PHASE 1 TRIAL OF PERSONALIZED NEOANTIGEN VACCINES IN COMBINATION WITH STANDARD CARE TO TREAT GLIOBLASTOMA

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The tumor microenvironment (TME) of glioblastoma (GBM) is populated by cells that foster immunosuppression. Reversing immunosuppression and promoting surveillance of the TME by T cells that recognize the antigens generated by tumor-specific mutations (neoantigens) is critical to eliminating the tumor cells. In a phase 1 clinical trial of newly diagnosed GBM, patients were treated with personalized neoantigen vaccines (PNV) combined with standard of care (resection, radiotherapy, chemotherapy with temozolomide, and TTFields). The neoantigens were identified using the OpenVax computational pipeline. Primary endpoints included safety and feasibility, and the secondary endpoints, PFS, OS, TME analysis, and immunogenicity assays. The study enrolled 12 patients, ages 32-84, between December 2017 and July 2020. With a feasibility endpoint of one successful PNV administration, all patients got at least 6. All developed PNV-related injection site reactions and flu-like symptoms grade ≤2. Concomitant use with TTFields did not increase toxicity. None of the patients exhibited dose-limiting toxicity within 30 days of receiving the PNV. However, one developed grade 3 SAE, consisting of seizures, neck pain, and progressive neurological deficits, after vaccine 10, culminating in a grade 5 SAE and brain demyelination 10 months later. Assays performed on this subject showed amplification of the endogenous neoantigen-specific responses with PNV. PNV-induced $CD4^+$ and $CD8^+$ T cells reactive against mutated protein sequences with $CD8^+$ T cell cross-reactivity against mutant and nonmutant epitopes. Other patients had immunogenicity against the vaccinated peptides. Overall, the 6 months PFS was 100%, with 67% 2-year survival and 58% 3-year survival. Although the mutation burden is low in GBM, neoantigens were detected in all tumors, and PNV were manufactured for all patients. PNV with long synthetic peptides combined with standard care treatment may help improve outcomes in GBM. Safety can be improved by developing tools to detect potential T cell cross-reactivity with normal self-epitopes. Clinical trial Information: NCT03223103. Funding: Cancer Research Institute - V Foundation CLIP Grant (CRI Award #3680), Novocure.