RISK EVALUATION OF IMMUNE CHECKPOINT INHIBITOR DIABETES THROUGH ISLET AUTOANTIBODIES & HLA TYPES IN A LARGE, REAL-WORLD COHORT

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Background From 2019–2022, we prospectively enrolled 1200 pan-cancer patients treated with immune checkpoint inhibitors (CPI) and identified three CPI-diabetes mellitus (DM) cases as part of the Radiohead study.1 Baseline and on-treatment blood samples were collected. From this longitudinal cohort, we evaluated whether islet autoantibodies and HLA typing could be used to predict a patient’s risk of developing CPI-DM.

Methods For islet autoantibody analysis, serum for 829 patients with both a baseline and early on-treatment sample were tested for GAD, IA-A, mIAA and ZnTA-8 autoantibodies using a radiobinding assay. HLA types were imputed from SNP genotypes generated using an Illumina GSAv3 array, using HIBAG2 and population-specific reference panels for 1029 patients. Fisher exact was used for autoantibodies and high-risk type 1 DM HLA types (DR3, DR4, DQ8, DQ2) associations. Logistic regression was used for combined HLA type and autoantibody risk prediction.

Results Of the 829-patient autoantibody subset, GAD was the most common autoantibody at 5.31%, followed by insulin at 3.74%. Two of the three (66%) CPI-DM patients had positive GAD, one prior to CPI initiation and the other emerging on treatment. For every 35 patients with pre-treatment GAD positivity, one would be projected to develop CPI-DM; this increases to one in 19 patients if GAD positive is determined at either pre or early on treatment. The presence of GAD at baseline and/or early on treatment but not the other autoantibodies was associated with CPI-DM development (relative risk 34.84, p=0.004).

All three CPI-DM subjects were carriers of known HLA risk genotypes for T1DM, compared to 50% of patients in the remaining cohort of 1026 patients. The DR4-DQ8 risk haplotype was present in 2 out of 3 CPI-DM patients (66%), in contrast to 18% in the rest of the cohort. There was insufficient statistical power for association testing, due to the low number of cases.

In the 769-patient combined cohort, for which both HLA type and autoantibody status was determined, presence of GAD at baseline (odds ratio 21.8, p=0.01) was predictive of CPI-DM development after adjustment for HLA DR4-DQ8; results were similar with adjustment for other individual T1DM high risk HLA types.

Conclusions Pre-treatment and/or early on treatment analysis of T1DM autoantibodies and HLA types have the potential to predict development of CPI-DM and might be a critical first step in risk stratification for this rare immune-related adverse event. Given the very small number of cases, these findings must be further validated in high-risk cohorts.

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