Growth inhibition and cell cycle arrest induced by 5-FU, Oxaliplatin, and Paclitaxel in human gastric cancer cells in vitro

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**Background** In addition to metastatic breast and head & neck cancers combination of 5-FU (FU), cisplatin (CDDP), and paclitaxel (PTX) has shown attractive clinical outcome in advanced gastric carcinomas. However, increased toxicity of this regimen is major dose-limiting factor. Oxaliplatin (LOHP), due to its favorable toxicity profile and antitumor activity against CDDP-resistant tumors, may be a good candidate to substitute CDDP. The purpose of this study is to provide rationale for the selection of schedule of proposed combination of FU, LOHP and PTX in human gastric cancer.

**Methods** We evaluated anti-proliferative activity (MTT assay after 72 continous exposure) and time course of growth inhibition (%GI: % reduction of cell number compared to control) and analyzed the cell cycle arrest effects induced by LOHP, 5-FU and PTX at IC_{50} and IC_{80} in a human gastric cancer cell line, SNU-1, in vitro. Results When determined by MTT assay after 72hr continuous exposure, IC_{50} and Emax were 9.4μM, 0.79μM, and 1.68 nM, and 96%, 91%, and 68% for FU, LOHP and PTX, respectively. Direct cell count study showed similar results for FU and LOHP, i.e., 47 to 54% and 80 to 90% GI at IC_{50} and IC_{80}. For PTX, however, 89% of GI was obtained by direct cell count, which was greater than Emax (68%) of MTT data after 72hr exposure at 10 nM. For all three agents, no significant cell cycle effect was observed at IC_{50}’s. At IC_{80}, FU induced S arrest along with G_{1} phase reduction and G_{2}/M abrogation, and LOHP and PTX resulted in G_{2}/M block along with G_{1} reduction in a time-dependent manner.

**Conclusion** These data indicate that (1) cytotoxicity of PTX may be underestimated in studies using MTT assay, (2) the concentration-dependent cell cycle effect may account for effect level-dependent synergistic interaction between FU and LOHP, and (3) cell cycle arrest induced by PTX accounted up to 80% of its overall GI, hence, combination regimen including PTX should be designed not to abrogate its G_{2}/M block in order to obtain maximal synergism.