cis-Diamminedichloroplatinum(II) (cisplatin or cis-DDP) is one of the most widely used cytotoxic anticancer drugs. The therapeutic effect is believed to arise from consequence of cisplat in binding to DNA. However, its clinincal efficacy is often limited due to the induction of secondary resistance. Classical anti-cancer drug resistance mechanism is frequently associated with overexpression of P-glycoprotein, a member of the ATP binding cassette family of transmembrane transport proteins capable of expelling certain cytotoxic drugs and maintaining their non-lethal intracellular level. Recently the finding that acquired multidrug resistance occurs in the absence of ATP binding cassette family protein overexpression has provided support for the existence of other mechanisms. We established cisplatin-resistant cell lines to study mechanisms of cisplatin resistance. Acquired resistant cells were obtained by growing K562 cells in stepwise increasing concentrations of cisplatin to produce resistant cell lines (K562/CDDP). The resistant cells represent resistant factor of 4.87. No differences were noted on drug accumulation between cisplatin resistant and sensitive cells. In addition, the levels of cisplatin bound to DNA in K562/CDDP decreased more rapidly than sensitive cells, suggesting that increased DNA repair capacity plays a partial role in the acquired resistance. Additionally, K562/CDDP cells were more resistant to apoptosis. DNA fragmentation and Western blot analysis showed that K562/CDDP cells had significantly more resistant to proteolytic activation of caspase-3 with higher levels of the anti-apoptotic protein Bcl-2. These results suggest that blocking of apoptosis through the suppression caspase-3 activation in K562 cells may be responsible for cisplatin resistance.

[PA1-4] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Comparison of antitumor activity between oxaliplatin and cisplatin given alone and in combination with 5-fluorouracil in human gastric cancer cells with different mismatch repair enzyme status.

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Oxaliplatin (LOHP) approved for metastatic colorectal cancers showed activity against various tumors including cisplatin (CDDP)-resistant tumors. Although its activity against gastric cancer has been suggested, no preclinical data are available to support its clinical application. We evaluated antitumor activity of LOHP alone and in combination with 5-FU and then compared with that of CDDP in five human gastric cancer cell lines *in vitro*. LOHP showed cytotoxicity similar to CDDP as determined by XTT assay with IC_{50} ranging from 1.58 to 17.0㎍/㎖. Deficiency of mismatch repair (MMR) enzyme causes resistance to many cytotoxic drugs including CDDP and 5-FU. SNU-1 cells are hMLH1-deficient due to a non-sense mutation resulting in protein truncation. However, no significant resistance to CDDP was observed in SNU-1 when compared with MKN-45 cells expressing hMLH1 abundantly. When combined with 5-FU, synergistic interaction of both LOHP and CDDP was dependent on cell line, dose ratio, and fraction affected. In MKN-45, both LOHP+5-FU and CDDP+5-FU showed similar synergistic interaction profiles. In MMR deficient-SNU-1, however, the synergism of LOHP+5-FU was greater than that of CDDP+5-FU. In summary, LOHP alone was as active as CDDP against human gastric cancer cells and its synergistic interaction with 5-FU was superior to that of CDDP. The present study indicates that LOHP may be a promising agent not only as monotherapy but also in combination with 5-FU against human gastric cancers.

[PA1-5] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Mechanism of Epibatidine-Induced Catecholamine Secretion in the Perfused Rat Adrenal Gland

Lim GH, KO ST