Effective eradication of glioblastoma stem cells by local application of an AC133/CD133-specific T-cell-engaging antibody and CD8 T cells

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Abstract

This paper describes the use of a bispecific antibody which can recruit T-cells specifically towards AC133+ cancer stem cells (CSCs), thereby activating the T cells and lysing the CSCs. Cancer stem cells (CSC) drive tumorigenesis and contribute to genotoxic therapy resistance, diffuse infiltrative invasion, and immunosuppression, which are key factors for the incurability of glioblastoma multiforme (GBM). The AC133 epitope of CD133 is an important CSC marker for GBM and other tumor entities. Here, we report the development and preclinical evaluation of a recombinant AC133×CD3 bispecific antibody (bsAb) that redirects human polyclonal T cells to AC133(+) GBM stem cells (GBM-SC), inducing their strong targeted lysis. This novel bsAb prevented the outgrowth of AC133-positive subcutaneous GBM xenografts. Moreover, upon intracerebral infusion along with the local application of human CD8(+) T cells, it exhibited potent activity in prophylactic and treatment models of orthotopic GBM-SC-derived invasive brain tumors. In contrast, normal hematopoietic stem cells, some of which are AC133-positive, were virtually unaffected at bsAb concentrations effective against GBM-SCs and retained their colony-forming abilities. In conclusion, our data demonstrate the high activity of this new bsAb against patient-derived AC133-positive GBM-SCs in models of local therapy. This kind of treatment could be beneficial, particularly when administered into surgically created resection cavities of highly invasive GBM containing AC133+ CSCs. The efficacy may further be enhanced by simultaneous targeting of CSCs with other surface markers, if present, or by combination with approaches inducing long-lasting antitumor immunity.

The original publication can be accessed here:

http://cancerres.aacrjournals.org/content/canres/early/2015/05/15/0008-5472.CAN-14-2415.full.pdf