Autologous TGFbeta-Resistant HER2/EBV-Specific Cytotoxic T Lymphocytes

National Cancer Institute

Source

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A preparation of transforming growth factor-beta (TGF-beta)-resistant Epstein-Barr virus (EBV)-specific cytotoxic T-lymphocytes (CTLs) directed to EBV through their native receptor and HER2 through a retrovirally transduced HER2 chimeric antigen receptor (CAR) with potential antineoplastic activity. Autologous EBV-specific CTLs are produced by exposing autologous CTLs to "stimulator" autologous EBV-transformed lymphoblastoid cell lines (EBV-LCLs). Subsequently, autologous EBV-specific CTLs are transduced with retroviral vectors expressing the mutant type II TGF-beta dominant-negative receptor (DNR), which blocks signaling by all three TGF-beta isoforms, and the HER2 CAR. After transduction, transgenic EBV-CTLs are expanded on EBV-LCLs. Upon administration, autologous HER2 chimeric receptor/TGFbeta dominant negative receptor-expressing EBV-specific cytotoxic T lymphocytes may bind to HER2-expressing tumors cells, which may result in CTL-mediated cell lysis and inhibition of tumor cell proliferation. Tumor-expressed TGF-beta inhibits T lymphocyte activation and expansion.