

In-depth assessment of metastatic castration-resistant prostate cancer with a high tumour mutational burden

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Background

A comprehensive assessment of biopsies from patients with metastatic castration-resistant prostate cancer (mCRPC) may identify a molecular subset of patients susceptible for immune checkpoint blockade.

Methods

197 biopsies and germline DNA from patients with mCRPC were whole genome sequenced (WGS) at an average of 114x and 38x. Tumour mutational burden (TMB) was defined as number of somatic single nucleotide variants and InDels per Mb of the genome, known mutational signatures (Alexandrov, Nature 2013) extracted by non-negative least squares regression as well as recurrent mutations reported in mismatch repair (MMR) patients (Kim, Cell 2013). Selected patients with high TMB, CDK12 biallelic inactivation or severe chromothripsis were further evaluated for; (a) MMR protein expression; (b) multiplex intratumoural immune cell phenotyping (VECTRA) with focus on CD3, CD8 (total and cytotoxic), regulatory T-cells and memory T-cells; (c) multiplex IC expression (VECTRA); (d) 8-color flow cytometry blood immune cell phenotyping, with high TMB patients compared with low TMB patients. Selected patients receiving anti-PD-1 therapy had additional immune phenotyping at C2, C3, C4 and at progression.

Results

The median TMB of the entire cohort was 2.9 (IQR 2.2 - 3.9). 14 patients (6.6%) had high TMB (>10 mutations/Mb) with a median TMB of 35. In 13/14 patients with high TMB, corresponding MMR deficiency (MMRd) signatures (6, 15, 20 and 21) were identified. Recurrent mutations in MMR genes were detected MSH2/MSH6, MSH3, MLH1; other recurrent mutations were in POLE, and in genes including JAK1, TTK, ZFHX3, ZFP36L2, ASXL1, and KMT2C. 23 patients had a BRCA2 inactivating aberration and/or corresponding BRCAness signature, with a median mutational burden of 5 mutations/Mb. 13 patients had a biallelic inactivation of CDK12, a corresponding signature comprising focal tandem duplications (Wu, Cell 2018), and a median mutational load of 2 mutations/Mb. Selecting for MSI/MMRd, and/or BRCAness and/or CDK12 biallelic inactivation, 49/198 (24.9%)

patients with mCRPC were identified. Immunohistochemistry confirmed MMRd and in matched primary tissue of evaluable patients. Five patients were referred for germline testing without MMR mutations. A trend for increased IT CD3+ cells were seen in MMRd ($p=0.06$); no relation was found between TMB and tumour PD-L1 expression. Patients were treated with anti-PD-1 therapy, with PSA>50% decline of 57% of hTMB patients ($n=7$), and a significant decline in circulating T-cell populations during immune checkpoint blockade, including CD4+PD-1+ ($p=0.02$) and CD8+PD-1+ ($p=0.007$).

Conclusions

25% of patients with mCRPC display a putative immunogenic signature, with either MSI/MMRd, BRCAness and CDK12 inactivation. 7.1% of patients harbor a high TMB with recurrent somatic mutations in MMR genes and/or POLE, as well in other novel genes associated with high mutational load prostate cancer.

Clinical trial identification

NCT01855477

Funding

This publication and the underlying study have been made possible partly on the basis of the data that Hartwig Medical Foundation and the Center of Personalised Cancer Treatment (CPCT) have made available to the study.

Conflict of Interest

There are no relevant conflicts to report