Investigating Homologous Recombination Deficiency in mCRPC through ctDNA

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Background & objectives

Homologous Recombination Deficiency (HRD) refers to the impairment of accurate repair of double-strand breaks. This condition can be targeted with poly ADP ribose polymerase inhibitors (PARPi), through synthetic lethality. We investigate this condition in the context of metastatic castration-resistant prostate cancer (mCRPC), using circulating tumour DNA (ctDNA) as a tumour surrogate.

Methods

To ensure we acquire informative results, we investigated the tumour fraction in blood samples of mCRPC patients from our biobank (n = 366), using aneuploidy as a tumour fraction surrogate. Patients that exhibited an elevated tumour fraction were selected for further analysis. A custom gene panel was designed, which enriched genes involved in the pathway. After establishing the accuracy of our assay using synthetic oligonucleotides (sensitivity 0.5%VAF), we performed targeted sequencing on 147 samples from 131 patients. Longitudinal urine samples from 2 patients (n = 9) were used, to examine whether the alterations could be detected in this analyte as well.

Results

We identified 86 patients that had an elevated tumour fraction. Additional patients were selected using the ichorCNA algorithm. Of the 131 mCRPC patients sequenced, 33 (24.81%) harboured a non-benign alteration in a classical HR gene, excluding tumour suppressor genes. Frequently altered genes included *BRCA2 (14.5%), ATM (13.0%), BRCA1 (9.38%) and CHEK2 (8.33%)*. At least one tumour suppressor gene was altered in 58 patients (43.6%). There were 42 (31.57%) patients that had no alterations detected in cfDNA. The urine samples were concordant with the plasma samples, exhibiting a lower VAF.

Conclusion

Our data indicate that the presence of tumour-derived nucleic acids in plasma and urine can provide information about the HRD status of the tumour inCRPC patients. Therefore, ctDNA and ucfDNA possibly hold promise in the clinical management of prostate cancer, in the context of HRD and PARPi treatment.