Autologous iC9-GD2-CAR-expressing VZV-specific T Lymphocytes

National Cancer Institute

Source

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Genetically modified, autologous varicella zoster virus (VZV)-specific T-lymphocytes transduced with a retroviral vector encoding a chimeric antigen receptor (CAR) specific for the disialoganglioside GD2, which contains the signaling domains for the co-stimulatory molecules CD28 and CD134 (OX-40), and the suicide gene, inducible caspase 9 (iCasp9 or iC9), with potential immunomodulating and antineoplastic activities. Upon intravenous administration, iC9-GD2-CD28-OX40-expressing T lymphocytes target the GD2 antigen on tumor cells for selective toxicity against GD2-expressing tumor cells. iCasp9 consists of a full-length caspase 9, including its caspase recruitment domain, linked to a human FK506 drug-binding domain with an F36V mutation (FKBP12-F36V). If the administered T cells lead to unacceptable side effects, the chemical homodimerizer AP1903 can be administered, which binds to the FKBP12-F36V drug binding domain, activates caspase 9, and results in apoptosis of the administered T-cells. Expression of the iCasp9 gene in T cells for adoptive transfer increases safety and broadens the scope for their clinical applications. The tumor associated antigen GD2 is overexpressed on the surface of almost all tumors of neuroectodermal origin. OX40 and CD28, both T-cell surface-associated co-stimulatory molecules, are required for full T-cell activation. An additional VZV vaccine can be administered to increase T-cell activity.