Targeted Cytosine Deaminase-Uracil Phosphoribosyl Transferase Suicide Gene Therapy Induces Small Cell Lung Cancer-Specific Cytotoxicity and Tumor Growth Delay - DTU Orbit (16/01/2019)

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Purpose: Small cell lung cancer (SCLC) is a highly malignant cancer for which there is no curable treatment. Novel therapies are therefore in great demand. In the present study we investigated the therapeutic effect of transcriptionally targeted suicide gene therapy for SCLC based on the yeast cytosine deaminase (YCD) gene alone or fused with the yeast uracil phosphoribosyl transferase (YUPRT) gene followed by administration of 5-fluorocytosine (5-FC) prodrug. Experimental design: The YCD gene or the YCD-YUPRT gene was placed under regulation of the SCLC-specific promoter insulinoma-associated 1 (INSM1). Therapeutic effect was evaluated in vitro in SCLC cell lines and in vivo in SCLC xenografted nude mice using the nonviral nanoparticle DOTAP/cholesterol for transgene delivery. Results: INSM1-YCD/5-FC and INSM1-YCD-YUPRT/5-FC therapy induced high cytotoxicity in a range of SCLC cell lines. The highest therapeutic effect was obtained from the YCD-YUPRT fusion gene strategy. No cytotoxicity was induced after treatment of cell lines of other origin than SCLC. In addition the INSM1-YCD-YUPRT/5-FC therapy was superior to an established suicide gene system consisting of the herpes simplex virus thymidine kinase (HSVTK) gene and the prodrug ganciclovir. The superior effect was in part due to massive bystander cytotoxicity of YCD-YUPRT-produced toxins. Finally, INSM1-YCD-YUPRT/5-FC therapy induced significant tumor growth delay in SCLC xenografts compared with control-treated xenografts. Conclusions: The current study is the first to test cytosine deaminase-based suicide gene therapy for SCLC and the first to show an antitumor effect from the delivery of suicide gene therapeutics for SCLC in vivo. Clin Cancer Res; 16(8); 2308-19. (C) 2010 AACR.

Keyword: CARCINOMA, MURINE MODEL, PROSTATE-CANCER, THYMIDINE KINASE GENE, PROMOTER, EXPRESSION, ADENOVIRUS-MEDIATED TRANSFER, IN-VIVO, MEMBRANE ANTIGEN, DELIVERY

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