Identifying mismatch repair-deficient prostate cancer for immune checkpoint therapy

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Background:
Immune checkpoint blockade has shown clinical benefit in mismatch repair deficient (dMMR) cancers, leading to accelerated FDA approval of pembrolizumab, a PD1-targeting agent, for the treatment of dMMR solid tumors. While the frequency of MMR deficiency is well defined in colorectal, uterine and other Lynch-spectrum cancers, there is limited data on dMMR prevalence in prostate cancer, response of dMMR prostate cancer to immune checkpoint blockade, and screening strategies for the identification of these tumors. We previously showed that genomic alterations in MMR genes occur in 2-3% of prostate tumors, and are frequently associated with higher mutation burden (Abida et al, JCO Precision Oncology 2017). Using computational and immunohistochemical analysis, we report the frequency of dMMR in a large prostate cancer genomic dataset, and initial response to immunotherapy in a subset of patients with dMMR tumors.

Methods:
Prostate cancer patients enrolled on an IRB-approved protocol for tumor genomic profiling. Newly acquired or archived fixed tumors and matched normal samples underwent targeted DNA sequencing using a clinical assay for analysis of somatic mutations and copy number alterations. Immunohistochemical staining was performed for MMR proteins MSH2, MSH6, MLH1 and PMS2. Mutational signature analysis was performed according to Alexandrov et al, Nature 2013. MSIsensor score was determined according to Niu et al, Bioinformatics 2014.

Results:
We sequenced 972 tumors from 839 patients with prostate cancer. 26 patients (3.1%) had a tumor with a genomic alteration in an MMR gene. 24 patients (2.9%) had a high mutation burden (≥ 10 mutations per megabase). 27 patients (3.2%) had an MSI sensor score of ≥ 5. In total 22 patients (2.6%) had 2 of the 3 above characteristics, which we define as dMMR. The majority of dMMR tumors harbored a high contribution from MMR mutational signatures and loss of an MMR protein by immunohistochemistry. A single case with 32 mutations per megabase had an MSI sensor score of 0, a PolE somatic mutation with concomitant high contribution from PolE signature. Of the 6 dMMR patients who had matched tumors from various time points available, 4 had acquired MMR deficiency in the later tumor. Of the 22 patients with dMMR tumors, 6 have received PD1/PDL1 blockade to date, including 1 patient with a RECIST complete response and another with a partial response.

Conclusions:
dMMR is identified through panel sequencing in 2-3% of patients with prostate cancer. With the FDA approval of pembrolizumab in dMMR deficient solid tumors, these patients are now candidates for standard immune checkpoint blockade, and may be identified through tumor sequencing or IHC for MMR proteins depending on institutional preference. It is not yet clear what proportion of patients with dMMR prostate tumors will benefit from immune checkpoint blockade.

Conflict of Interest: None

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