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IMMUNOTHERAPY

Adaptive resistance to CARs in glioma

> “…more regulatory T cells, more PD-L1 expression, and other immuno-suppresive markers present after CAR T-cell treatment compared with before”

Glioblastoma (GBM) is one of the most common brain tumours and portends a poor prognosis; patient survival durations are typically <6 months for those with recurrent disease following surgery. Around 30% of newly diagnosed patients express the aberrant EGFR variant III (EGFRvIII), which is associated with unfavourable outcomes. Although brain tumours have an immunosuppressive microenvironment, T-cell-based therapies utilizing chimeric antigen receptors (CARs) have shown promise in this disease. These encouraging data prompted researchers to conduct a first-in-human clinical trial of a CAR-modified T cells directed at the EGFRvIII antigen in 10 patients with recurrent GBM.

In total, 10 patients received a single intravenous infusion of autologous anti-EGFRvIII CAR T cells, with assessment of target expression within the tumour. The manufacturing and infusion of the anti-EGFRvIII CAR T cells was feasible and safe, with no evidence of off-tumour toxicity or cytokine-release syndrome. Marcela Maus, senior author of the trial, comments on the main study findings: “targeting EGFRvIII was safe, without on-target or off-target toxicities. We found that the CAR T-cells readily infiltrate brain tumours, which is not trivial because of the blood–brain barrier. Importantly, levels of EGFRvIII expression in tumour cells either decreased or were eliminated following CAR-T-cell infusion.”

One patient had stable residual disease for >18 months of follow up. Seven patients had surgical intervention following anti-EGFRvIII CAR-T-cell infusion, which enabled tissue-specific analysis and *in situ* assessment of the tumour microenvironment. Notably, in five of the seven patients, the EGFRvIII antigen decreased, accompanied by an increase in the expression of inhibitory molecules compared with pre-infusion samples. The researchers showed that the infused product could traffic to the tumour, proliferate *in situ*, and exert anticancer activity that upregulated compensatory adaptive resistance mechanisms, such as increased expression of PD-L1 and IDO1. Collectively, these findings illustrate that the brain tumour microenvironment is not static; rather, many pathways are actived simultaneously in response to therapy. As Maus elaborates: “the brain tumour itself displayed an adaptive response, with increased immunosuppression. Moreover, there were more regulatory T cells, greater PD-L1 expression, and other immunosuppressive markers present after CAR T-cell treatment compared with before.”

In terms of what these findings indicate for the future, Maus laments: “not surprisingly, it is probably going to take more than a single antigen target to effectively eliminate GBM tumour cells: we will have to target more antigens, and block one or more of the immunosuppressive pathways that inhibit T-cell function.”

Lisa Hutchinson

ORIGINAL ARTICLE O'Rourke, D. M. *et al.* A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci. Transl Med.* http://dx.doi.org/ 10.1126/scitranslmed.aaa0984 (2017)