Predicting immunotherapy outcomes in endometrial cancer using multi-omic cell-free dna analysis

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Abstract

Immunotherapy improves outcomes for patients with advanced endometrial cancer (aEC) however, not all patients respond equally to treatment. Circulating tumour DNA (ctDNA) offers a minimally invasive biomarker approach for real-time tumour profiling to guide treatment decisions. We aimed to identify actionable biomarkers to predict and monitor immunotherapy response in aEC through multi-omic ctDNA analysis.

Methods: Longitudinal plasma samples (n=134) were analysed from individuals with deficient mismatch repair (dMMR) (n=32) and proficient MMR (pMMR) (n=32) aEC in the PHAEDRA clinical trial who received single agent durvalumab (anti PD-L1) therapy. We used ctTSO500 for comprehensive serial ctDNA mutational profiling and bioModal duet +modC sequencing to capture genome-wide methylation and genomic alterations. In parallel, we developed a rapid and robust ctDNA test combining a methylation-sensitive restriction digest and ddPCR for sensitive detection of MLH1 promoter methylation (mMLH1).

Results: Multi-omic ctDNA analysis was able to accurately identify aEC subtypes linked to key differences in clinical outcomes. In particular, dMMR patients showed a differential response to treatment, with individuals harbouring hereditary or sporadic MMR mutations showing the highest clinical response rates (100%) compared to patients with mMHL1 (37.5%) according to ctDNA analysis. Somatic driver mutations were detected in most dMMR patients (86.7%) with mutations in ARID1A, PTEN and TP53 being the most common. While JAK1 mutations were more prevalent in non-responders suggesting a role in immune evasion, oncogenic drivers alone did not predict response ($p=0.056$). Increased ctDNA levels at baseline was significantly associated with shorter progression-free and overall survival ($p<0.05$) whilst ctDNA dynamics following two immunotherapy cycles accurately predicted long term treatment outcomes. Our mMLH1 ctDNA assay accurately detected MLH1 promoter hypermethylation in all patients where the ctDNA fraction was >2% by ichorCNA copy number analysis. Moreover, our assay detected mMLH1 in two dMMR participants where tissue testing was uninformative and two pMMR patients thought to have acquired methylation following previous chemotherapy, highlighting the importance of a serial testing approach. Global methylation profiling is ongoing to identify differentially methylated regions (DMRs) associated with immunotherapy outcomes.

Conclusion: These results demonstrate the potential of multi-omic ctDNA analysis in aEC, combining genomic and epigenomic profiling to guide immunotherapy treatment.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.