AACR 2011)

- Dose escalation plus expansion in 38 patients
- G 1/2 nausea/diarrhoea/rash, and G3 fatigue seen but DLT not reached at doses up to 20mg/kg iv weekly.
- 9 patients had RECIST SD, 5 treated > 4 months

phase 2 combination studies ongoing, based on preclinical data, involve both targeted and cytotoxic agents, including weekly paclitaxel
MM-121 plus weekly paclitaxel... Liu et al (974 PD)

Feasibility study in ovarian and breast cancer, accrual ongoing. n=28, 16 ovarian and 12 breast cancer.

- Schedule: MM-121 20-40mg/kg i.v. starting dose, then 12-20mg/kg i.v. weekly or 3 weeks on/1 week off paclitaxel: 80mg/m² i.v. weekly.
- DLT: not reached.

<table>
<thead>
<tr>
<th>Main Toxicity</th>
<th>Any Grade</th>
<th>G3 / G4</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>52%</td>
<td>15%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>48%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>40%</td>
<td>7%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37%</td>
<td>11%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>33%</td>
<td>11%</td>
</tr>
</tbody>
</table>
MM-121 plus weekly paclitaxel... Liu et al (974 PD)

- PR = 4
- SD = 10 (> 4m in 5)
- PD = 2
- med PFS = 28w

Q. how does this compare with weekly paclitaxel alone?
combination is feasible with toxicity not significantly different from weekly paclitaxel alone

efficacy in small numbers encouraging; a randomised trial in relapsed patients is clearly warranted

can a predictive biomarker be identified to aid patient selection?
development in targeted therapy for ovarian cancer

final word:

– real progress on 2 fronts:

1) established role for anti-VEGF therapeutics, particularly in context of maintenance treatment.

2) emerging identification of new molecular targets specific for (5) subtypes, leading to improved patient selection, potentially for combination approaches.