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EDITORIAL

CAR-T cells for H3K27-altered diffuse midline gliomas: where do we stand?

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Among the pediatric brain tumors, diffuse midline gliomas (DMG) harboring a mutation in histone H3K27 have the deadliest prognosis [1]. These tumors are most commonly found in the midline structures of the brain resulting in cranial nerve palsies and diplopia at clinical presentation [1]. Standard of care is radiation therapy although this is predominately palliative. At a molecular level, lysine (K) 27 is most commonly replaced by a methionine (M) but regardless of the specific histone H3 mutation, there is a global reduction in H3K27 trimethylation. This mutation most often occurs at one of two genes; most commonly the H3F3A gene resulting in the canonical H3.3K27M but also the HIST1H3B resulting in H3.1K27M [1–3]. Although these tumors have a relatively low mutational burden in comparison to other cancers, other mutations contributing to tumoriogenesis have been documented including TP53 and PDGFRA, both of which are implicated in as driving mutations of proliferation in a variety of cancers [4,5]. Over the decades, conventional chemotherapy and more recently, targeted agents have still failed to provide any survival benefit [6].

With other cancers yielding to new immune-based therapies, many have sought to implement similar strategies into the treatment of DMG. There are multiple ongoing or recently completed clinical trials evaluating the use of checkpoint inhibitors although a study with PD1 administration did not show any benefit compared with radiation therapy alone [7]. Vaccine-based therapies are also under preclinical and clinical evaluation. Recent results from early clinical trials demonstrated the safety and clinical effect in some patients following administration of a H3.3K27M-specific peptide vaccine with phase 2 studies now underway, including one in combination with a PD1 checkpoint inhibitor [1,7]. Other peptide-based vaccines targeting EGFRvIII and surviving in addition to dendritic cell vaccines are in clinical trial as well [1,7]. The final immunotherapy under investigation is CAR-T cell therapy, which will be discussed in further detail below.

Immunotherapies are dependent on the tumor immune microenvironment. With increased tissue samples being acquired via surgical biopsies, studies have further elucidated details pertaining to the DMG immune microenvironment [8]. There is sparse infiltration of $CD3^+$ and $CD8^+$ lymphocytes as well as few NK cells although, in comparison to pediatric high grade gliomas (pHGG), there were more $CD4^+$ Treg cells, eosinophils, neutrophils and dendritic cells. Additionally, there are very low levels or no proinflammatory cytokines and limited chemokines [7,8]. For example, there are significantly lower levels of TGFβ when compared with hemispheric pHGG [7]. These findings have resulted in experts labeling K27-altered DMG as immunologically "cold". There is some evidence to suggest a difference between H3.1-K27 altered and H3.3K27-altered tumors, with the former expressing a more immunosuppressive state and the latter having a more inert immune status [7]. The roles of adjuvant therapies can also modulate the immune microenvironment. Corticosteroid use can further suppress the global immune environment, including that of the tumor while radiation therapy may impact the tumor immune microenvironment through multiple mechanisms that can increase suppression while increasing antigen presentation [8]. The exact biological mechanism and the consequences of RT to the immune microenvironment in these tumors is an area of current study [8]. As more information pertaining to the DMG tumor microenvironment in uncovered, immune-related therapies will need to be adjusted accordingly to maximize their potential for success.

Chimeric antigen receptor (CAR)-T cells are autologously-derived engineered receptors that bind to a tumor specific antigen and activate cytotoxic lymphocytes, usually T cells, that can subsequently elicit

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