

M. LOHP and PTX induced G<sub>2</sub>/M arrest, 5-FU S phase increase, and ZD1839 G<sub>1</sub> increase in a concentration-dependent manner. A previously developed cytostatic TPi model (Jpn J Cancer Res 91:1303) was used to assess the contribution of cell cycle arrest to overall growth inhibition, and 64% and 80% of the overall growth inhibition at IC<sub>80</sub> after 72hr was attributed to cell cycle arrest for LOHP and PTX, respectively. When combined, PTX+ZD1839 showed the greatest synergism and LOHP+ZD1839 was also synergistic. The cell cycle effect and apoptosis induced by PTX were potentiated by the coadministration of ZD1839. This study demonstrates the antitumor activity of ZD1839 against human gastric carcinoma cells and its synergistic interaction with LOHP and PTX. These results provide a preclinical rationale for future clinical development of ZD1839 and its use in combination with LOHP or PTX against MMR deficient human gastric cancers that express EGFR.

[OA-3] [ 10/18/2002 (Fri) 11:50 - 12:00 / Hall A ]

### Pharmacodynamics of anticancer activity of tirapazamine and paclitaxel against human NSCLC

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Hypoxia in solid tumors is known to contribute to intrinsic chemoresistance. Tirapazamine (TPZ), a hypoxia-selective cytotoxin, showed synergism with radiation or cytotoxic agents. Paclitaxel (PTX) is a highly active anti-cancer agent against Non small cell lung cancer (NSCLC), however, due to poor penetration into central hypoxic region of tumor tissue, combination with TPZ has been suggested to enhance its efficacy. We investigated pharmacodynamics of cytotoxicity, cell cycle arrest and apoptosis induced by TPZ and PTX in monolayers and histocultures of A549 human NSCLC cells. Hypoxic cytotoxicity ratios (HCR) of TPZ in monolayers increased with longer drug exposure. In monolayers, the values of n50 (CnxT=k model, at 50% inhibition level) were not greater than 0.5 for TPZ and PTX, indicating greater importance of exposure time than drug conc. In monolayers, TPZ and PTX induced conc-dependent cell cycle arrest (G<sub>2</sub>/M), and hypoxic condition (2% O<sub>2</sub>) potentiated cell cycle effect of TPZ by 10 folds compared to normoxic condition. In histocultures, n50 for TPZ was 1.3, indicating greater importance of drug conc than exposure time. Cytotoxicity and cell cycle effect of PTX were significantly reduced in histocultures. However, cell cycle effect induced by TPZ in histocultures was similar to that in monolayers under hypoxia. TPZ and PTX induced apoptosis in cells in G<sub>1</sub>/S phase and G<sub>2</sub>/M phase, respectively. These data indicate that (1) pharmacodynamics of TPZ and PTX in monolayers is significantly different from that in 3-dimensional histocultures, which represents *in vivo* solid tumors, and (2) both TPZ and PTX induced G<sub>2</sub>/M arrest, but different cell cycle-specific apoptosis was observed. Grant 2000-0-214-001-3 from KSEF.

[OA-4] [ 10/18/2002 (Fri) 12:00 - 12:10 / Hall A ]

### The Differential Roles of Glutamine Synthetase in Methylmercury Neurotoxicity

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Methylmercury (MeHg), a potent neurotoxicant, produces neuronal death that may be partially mediated by glutamate. Glutamine synthetase (GS), a glial-specific enzyme, catalyzes the synthesis of glutamine from glutamate and ammonia and is associated with ischemic injury and neurological diseases. Objectives of this experiment are to investigate whether *in vivo* and *in vitro* MeHg exposure have adverse effects on GS and whether duration of exposure to MeHg and glutamate co-treatment play a role in MeHg-induced toxicity. GS activity was measured in cell-free brain homogenate of untreated rats, mice treated with MeHg (2, 4, 10 mg/kg for 1 days), primary cultured glial cells.