**Conventional and novel biomarkers predict checkpoint inhibitor associated autoimmune diabetes**

Introduction

Checkpoint inhibitor-associated autoimmune diabetes (CIADM) occurs in 0.5-1% of checkpoint inhibitor-treated patients. It is a life-altering complication which necessitates life-long insulin treatment. Biomarkers that predict type 1 diabetes (T1D) are not reliable for CIADM prediction, with most people having no detected auto-antibodies, and no high-risk HLA haplotypes. Some patients have protective alleles. As ICI indications expand, ability to predict CIADM is of increasing importance.

Aim

To identify biomarkers for prediction of CIADM.

Methods

From our prospective biobank, 14 CIADM patients who had metastatic melanoma treated with anti-PD-1±anti CTLA4 were identified. Controls were selected from the same biobank, matched 2:1 including for presence of other immune complications. Pre-treatment, on-ICI and post-CIADM serum and peripheral blood mononuclear cells (PBMCs) were analysed. Serum was analysed for T1D autoantibodies, C-peptide, glucose and cytokines. PBMCs were profiled using flow cytometry. Pancreatic volume was measured using CT volumetry.

Results

Pre-treatment, CIADM patients had smaller pancreatic volume (27% reduction, p=0.044) and higher anti-GAD antibody titres on an agglutination PCR assay (median 2.9 versus 0, p=0.01). They had significantly higher baseline proportions of Th17 helper cells (p=0.03), higher CD4+ central memory cells (p=0.04) and lower naïve CD4+ cells (p=0.01). With ICI treatment, greater declines in pancreatic volume were seen in CIADM patients (p<0.0001). Activated CD4+ subsets increased significantly in CIADM and controls with immune-related adverse effects (IRAE) but not controls without IRAE.

Using only pre-checkpoint inhibitor results, pancreatic volume, anti-GAD antibody titre and baseline immune flow profile were highly predictive of CIADM development, with a ROC area under the curve (AUC) of >0.96, and sensitivity of >90%.

Conclusion

People who develop CIADM are immunologically predisposed and have antecedent pancreatic and immunological changes that accurately predict disease with excellent sensitivity. These biomarkers could be used to guide ICI use, particularly when planning treatment for low-risk tumours.