Platinum-based therapy selects for an angiogenic enriched tumour micro-environment in High Grade Serous Ovarian Cancer

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Background

1. Angiogenesis is a key pathological feature of epithelial ovarian cancer (EOC) and anti-angiogenics have dominated the field of drug development in EOC.
2. There are no clinically approved predictive biomarker to preselect the subgroup of high grade serous ovarian cancer (HGSOC) that will derive benefit from anti-angiogenic therapy.
3. Relapse post platinum-based therapy is associated with a beneficial response to anti-angiogenics.
4. In-vitro and in-vivo angiogenesis assays demonstrate that platinum resistant cell lines are sensitive to Cetuximab and Nintedanib.

Methodology

Platinum therapy selects for an angiogenic phenotype in HGSOC and is associated with upregulation of VEGF expression.

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A. Plasminogen activator urokinase (PAU) treated HGSOC cell lines display higher angiogenic potential than their platinum resistant counterparts.

B. OVCAR3 and OVCAR4 HGSOC platinum-resistant cell lines have higher basal VEGFa expression relative to their parental platinum-sensitive counterparts.

C. Platinum therapy selects for an angiogenic phenotype in relapsed HGSOC. Maintenance Cediranib: 0.94 (0.64-1.39) p=0.007074 (0.8225 to 1.057).

D. Platinum resistant/Intermediate-sensitive disease (platinum resistant) platinum-based chemotherapy select for an angiogenic enriched tumour micro-environment.

E. Maintenance Cediranib: 0.96 (0.8633 to 1.057) p=0.004868 (0.8633 to 1.057).

Conclusions

1. The clinical and pre-clinical data discussed has potentially significant clinical implications in the management of treatment-relapsed HGSOC.
2. Platinum-resistance (innate and acquired) in relapsed HGSOC is an indicator for response to anti-angiogenics.
3. We have found that relapse post platinum-therapy in HGSOC is associated with an angiogenic biology.
4. 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.