DNA Mismatch Repair Protein Deficiency (MMRD) and Programmed Cell Death Ligand-1 (PD-L1) Expression in Metastatic and High-Risk Localized Prostate Cancer

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Background: Tumor PD-L1 expression correlates with response to PD-L1/PD-1 blockade therapy in general. Positivity is seen in approximately 14% of primary prostate cancer (PCa) in our recent study (1). PD-L1 expression was associated with clinicopathologic characteristics found in aggressive PCa. It is unknown if metastatic prostatic cancer shows similar PD-L1 expression levels. In this study, we use immunohistochemistry (IHC) to assess tumor PD-L1 expression and DNA mismatch repair protein deficiency (MMRD) in metastatic prostate cancer (mPCa) and high-risk localized prostate cancer (HLPCa).

Methods: A series of forty one cases of mPCa and fifty cases of HLPCa were retrospectively collected at our institution (from 1999 to 2017), with clinicopathologic parameters annotated. The most representative FFPE block containing the largest dimension and highest Gleason grade of tumor (in HLPCa) was selected and subjected to IHC to examine the expression of PD-L1, MMR proteins (MSH2, MLH1, MSH6, and PMS2), ERG, and PTEN. PD-L1 positivity was defined by membranous staining in ≥ 1% of tumor cells and scored semiquantitatively as 1-4%, 5-24%, 25-49%, and ≥ 50%. PTEN loss was defined as negative staining in ≥5% tumor cells. ERG was graded as presence or absence of staining. MMR proteins were scored as complete loss or retained expression.

Results: There was no significant difference in racial composition or IHC expression of PTEN and MMR proteins or PD-L1 positivity between the mPCa and HLPCa cohorts. 17% of mPCa and 26% of HLPCa express PD-L1 in ≥1% of tumor cells. PD-L1 expression was enriched in non-osseous metastasis (24%) in comparison to osseous metastasis (6%) (p = 0.215). A total of 3 MMRD cases were found in both cohorts, including 2 in mPCa, 1 in HLPCa, respectively. All three MMRD cases were ERG-negative, with MSH2&MSH6 losses in two cases and PMS2 loss in the third case. 1 of 3 MMRD cases were PD-L1-positive. MMRD was not significantly associated with PD-L1 positivity.

Conclusions: MMRD is rare in high-risk and metastatic PCa, and is not significantly associated with PD-L1 expression. Approximately 20% of high-risk and metastatic PCa shows PD-L1 positivity in ≥1% of tumor cells. Metastatic PCa in bony locations are rarely positive for PD-L1, indicating a potential resistance to PD-1/PD-L1 treatment in this disease group.

Future Directions: An expanded study is ongoing to validate these preliminary findings. Importantly, our findings provide the rationale for a forthcoming clinical trial of Nivolumab in patients with high-risk biochemically recurrent PCa. Proposed correlative studies will include correlation of clinical responses with tumor PD-L1 expression, subtypes of tumor-infiltrating T cells, tumor genomic alterations, soluble biomarkers in peripheral blood samples, and T-cell recognition of tumor neoantigens.