Angiogenesis in Ovarian Cancer

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1. Epithelial Ovarian Cancer: epidemiology
2. Angiogenesis-normal tissues vs cancer
3. Angiogenic pathways important in ovarian cancer
4. Novel agents targeting angiogenesis in ovarian cancer
Epithelial Ovarian Cancer (EOC) Incidence and Mortality (UK)

- **Incidence in UK**
  - 6,719 cases in 2007
  - 5th commonest cancer
  - Second most common gynecologic cancer
  - 1.5% lifetime risk of getting ovarian cancer

- Despite front line surgery and chemotherapy:
  - 70 - 80% women relapse <3 years
  - Majority are retreated with platinum

- Median survival after 1st relapse is 30 months

- Modest improvements over the past 15 years - new treatment paradigms required to improve survival

1 Cancer Research UK
Angiogenesis

- Angiogenesis refers to the process of the formation of new vessels,
- Complex and involves a large number of cytokines and associated receptors.
- Normal tissues in adult life:
  - occurs sporadically e.g. during the menstrual cycle and in wound healing
- Tumours: angiogenesis constitutively active
- Angiogenesis essential process for oncogenesis, tumour growth and progression
Angiogenesis in Normal Tissues

Angiogenesis in Tumours: abnormal vessel structure and function

Hypoxia and Acidosis Key Features in Tumour Progression and Treatment Resistance

- Genomic instability & unfolded protein response
- Angiogenesis
- Inflammation, fibrosis, & immunosuppression
- Switch to anaerobic metabolism
- Resistance to apoptosis/autophagy
- EMT & metastasis
- Resistance to radiotherapy, chemotherapy and immunotherapy
- Induction of cancer “stem cell” phenotype

EOC: angiogenic pathways

Major molecular pathways involved:

- Vascular Endothelial Growth Factor (VEGF)
- Angiopoietin pathway and Tie2 Receptor
- Platelet Derived Growth Factor (PDGF)
- Fibroblast Growth Factor (FGF)

- Activation of intracellular pathways such as JAK and STAT, PI3 kinase and MAP kinase pathways are all key components of angiogenesis
Angiogenesis: targeting the angiogenesis pathways in EOC

Clarke and Hurwitz, J of Gastrointestinal Oncology, 2013
EOC - VEGF pathway:

- VEGF: 3 isoforms: VEGF A, B and C
  - regulates new vessel growth and promotes survival of immature vasculature
  - VEGF signals via surface receptors: VEGFR1, 2, 3
  - VEGFA is main isoform involved in angiogenesis and signals via VEGFR2
  - Activation of intracellular pathways such as JAK and STAT, PI3 kinase and MAP kinase pathways are all key components of angiogenesis
VEGF is dominant pathway in EOC

- VEGF produced by ovarian cancer cells and stimulates ovarian cancer cell proliferation and evasion from apoptosis \(^2\)
- VEGF increases permeability of tumor vasculature- induces formation of malignant ascites \(^1\)
- Tumour selectivity-expression of VEGF and VEGFR is higher in ovarian cancer than in normal ovarian tissue \(^2,3\)

- VEGF ligand overexpressed in ovarian tumors \(^4\)
  - Correlates with ascites formation
  - Poor prognosis
  - Reduced survival

VEGF-A, C and D: over expressed in 40% of ovarian cancers

C: primary ovarian cancer
M: metastasis
Clinical trials-VEGF Associated with poor survival

Anti-angiogenic Agents Targeting the VEGF Pathway

(Aflibercept) Bevacizumab

Bevacizumab
EOC Novel Agents: Bevacizumab/Avastin

- **Anti-VEGF monoclonal antibody**
  - targets formation of new blood vessels within cancers
  - Binds to VEGF-A extracellularly and prevents its interaction with VEGFR2 receptor, thus inhibiting angiogenesis

- 2 Phase 3 trials demonstrate efficacy: ICON7 and GOG218

- **EMA license 2012**: bevacizumab in combination with carboplatin and taxol in newly diagnosed ovarian cancer
EOC Trials First line: bevacizumab and chemotherapy increases PFS

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen(s)</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>GOG218¹</td>
<td>(A) Carboplatin/paclitaxel</td>
<td>10.3 mos</td>
<td>39.3 mos</td>
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<td>(B) Carboplatin/paclitaxel/bevacizumab</td>
<td>11.2 mos</td>
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<td>(C) Carboplatin/paclitaxel/bevacizumab + bevacizumab maintenance</td>
<td>14.1 mos <em>(p&lt;0.001)</em></td>
<td>39.7 mos</td>
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<tr>
<td>ICON7²</td>
<td>(A) Carboplatin/paclitaxel</td>
<td>20.3 mos</td>
<td>44.6 mos</td>
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<td>(B) Carboplatin/paclitaxel/bevacizumab + bevacizumab maintenance</td>
<td>21.8 mos <em>(p=0.04)</em></td>
<td>45.5 mos</td>
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Bevacizumab well tolerated.

Main toxicities:
- hypertension,
- proteinuria
- Venous Thromboembolism

No GI perforation
Recurrent EOC: Bevacizumab

- **Oceans Trial**
  - N= 484 patients with Platinum Sensitive Relapse (PSR)
  - First relapse >6 months from primary therapy
  - Carboplatin (AUC4)/ Gemcitabine (1000mg/m²) +/- Bevacizumab (15 mg/kg) followed by maintenance therapy; q 3/52 until progression/toxicity
  - No prior chemotherapy for relapse
  - Cytoreductive surgery for relapse was permitted

1. Aghajanian C et al. JCO 2012;30:2039-2045
Oceans Trial: Kaplan-Meier estimates of progression-free survival (PFS) ¹

1. Aghajanian C et al. JCO 2012;30:2039-2045
OC: recurrent disease anti-angiogenics + chemotherapy increase PFS

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<tr>
<td>OCEANS¹</td>
<td>(A) Carboplatin/gemcitabine (CG) (B) CG/bevacizumab + bevacizumab maintenance</td>
<td>8.4 mos 12.4 mos</td>
<td>35.2 mos 33.3 mos</td>
</tr>
<tr>
<td>GOG213²</td>
<td>(A) Carboplatin/paclitaxel (CP) (B) CP/bevacizumab + bevacizumab maintenance</td>
<td>10.4 mos 13.8 mos (p&lt;0.0001)</td>
<td>37.3 mos 42.2 mos (p=0.056)</td>
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<tr>
<td>AURELIA³</td>
<td>(A) Chemotherapy (paclitaxel, PLD, or topotecan) (B) Chemotherapy + bevacizumab</td>
<td>3.4 mos 6.7 mos (p&lt;0.001)</td>
<td>13.3 mos 16.6 mos</td>
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¹Aghajanian et al., J Clin Oncol 2012; ²Coleman et al., SGO 2015; ³Pujade-Lauraine et al., J Clin Oncol 2014;
Angiogenesis pathway: PDGF

- PDGF may be activated in response to VEGF inhibition resistance
- PDGF has four isoforms A-D via PDGFR
- PDGF secreted by endothelial cells at site of angiogenesis and recruits pericytes to stabilise maturing blood vessels.
- Acts in concert with VEGF in order to promote new vessel formation and stabilize newly synthesized vessels
- Activation via PDGF Receptor (PDGFR)
  - up regulation of angiogenic events.
  - signaling via the PI3K/Akt pathway
EOC angiogenesis pathway: PDGF

- PDGFR is expressed in ovarian carcinomas and in malignant ascites
  - associated with a poorer prognosis in EOC

- Negative trials of PDGF/ Kit inhibitors such as Imatinib

- But positive trials of agents that target both PDGFR and VEGFR such as Cediranib (ICON6) and Nintedanib (AGO-OVAR12)

1. Lassus et al, Br J Ca, 2004;91
2. Coleman et al, Gynae Oncol 2006, 101
3. Matei et al, Cancer 2008, 113
4. Ledermann, Lancet 2016, 387
5. Dubois, JCO 2013, 31
Anti VEGF/PDGF Oral Tyrosine Kinase Inhibitors (TKI)
VEGF/PDGF Receptor Small Molecule Tyrosine Kinase inhibitors

- **Front line:**
  - **Pazopanib** (VEGFR 1-3, PDGFR, c-Kit)
  - Maintenance: AGO OVAR16;
    - n=940; PFS 5.6 months improvement with pazopanib (17.9 mo vs 12.3 mo); No OS benefit. ¹

- **Nintedanib** (VEGFR 1-3, FGFR1-3, PDGFR)
  - Concurrent chemotherapy and maintenance: AGO OVAR12
  - First line/ phase 3 trial/ nintedanib vs placebo;
    - PFS: 17.3 (nintedanib) vs. 16.6 months; HR=0.84;
    - **Low risk patients (optimal debulking): PFS 27.1 (Nintedanib) vs 20 months (Placebo).** ²

¹. Dubois,
². Dubois, JCO 2013
Front Line Treatment EOC: Anti-angiogenics + chemotherapy increases PFS

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<tr>
<td>AGO-OVAR 12(^4,5)</td>
<td>(A) Carboplatin/paclitaxel</td>
<td>17.2 mos</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>(B) Carboplatin/paclitaxel/nintedanib + nintedanib maintenance</td>
<td><strong>16.6 mos (p=0.02)</strong></td>
<td>NR</td>
</tr>
<tr>
<td>AGO-OVAR 16(^6)</td>
<td>(A) Platinum/taxane</td>
<td>17.9 mos</td>
<td>OS HR 1.08</td>
</tr>
<tr>
<td></td>
<td>(B) Platinum/taxane + pazopanib maintenance</td>
<td><strong>12.3 mos (p=0.002)</strong></td>
<td>(p=0.499)</td>
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\(^1\)Burger et al., N Engl J Med 2011; \(^2\)Perren et al., N Engl J Med 2011; \(^3\)Oza et al., Lancet Oncol 2015; \(^4\)du Bois et al., ESGO 2013; \(^5\)Kristensen et al., ASCO 2014; \(^6\)du Bois et al., J Clin Oncol 2014
Recurrent EOC

- **Cediranib:**
  - *In vitro* activity against VEGF1-3, PDGFR, cKit
  - >800-5000 fold selectivity for VEGFR-2
  - Inhibits growth of established xenografts in lung, colorectal, prostate, breast and ovary.
  - **Phase II trials showed activity as a single agent in ovarian cancer**
  - **ICON6 Trial** – phase 3 randomised trial; Cediranib (20 mg) concurrent chemotherapy + maintenance

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1. Wedge et al Cancer Res 2005
2. Matulonis et al 2009
3. Hirte et al 2010
4. Ledermann et al, ESMO 2013
Overall survival

Restricted mean survival time increases by 2.7 months with maintenance treatment (over two years)

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<tr>
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<th>Chemo.</th>
<th>Maint.</th>
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<td>OS events, n (%)</td>
<td>63 (53.3)</td>
<td>75 (45.7)</td>
</tr>
<tr>
<td>Median, months</td>
<td>20.3</td>
<td>26.3</td>
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<tr>
<td>Log-rank test</td>
<td>p=0.042</td>
<td></td>
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<tr>
<td>HR (95% CI)</td>
<td>0.70 (0.51 – 0.99)</td>
<td></td>
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<tr>
<td>Test for non-proportionality</td>
<td>p=0.0042</td>
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<td>Restricted means, months</td>
<td>17.6</td>
<td>20.3</td>
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1 Ledermann et al, ESMO 2013
Randomised Phase II - olaparib v cediranib + olaparib (n=90):
- Relapsed ovarian cancer
- BRCA WT + Mutant
- Cediranib 30 mg/ Olaparib 200mg bd

**Results**
- Median PFS: Ced/Olap 17.7 mo vs Olap 9.0 mo (HR 0.42, 95% CI 0.23-0.76, p=0.005).
- Toxicity: fatigue (27% Ced/Olap vs 7% Olap), diarrhoea (23% vs 0%), and hypertension (39% vs 0%).

**NCI led Phase III study now enrolling**

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Kaplan-Meier curves for progression-free survival in the ITT population

Med PFS: Ced/Olap 17.7 mo vs Olap 9.0 mo
ORR: Ced/Olap 84% vs 56% olap

1 Lui et al, Lancet Oct 2014
OC: targeting the angiogenesis pathway Angiopoietins

- Angiopoietin (Ang) protein: Ang-1 and Ang-2
  - interact with the Tie2 receptor.\(^1\)
- Ang2 +/- other pro-angiogenic factors e.g VEGF enhance new vessel production
- Ang-2 promotes endothelial cell migration \(^2\)
- Blockage of Ang binding to Tie2 receptor leads to decreased sprouting and reduction of the number of tumor vessels. \(^3\)

1. Reiss, Recent Res Can res, 2010,180
2. Petrillo, Exp Opin Investig Drugs, 2012,21
3. Oliner, Cancer Cell 2004, 6
Novel Agents: Trebananib: TRINOVA 1

- Trebananib: TRINOVA 1

  - **TRINOVA 1 trial**: Trebananib +/- weekly taxol
  - **N = 919**: Phase III randomised trial
  - **Relapse < 12 months from prior therapy**
  - **Included platinum resistant patients**

  **Results**:
  - **PFS**: 7.2 months [5.8–7.4] vs 5.4 months
  - [95% CI 4.3–5.5, hazard ratio 0.66, 95% CI 0.57–0.77, p<0.0001]
  - No OS benefit seen: 19.3 months in the Trebananib arm versus 18.3
EOC angiogenesis: FGF pathway

FGF may also play a role in angiogenesis acting alongside other pro-angiogenic factors such as VEGF.¹

- FGF involved in tumor cell proliferation in ovarian cancer ¹
- FGF signaling pathway involves downstream proteins e.g MAPK, PI3K/Akt cascade ²
- FGF pathway may crosstalk with other pathways such as the Notch pathway ³

- Nintedanib also targets FGFR- benefit in low risk patients (optimal debulking): PFS 27.1 (Nintedanib) vs 20 months (Placebo). ⁴

3. Akai, Genes Dev 2005,19
4. Dubois, JCO 2013
Conclusions

- Angiogenesis plays a key role in ovarian tumour growth
- To date the greatest success has been in targeting the VEGF/ PDGF pathway
- Combination anti-angiogenics together with chemotherapy has led to PFS benefit in multiple settings of ovarian cancer
- Increasing interest in anti-angiogenics + novel agents e.g PARP inhibitors/ Immunotherapy
- Molecular profiles of response still required