British Association of Gynaecological Pathologists Grant Application (BAGP)

Project title: L1CAM expression in endometrioid ovarian carcinoma

1. Researchers

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2. Background

The Cancer Genome Atlas identified four genomic groups of endometrial carcinoma that correlate with clinical outcome.[1] It also divides endometrial carcinoma into biologically distinct groups. This research identified a novel group of tumours with mutations in the polymerase epsilon exonuclease (POLE) domain that infers an excellent prognosis.

Two groups with intermediate prognosis were defined as 'copy number low' and 'microsatellite unstable', respectively, while a subset of tumours, defined by a 'copy number high' status, experienced poor prognosis. Talhouk et al further validated these findings and proposed a molecular-algorithm based on relatively cost-effective surrogate tests akin to those performed in the TCGA analysis.[2]

Testing for p53, mismatch repair proteins (MMR), and polymerase ε (POLE) exonuclease domain mutations was able to correlate findings with clinical outcome and was found to improve patient stratification when used in combination with current clinic-pathological risk factors. The proposed classification has since then provided important insight into the biology of this prevalent gynaecological disease and provided a tool to better assess the prognosis and therapeutic options for endometrial cancer patients.

The morphologic and biologic similarities between ovarian and endometrial endometrioid carcinomas suggest similarities in their genomic makeup. P53, MMR, and POLE have been described individually in ovarian endometrioid carcinoma, yet this molecular classification algorithm has only once recently been applied to ovarian endometrioid carcinomas and the role of these markers in predicting the molecular profile and thus the prognosis has still not been fully explored and replicated. Parra-Herran et al discovered that the molecular algorithm can be applied to ovarian endometrioid carcinomas and these molecular aberrations may be associated with patient prognosis, akin to endometrial cancer.[3] Moreover, this tool for molecular classification has not been used in the UK.

The work at our centre to date has been to standardise this algorithm on a limited number of ovarian endometrioid carcinoma specimens and identify the frequency of each molecular aberration. Of the 35 cases identified by the inclusion criteria, 1/35 (2.6%) showed *POLE* exon 9 mutation, 3/35 (8.6%) showed abnormal p53 expression and 5/35 (14.3%) had abnormal MMR protein expression on immunohistochemistry. The remaining 26 (74.3%) had no specific molecular risk profile.

As a considerable number of this cohort was not classifiable, it is imperative to be able to subdivide this group according to molecular profile.

L1 cell adhesion molecule (L1CAM) has repeatedly shown to be associated with aggressive disease behaviour. In vitro, L1CAM enhances proliferation, cell migration adhesion and chemo-resistance.[4] A significant number of publications in endometrial endometrioid carcinoma have shown that L1CAM further stratifies patients with no specific molecular risk profile. It has been shown to be a significant predictor of worse outcome in this group and a significant prognosticator for disease-specific survival after multivariate analysis.[5] Of the few publications that investigate L1CAM prognostic impact in ovarian endometrioid carcinoma, similar outcomes have been concluded.[6]

To date, no research has aimed to combine the molecular algorithm with L1CAM status in this subgroup of ovarian carcinomas.

These conclusions suggest L1CAM could serve as a biomarker for predicting outcome and response to chemotherapy in a clinical setting.

3. Aims

- To investigate the molecular subtypes* of endometrioid ovarian carcinomas (*as defined by the Cancer Genome Atlas for endometrial carcinoma)
- Investigate L1CAM immunohistochemistry in the same case series for which MMR/p53/POLE is available, with the aim of subdividing cases without molecular profile into prognostic groups
- To standardise the techniques used in molecular subtyping of endometrial carcinoma with a view to assess the cost and logistical implications for use in routine clinical diagnostic practice

4. Methods and materials

This study will be a retrospective analysis of ovarian endometrioid cases surgically treated at our centre from 2006 to date. The study has obtained ethical approval and appropriate consent has been sought for tissue analysis.

The molecular classification algorithm proposed by Talhouk et al has been used in the assessment of ovarian endometrioid tumours. Mismatch repair and p53 mutation status will be investigated using immunohistochemical staining on whole slides on formalin-fixed paraffin-embedded tumour samples stored at our centre. POLE mutational analysis has been investigated using Sanger sequencing technologies.

L1CAM immunohistochemistry will be performed on whole slides cut from formalin-fixed paraffin embedded tissue.

Once cases have been classified according to their molecular subgroup, clinico-pathological information and follow-up data including time to recurrence, last date of follow up status at follow up and mortality will be obtained from patient electronic records. Information will be used to estimate the prognostic value of the molecular classifier and correlate the clinic-pathological characteristics to molecular subgroups.

5. Intended outcomes:

a. Apply the molecular classifier algorithm to ovarian endometrioid carcinomas.

b. Assess the extent to which the molecular categories found in endometrial endometrioid carcinomas apply to ovarian endometrioid carcinomas.

c. Investigate L1CAM immunohistochemistry in the same case series for which MMR/p53/POLE is available, with the aim of subdividing cases without molecular profile into prognostic groups

d. Standardise all new techniques in the molecular pathology laboratory at the Royal London Hospital for future use as a screening method molecular classification of endometrial carcinoma.

e. Correlate the molecular subgroups with stage and outcome

6. Expected expenditure and costs

This funding will able us to perform immunohistochemistry analysis for L1CAM on all cases from our centre. It will also support our aim to contribute cases to a large international collaboration. Additionally, it will help us present this data series at appropriate meetings.

References

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