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NY-ESO-1 TCR/sr39TK Lentiviral Vector-transduced Autologous PBSCs

National Cancer Institute

Source

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Human autologous peripheral blood stem cells (PBSCs) transduced with a lentiviral vector (LV) encoding a T-cell receptor (TCR) specific for the cancer-testis antigen NY-ESO-1, and carrying the positron emission tomography (PET) reporter/suicide gene sr39TK, a mutant form of the herpes simplex virus type 1 thymidine kinase gene (HSV-1 TK), with potential immunostimulating and antineoplastic activities. Upon isolation, transduction, expansion ex vivo, and reintroduction into the patient, the NY-ESO-1 TCR/sr39TK LV-transduced autologous PBSCs recognize and bind to NY-ESO-1-overexpressing tumor cells. This may result in a specific cytotoxic T-lymphocyte (CTL)-mediated killing of NY-ESO-1-positive tumor cells. NY-ESO-1, a tumor-associated antigen (TAA), is found in normal testis and on the surface of various tumor cell types. The incorporation of sr39TK allows for the ganciclovir (GCV)-mediated cell killing of the gene-modified PBSCs if serious adverse effects occur. sr39TK converts the nucleoside prodrug GCV into GCV monophosphate (GCV-MP), which is in turn phosphorylated by cellular kinases to the cytotoxic nucleotide GCV-triphosphate (GCV-TP); the TP form competitively inhibits deoxyguanosine triphosphate (dGTP) incorporation into DNA and inhibits DNA synthesis, causing DNA damage and cell death in the sr39TK-expressing PBSCs. In addition, sr39TK allows for PET imaging of the gene-modified PBSCs upon subsequent administration of radio-labeled substrates, such as 9-(4-[18F]-fluoro-3-[hydroxymethyl]butyl)guanine ([18F]-FHBG). The monophosphorylation of [18 F]-FHBG is catalyzed by sr39TK; this promotes triphosphorylation and accumulation of [18F]-FHBG in the PBSCs, which allows in vivo imaging and tracking of the PBSCs upon PET. Compared to wild-type HSV-TK, the mutant form has increased prodrug phosphorylating capacity and enhances the cell killing by GCV.