Protoparvovirus

Oncolytic viruses, including the autonomous protoparvovirus H-1 (H-1PV), show great promise as novel immunotherapy tool.

The rat H-1 parvovirus (H-1PV) suppresses tumors in preclinical glioma models, through both direct oncolysis and stimulation of anticancer immune responses. This was the basis of ParvOryx01, the first phase I/IIa clinical trial of an oncolytic parvovirus in recurrent glioblastoma patients. H-1PV (escalating dose) was administered via intratumoral or intravenous injection. Tumors were resected 9 days after treatment, and virus was re-administered around the resection cavity. Primary endpoints were safety and tolerability, virus distribution, and maximum tolerated dose (MTD). Progression-free and overall survival and levels of viral and immunological markers in the tumor and peripheral blood were also investigated. H-1PV treatment was safe and well tolerated, and no MTD was reached. The virus could cross the blood-brain/tumor barrier and spread widely through the tumor. It showed favorable pharmacokinetics, induced antibody formation in a dose-dependent manner, and triggered specific T cell responses. Markers of virus replication, microglia/macrophage activation, and cytotoxic T cell infiltration were detected in infected tumors, suggesting that H-1PV may trigger an immunogenic stimulus. Median survival was extended in comparison with recent meta-analyses. Altogether, ParvOryx01 results provide an impetus for further H-1PV clinical development [1)].

In a first phase I/IIa clinical trial (ParvOryx01), H-1PV was safe and well tolerated when locally or systemically administered to recurrent glioblastoma patients. The virus was able to cross the blood brain barrier after intravenous infusion. Importantly, H-1PV treatment of glioblastoma patients was associated with immunogenic changes in the tumor microenvironment. Tumor infiltration with activated cytotoxic T cells, induction of cathepsin B and inducible nitric oxide (NO) synthase (iNOS) expression in tumor-associated microglia/macrophages (TAM), and accumulation of activated TAM in cluster of differentiation (CD) 40 ligand (CD40L)-positive glioblastoma regions was detected. These are the first-in-human observations of H-1PV capacity to switch the immunosuppressed tumor microenvironment towards immunogenicity. Based on this pilot study, Angelova et al. present a tentative model of H-1PV-mediated modulation of glioblastoma microenvironment and propose a combinatorial therapeutic approach taking advantage of H-1PV-induced microglia/macrophage activation for further (pre)clinical testing [2)].

1)
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2)
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