Molecular characterization of immune-related severe adverse events (irSAE).

Background

- Immune checkpoint inhibitors (ICIs) have made a profound impact on the treatment of a variety of cancers.
- However, toxicities can occur that cause significant morbidity and/or mortality.
- Clp can cause unique autoimmune toxicities, resulting in inflammation of numerous organ systems, in some cases fatal.
- The molecular underpinnings of these toxicities have not been extensively explored.

We recently reported a small case series of 2 patients with myocarditis resulting in death arising following treatment with anti-PD-1.

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We hypothesize that molecular analysis of ICI-AI tissues will identify causal factors in the etiology of these toxicities, and how to better predict, prevent, and treat them.

Objectives

1) To characterize the molecular features of ICI-AI, including severe refractory immune-related colitis, myocarditis (MC), and encephalitis following ICi treatment.
2) To determine the similarities and differences in immune components between ICI-Ai and inflammatory bowel disease (IBD).
3) To evaluate TCR profiles in ICI-Ai disease specimens.

Hypotheses

We hypothesize that molecular analysis of ICI-AI tissues will identify causal factors in the etiology of these toxicities, and how to better predict, prevent, and treat them.

Methods

1) To characterize the molecular features of ICI-AI, we collected healthy and afflicted tissue from a series of cancer patients with immune-related diseases.
2) We performed:
   1) Standard immunohistochemistry,
   2) RNA sequencing for >2000 immune-related genes (HTG EdgeSEQ)
   3) TCR sequencing by ImmunoSEQ (Adaptive Biotechnology) to evaluate TCR clonality in diseased specimens.
   4) Digital spatial profiling for 20 immune-related protein biomarkers performed in conjunction with nanoString.

Conclusions

- Many similarities in terms of protein and mRNA expression patterns can be identified across auto-immune and ICI-induced colitis specimens.
- A tendency toward greater T cell infiltration and reduced B cell infiltration was identified in ICI-C specimens.
- Shared T cell clones were detected in all sample types, suggesting the possibility of TCR-mediated autoimmunity and commonalities.
- However, the identity of the target antigen is not known and HLA haplotyping has not yet been performed.
- Continued studies of differentially expressed cell types and gene expression patterns may help better understand the disease process in ICI-C.
- A unique case of fatal encephalitis identified an extremely high degree of clonality (>20% T cells in the inflamed brain), suggesting a unique antigen target.

Acknowledgements

We would like to thank nanoString, HTG, and Adaptive for their support in this project, as well as patients and families who have agreed to provide tissue for these analyses.