Tumor surveillance using liquid biome in diffuse intrinsic pontine glioma

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Introduction

Immunotherapeutic approaches are being developed to treat diffuse intrinsic pontine glioma (DIPG), the deadliest childhood brain tumor. MRI is the gold standard for monitoring tumor response to therapy, but is limited by pseudoprogression: when transient inflammation of the tumor microenvironment falsely resembles progression on MRI. Thus, it is critical to develop alternative methods of monitoring tumor response, for use alongside MRI. Here, we use our digital droplet PCR liquid biopsy platform to detect H3F3A mutation – the most common DIPG driver mutation – in circulating tumor DNA (ctDNA) derived from plasma of DIPG patients at diagnosis. We then serially monitor H3F3A mutation allelic frequency (MAF) in plasma collected throughout the course of treatment, in order to correlate changes in MAF to tumor response. Patients received multimodal immunotherapy aimed at inducing immunogenic cell death selectively in tumor cells; if successful, this treatment would decrease tumor burden, which we expect to correlate to lower H3F3A MAF in plasma collected post-treatment. Thus, longitudinal MAF monitoring may provide a surrogate biomarker for non-invasively monitoring tumor response, as a complementary method to traditional MRI.

Methods

- Extract circulating tumor DNA from plasma collected at diagnosis, and throughout course of immunotherapy
- Screen for hotspot H3F3A mutation allelic frequency (MAF) using ddPCR
- Monitor changes in H3F3A MAF and correlate to clinical outcomes

Hypotheticals

- Circulating tumor DNA in plasma can be screened for key driver mutations, including H3F3A (somatic mutation found in 80% of DIPG tumors)
- Longitudinal analyses of H3F3A mutation allelic frequency in plasma collected throughout treatment may provide a surrogate biomarker for tumor response

Results

- Baseline H3F3A MAF in plasma obtained at diagnosis for all patients enrolled in trial. Cut-off at MAF of 0.001% represents samples that are positive for the mutation. * Denotes samples known to be either variant of histone 3 mutation (H3F3A or HIST1H3B).
- Serial monitoring of H3F3A mutation allelic frequency in plasma throughout immunotherapy treatment

Conclusions

- H3F3A driver mutation is detectable in plasma at diagnosis
- Non-invasive tumor genotyping when tissue is scarce
- Changes in H3F3A MAF can be serially monitored as a potential biomarker for tumor response, for use alongside MRI

Future directions

- Screen for HIST1H3B variant, and other hotspot mutations associated with DIPG
- Integrate clinical date to validate MAF as accurate biomarker for immunotherapy response

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