The British Association of Gynaecological Pathologists Research Bursary Application 2021

Title

Correlation of inflammatory response, PD-L1 expression and microsatellite instability with five-year survival data in endometriosis-associated ovarian cancer (EAOC) patients.

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Background

Endometrioid and clear cell carcinomas of the ovary each account for around 10% of ovarian carcinomas and both are associated with the presence of ovarian endometriosis.[1] There is limited evidence in the medical literature regarding the prognostic relevance of tumour infiltrating lymphocytes in EAOCs. Some studies indicate that molecular classification of endometrioid ovarian carcinoma can help delineate a subgroup of patients who may benefit from immune checkpoint inhibitor therapy, irrespective of tumour PD-L1 status, as is the case with endometrioid carcinomas arising in the uterine corpus.[2] Microsatellite instability (MSI) is associated increased expression of PD-L1 in ovarian clear cell carcinomas suggesting that check point inhibitor therapy may be an effective management option in these patients also.[3] PD-L1 expression correlates with extent of tumour infiltrating lymphocytes in high-grade serous carcinoma and confers an improved prognosis in this group.[4] However, this effect has not been clearly seen in studies of EAOC.[4] Furthermore, it has been shown that the presence of tertiary lymphoid structures (TLS) in histopathological sections of carcinomas of the gastrointestinal tract, breast and lung tend to have a favourable prognostic outcome. This is also true in studies of metastatic high-grade serous carcinoma but is yet to be demonstrated in EAOC.[5]

The aim of this project is to correlate carcinoma-associated immune response, including presence or absence of TLS, level of PD-L1 expression and MSI status in tissue sections of EAOC and correlate with five-year survival data. We intend to determine the prognostic significance of these histopathological biomarkers for improved patient information and management.

Null hypothesis: There is no difference in five-year survival outcome in EAOCs relative to the degree of lymphocytic response as characterised by the extent of tumour immune response (TIL) and presence of TLS.

Methods

This is a retrospective observational cohort study. The histological features (listed in bold) of 44 cases of endometrioid and 30 clear cell ovarian carcinomas will be compared with age-matched controls of endometriosis recorded in our surgical database which commenced in 2015. The composition of the **inflammatory response** will be assessed with a differential cell count of inflammatory cells types based on morphology in addition to immunohistochemistry for subset description of lymphocytes (CD4 for helper T cells, CD8 for cytotoxic T cells, CD20 for mature B lymphocytes, CD56 and CD57 for immature and mature natural killer T cells). The presence of tertiary lymphoid structures will be noted with aid of CD21 immunohistochemistry to detect a follicular dendritic network. **Architectural**

features of the malignant invasive front (pushing versus infiltrative), architectural patterns solid verus gland forming (<5%/ 5-50%/>50% solid component), percentage papillary component and any other pattern of note will be recorded alongside **lymphovascular space invasion** (not present, less than 3 foci, or more than 3 foci). **Characteristics of peri-tumoural stroma**, where present, will be categorised as desmoplastic, myxoid, hyaline, or normal ovarian stroma. Degree of **PD-L1 expression,** using the Roche SP263 clone, will be scored by both combined proportion and tumour proportion methods. **MSI status** will be defined by rapid, automated PCR analysis using the Idylla™ system. Univariate analysis of these parameters will be performed and Kaplan-Meier curves created based on five-year follow up data to ascertain their significance for patient outcome. NHS Research Ethics Committee approvals are given for this research in relation to use of human tissue archives for identification of biomarkers in ovarian cancer (Reference 15/WA/0065).

Expected Results and Potential Impact

We expect to contradict the null hypothesis and show that high levels of tissue immune response and presence of TLSs improve patient outcomes. This study aims to corroborate the limited evidence in the literature and brings all components of the tumour immune response, with checkpoint inhibitor and MSI status together in one study of both EAOC types. Previously unreported information will be generated about the relevance of tertiary lymphoid structures in this particular group of carcinomas. The findings will help support future research applications which will explore the tumour microenvironment of these tumours at a molecular level using spatial transcriptomics. Furthermore, our findings will support development of therapeutic clinical trials for checkpoint inhibitor treatment in this subset of ovarian carcinomas with the survival benefits this could bring to our patients. Success of this application will go towards immunohistochemistry costs. Biocartis have agreed to fund MSI analysis cartridges for the Idylla™ platform.

References

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