Objectives

Paclitaxel targets tumor cells in M phase of the cell cycle. Cells in other phases survive the insult and repopulate the tumor. PNC-27 is a peptide synthesized of amino acids of the p53-HDM2 binding domain that kills various cancer cell lines. In this study we assessed the sensitivity of ovarian cancer cells that survive treatment with Paclitaxel to PNC-27.

Methods

Mature ovarian cancer cells (ID8) were maintained in DMEM media. For measurement of cytotoxicity in vitro, cells were exposed for 12 hours to Paclitaxel at various concentrations. After 12 hours the drug containing medium was removed and the cells were cultured for 24 hours in medium containing various concentrations of PNC-27. Viability was assessed with the use of MTT assay. Survival fractions were plotted against drug concentrations and the data were fitted to logistic dose-response curves. The 50% Inhibitory Concentration (IC50) was obtained from the fit parameters that achieved the lowest $\chi^2$ value. Isoeffective combinations were used to create isobolograms. Combination indexes were calculated to assess the interaction between Paclitaxel and PNC-27.

Results

A 12-hour exposure to Paclitaxel rendered incomplete killing and a maximal cytotoxicity of 80% was reached at 100ug/ml. Cells were more responsive to increased exposure time than to increased dose and 100% cytotoxicity was obtained at 48 hours. PNC-27 mediated comprehensive, dose-dependent killing. The IC50 for a 24-hour exposure was 58ug/ml, while 100% cytotoxicity was achieved at 300ug/ml.

Combination indexes for various doses of Paclitaxel and PNC-27

Our data demonstrate in vitro synergism between PNC-27 and Paclitaxel. PNC-27 could eliminate cells surviving Paclitaxel and provide survival benefit.