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OP0126

IS IMMUNE CHECKPOINT INHIBITORS THERAPIES SAFE AND EFFECTIVE FOR PATIENTS WITH CANCER AND PREEXISTING AUTOIMMUNE DISEASE?

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Background: Immune checkpoints inhibitors (ICIs) are associated with frequent immune-related adverse events (irAEs). Most patients with preexisting autoimmune disease (PAD) have been universally excluded from clinical trials and ICIs are not recommended for patients with cancer and PAD due to the unknown safety. In this study, we aim to evaluate the safety and efficacy of ICIs in patients with PAD and cancer.

Objectives: Systematic searches were performed of PubMed, EMBASE, and the Cochrane library from inception through September 2019 for observational studies reporting safety and efficacy data among ICIs-treated patients with cancer and PAD. A random effects meta-analysis was performed to calculate pooled incidence rates of PAD flare, irAEs and response.

Methods: Systematical search of PubMed, EMBASE and Cochrane Library plus a hand search of conference proceedings were performed for observational studies that reported cancer incidence in patients with RA treated with biologics or tofacitinib with active comparator of conventional DMARDs (csDMARDs) or TNFi. The pooled relative risk (RR) and 95% confidence interval (CI) were calculated with fix-effects or random-effects model.

Results: A total of 619 ICI-treated patients with PAD in 14 publications were finally identified. In the random effects meta-analysis, pooled incidence of PAD flares, *de novo* irAEs or both of any grade was 60% (95% CI 52%-68%). Viewed separately, there were 219 and 206 patients experiencing PAD exacerbation and *de novo* irAEs of any grade, yielding a pooled incidence of 35% (95% CI 29%-41%) and 33% (95% CI 24%-42%) respectively. Of these, most of flare and *de novo* irAEs were graded as mild (grade 1-2) (pooled proportion: 82%, 95%CI 72%-91%; 65%, 95%CI 54%-76%, respectively). Rheumatoid arthritis was associated with a trend toward higher flare occurrence compared with another individual PADs (RR=1.25-1.88). With respect to efficacy, 136 patients showed complete or partial response, corresponding to a pooled response rates of 30% (95% CI 22%-39%). There were no statistical differences between patients with and without immunosuppressive therapy at ICI start regarding flare (RR: 1.08, 95% CI 0.72-1.62), but a trend towards lower response rates was observed in patients with baseline immunosuppressants (RR: 0.58, 95% CI 0.26-1.33).

Conclusion: Immune toxicities are frequent in ICI-treated patients with PAD but often mild and manageable without discontinuing therapy. Rheumatoid arthritis is associated with a trend toward more flares. ICI treatment are effective and not absolute contraindication in PAD patients, but close monitoring and multidisciplinary collaboration should be contemplated, especially for those concomitantly receiving immunosuppressant or having rheumatoid arthritis.

References:

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Figure 1. Pooled effect estimates in ICI-treated patient with PAD (A) PAD flare, *de novo* irAEs or both; (B) PAD flare; (C) *de novo* irAEs. ICI: Immune checkpoint inhibitors; PAD: Preexisting autoimmune disease; irAEs: Immune-related adverse events.

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Immunity in rheumatic disease

OP0127

TRANSCRIPTIONAL ACTIVITY OF SURVIVIN CONTRIBUTES TO MATURATION AND FUNCTION OF THE INTERFERON-GAMMA PRODUCING T CELLS IN RHEUMATOID ARTHRITIS

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Background: Interferon gamma (IFN γ) signalling and downstream effects make important contribution in pathogenesis of rheumatoid arthritis (RA). Here, we propose a mechanism by which oncoprotein survivin participates in development of IFN-dependent repertoire of T cells in RA patients.

Objectives: We study the role of survivin in the phenotype of CD4 T cells of RA patients.

Methods: CD4 cells of RA patients and healthy controls were purified from blood, activated and subjected to RNAseq, ChIPseq with antibodies to survivin (BIRC5) was performed on CD4+ cells. Histone H3 ChIPseq was performed using antibodies to H3K27ac, H3K27me3 and H3K4me3. Statistical analysis was performed in R-studio using the Bioconductor package DESeq2, clustering using Spearman and Ward.D2.

Results: Unsupervised clustering of CD4 samples by expression of 48 core Th cell markers identified subsets of CD28^{hi}CD27^{hi}IFN γ central memory cells (Tcm), CD28^{lo}CD27^{lo}IFN γ effector memory cells (Tem) and CD28^{null}CD27^{null}IFN γ terminal effector cells (Tte). Tte cells showed classical features of Th1 cells including high levels of TBX21, TNF α and IL32 and signs of activation in IFN signalling machinery. Interestingly, they combined the features of peripheral Tregs CD25^{hi}Foxp3^{hi}IKZF2^{neg} and IL10 producing cells together with type 1 regulatory cells, which rely on transcription factors BATF and IRF1 for the differentiation and produced high amounts of perforin and granzyme B. Importantly, Tte CD4 cells had also high transcription of BIRC5 (p=1.15e-18).

To study if BIRC5 is a part of IFN signalling, CD4 cells were cultured with survivin inhibitor YM155 and activated with IFN γ . RNAseq analysis revealed 2033 (FC<2.0, n=336) differentially expressed genes in the IFN stimulated cultures. Interestingly, a substantial number of these IFN-dependent genes was significantly reduced in the survivin-deficient cultures and included among others CD28, FoxP3, IKZF2, ICOS, BATF, PRDM1, CXCR3, IRF4 and IRF8. Analysis of the peak sequences identified enrichment for composite motifs for IRFs (ETS:IRF, p1.0e-124; bZIP:IRF, p=1.0e-640), indicating that survivin is important for IFN γ signalling. Numerically, the peaks containing ETS:IRF motifs were most prevalent and identified in total within 49.7% of all survivin-ChIP peaks. Frequent was co-localisation of the IRF:bZIP and IRF:ETS motifs within the survivin peaks. Among the IRF motifs dominated those suitable for IRF1 (p=1.0e-127) and IRF8 (p=1.0e-84). However, the DNA binding motifs of these two are alike.

Encouraged by the survivin ChIPseq results, we wanted to know its relation to histone marks. We observed that 50% of survivin peaks containing both IRF:bZIP and IRF:ETS motifs are co-localized with the H3K27ac marks. In total, 16 of 48 core Th cell markers used for patients clustering were identified by survivin ChIPseq, co-localized with IRF composite motifs and histone marks. They were also dependent of survivin for expression.