Platinum therapy resistance is associated with an enrichment of tumour angiogenesis in epithelial ovarian cancer

Nuala McCabe1,*, Aya El Helali1,*, Christopher Steele3, Naomi Dickson1,*, Lara Dura Perez1,*, Christina O’Neill4, Reinhold Medina4, Laura Knight3, Charlie Gourley2, W Glenn McCluggage1,*, Denis P Harkin3, Richard Wilson1,*, Alan W Stitt4, Richard D Kennedy1,*,2,3

1Almac Diagnostics, 19 Seapoint Industrial Estate, Craigorven, UK; 2Department of Pathology, Royal Group of Hospitals Trust, Belfast, UK; 3University of Edinburgh Cancer Research UK Centre, UK; 4Centre for Experimental Medicine, Queen’s University Belfast, Northern Ireland

Abstract

Background

Angiogenesis is a key pathological feature of epithelial ovarian cancer (EOC) and anti-angiogenic agents have dominated the field of drug development in EOC. However, only progression-free survival benefit has been observed from use of anti-angiogenic agents in EOC, with no evidence of overall survival benefit. High grade serous ovarian cancer (HGSOC) is the most prevalent form of EOC and is associated with poor outcomes. Currently, there are no clinically approved predictive biomarkers to identify HGSOC patients that will derive benefit from anti-angiogenic therapy.

Aims

The overall aim of this study was to define a novel stratifying approach for selection of EOC patients most likely to benefit from anti-angiogenic therapy. Study objectives were as follows:

- To investigate the relationship between prior exposure to platinum-based chemotherapy and response to anti-angiogenic agents in EOC
- To determine the dominant angiogenesis signalling axis in platinum resistant EOC
- To determine the robustness of platinum resistance as a stratifier for response to anti-angiogenic agents in EOC

1. Platinum Therapy Resistance is Associated with Response to Anti-Angiogenic Agents in Clinical Trials

Table 1. Review of phase III/II clinical trials to determine the effect of anti-angiogenic agents in the management of advanced ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-Angiogenic Agent</th>
<th>Phase</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td><strong>Bevacizumab</strong></td>
<td>III</td>
<td>20%</td>
</tr>
<tr>
<td>Study 2</td>
<td><strong>Cediranib</strong></td>
<td>II</td>
<td>15%</td>
</tr>
</tbody>
</table>

2. Platinum Therapy Selects for an Anti-Angiogenic Phenotype in HGSOC

Table 2. PFS and OS benefit from anti-angiogenic agents in EOC relative to platinum sensitivity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>0.70</td>
<td>0.76</td>
</tr>
<tr>
<td>Cediranib</td>
<td>0.71</td>
<td>0.76</td>
</tr>
</tbody>
</table>

3. PDGFRα is associated with activating the angiogenesis signalling pathway in platinum resistant HGSOC

Figure 1. Western blot demonstrating increased PDGFRα expression in 3 platinum resistant ascites-derived primary cells relative to the platinum-sensitive primary cells. B. OVCAR3 and OVCAR4 platinum-resistant cell lines have higher basal VEGF-A expression relative to their parental platinum-sensitive cell lines. C. OVCAR3 platinum resistant cell line demonstrate increased microbubble length (μm) when in co-culture with the Endothelial cell forming cells (ECFC). D. In-vivo matrigel plug assay to determine the MVD in the OVCAR3 isogenic cell line in co-culture with EPCs. The OVCAR3 platinum-resistant cell lines have a higher angiogenic potential compared to the EPCs cell line (p=0.014). E. Graph illustrating MVD in the pre and post-chemotherapy paired patient samples. F. In-vivo matrigel plug assay illustrating that bevacizumab has specificity for the OVCAR3 platinum-resistant cell line which is demonstrated by a reduction in MVD (p value: 0.051).

Conclusions

- The clinical and pre-clinical data discussed has potentially significant clinical implications in the management of treatment-relapsed HGSOC.
- Platinum-resistance in relapsed HGSOC is an indicator for response to anti-angiogenic agents.
- The novel identification of chemotherapy-mediated selection for an angiogenic phenotype in EOC, through upregulation of the PDGFRα-VEGF-A signalling pathway.
- Targeted inhibition of PDGFRα using (TKI or siRNA knockdown) reverses platinum therapy resistance in EOC.
- This clinical and pre-clinical data supports the use of anti-angiogenic agents in the first and second line setting in patients with innate and acquired resistance to platinum therapy, respectively.

Acknowledgements:

All this work would not be possible without the dedication of patients and their families who have consented to take part in the primary cell generation study. This work was supported by Invest NI through the European Sustainable Competitiveness Programme 2007-2013, European Regional Development Fund (ERDF), and Almac Diagnostics Research and Development Department. The samples used in this research were received from the Edinburgh Cancer Research Centre. Ethical approval was obtained from the Ethical Local Research Ethics Committee (Ref: 07/0121/15).

Contact: nualamccabe@almacgroup.com