

Enhanced antitumor efficacy of telomerase-selective oncolytic adenoviral agent OBP-401 with docetaxel: Preclinical evaluation of chemovirotherapy

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Oncolytic adenoviruses are being developed as novel anticancer therapeutics and currently undergoing clinical trials. We previously demonstrated that telomerase-specific replication-competent adenovirus (Telomelysin: OBP-301), in which the human telomerase reverse transcriptase (hTERT) promoter regulates viral replication, efficiently killed human tumor cells. We further constructed OBP-401 (Telomelysin-GFP) that expresses the green fluorescent protein (GFP) reporter gene under the control of the cytomegalovirus promoter in the E3 region to monitor viral distribution. Here, we examined the feasibility of a single-agent therapy with OBP-401 as well as of combining OBP-401 with chemotherapeutic agents. Infection of OBP-401 alone or followed by the treatment of a chemotherapeutic drug, docetaxel (Taxotere), resulted in a profound *in vitro* cytotoxicity and GFP expression in various human cancer cell lines originating from different organs (lung, colon, esophagus, stomach, liver and prostate), although the magnitude of antitumor effect varied among the cell types. Other chemotherapeutic drugs such as vinorelbine (Navelbine) and SN38 (the potent active metabolite of irinotecan) combined with OBP-401 also inhibited the growth of human cancer cells. Quantitative real-time PCR analysis demonstrated that docetaxel did not affect viral replication. For *in vivo* evaluation, *nu/nu* mice xenografted with H1299 human lung tumor received intratumoral injection of OBP-401 and intraperitoneal administration of docetaxel. Analysis of growth of implanted tumors showed a significant, therapeutic synergism, although OBP-401 alone and docetaxel alone showed modest inhibition of tumor growth. Thus, OBP-401 in combination with docetaxel efficiently enhances the antitumor efficacy both *in vitro* and *in vivo*, and the outcome has important implications for tumor-specific oncolytic chemovirotherapies for human cancers.

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