Search for optimal schedule for combination efficacy of oxaliplatin and 5-FU in human gastric cancer cells in vitro

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Background Oxaliplatin (LOHP) showed a broad spectrum of in vitro and in vivo cytotoxicity in both cisplatin-sensitive and -resistant tumor models when administered alone and in combination with 5-FU (FU). Among many different combination schedules of LOHP and FU challenged, standard treatment schedule has not been proposed. We have shown the synergistic interaction between LOHP and FU at 1:1 molar ratio in MKN-45 human gastric cancer cells. Searching for optimal combination schedule, we evaluated in MKN-45 cells cytotoxic interaction of LOHP and FU given by different schedules of sequential and simultaneous administration.

Methods The cytotoxic interaction between LOHP and FU was studied by comparing IC_{50} determined by MTT assay and Combination Index (CI) calculated by Chou and Talalay method. The cell cycle arrest effect was also monitored following single and combination exposures.

Results When given alone, prolonged exposures to each agent produced increased cytotoxicity, i.e., IC_{50} was 1.82 ±0.59μg/ml and 0.384±0.237μg/ml for 4hr-and 72hr-LOHP, and 1.69±0.608μg/ml and 0.477±0.164μg/ml for 2hr-and 72hr-FU exposure, respectively. Exposure to 4hr-LOHP followed by 2hr-FU and reverse sequence showed antagonism. With 72hr-continuous exposure to FU, 4hr-LOHP given at 2hr post FU treatment showed synergistic interaction with lower IC_{50} compared to LOHP given before FU (0.254±0.019 vs 0.392±0.214μg/ml, p=0.05), indicating the increased cytotoxic interaction by simultaneous exposure. With 4hr-LOHP, simultaneous exposure to FU for 4hr compared to 2hr showed lower IC_{50} (0.955±0.646μg/ml and 0.344±0.236μg/ml, p=0.04). Further increase of FU exposure time up to 72hr, however, did not result in significant decrease in IC_{50} (0.344±0.236μg/ml (4hr) vs 0.254±0.019μg/ml (72hr), p=0.239). In cell cycle distribution study, simultaneous 4hr-LOHP and 4hr-FU resulted in G_{1} increase and S phase reduction, similar to LOHP given alone, and simultaneous 4hr-LOHP and 72 hr-FU induced S phase increase along with G_{1} and G_{2}/M reduction, similar to FU alone. This indicates that prolonged exposure to FU from 4hr to 72hr, when simultaneously given with 4hr-LOHP, changed cell cycle distribution, but did not result in increased cytotoxic interaction.

Conclusion Our data suggest that simultaneous exposure to LOHP and FU for 4hr may represent a better choice with less toxicity compared to commonly used protracted FU infusion, which warrants further evaluation.