Inhibition of Heme Oxygenase-1 Enhanced Antitumor Effect of Gemcitabine in Cholangiocarcinoma

Sarinya Kongpetch
Department of Pharmacology, Faculty of Medicine, KKU

Poster

Background and objective: Heme oxygenase-1 (HO-1) is a key enzyme exerting potent cytoprotection, cell proliferation especially the resistance to anticancer agents. This study aimed to investigate the roles of HO-1 in human cholangiocarcinoma (CCA) cells, whether inhibit HO-1 could increase the cytotoxic effect of gemcitabine (Gem) in CCA cell *in vitro* and *in vivo* using mice bearing CCA tumor-xenograft.

Methods: The cytoprotective role of HO-1 in CCA cell (KKU-100) was assessed by using HO-1 inhibitor (ZnPP). The cytotoxic effects of combinations of Gem with ZnPP were assayed by fluorescence dye staining (AO/EB). Western blot analysis determined p21, cytochrome c with using b-actin as loading control. *In vivo* study; nude mice bearing KKU-100 xenograft were treated with combination of Gem and ZnPP. Mice tissues were performed immunohistochemistry for p21, p53 and mdm2.

Results: Inhibition of HO-1 by zinc protoporphyrin IX (ZnPP) sensitized KKU-100 to the cytotoxicity of Gem. The combination of ZnPP and Gem triggered protein related apoptosis and suppress-growth by enhancing the release of cytochrome c, and increased $p21^{Cip/WAF1}$ levels, compared to both treatments alone. *In vivo*, ZnPP significantly potentiated the effects of GEM to suppress tumor-growth. From immunohistochemistry, the tumor suppressor protein; p53 and p21 were highly expressed in the combination group where mdm2 expression was not detected.

Conclusions: Inhibition of HO-1 potentiated antitumor effect of Gem in CCA tumor. Targeted inhibition of HO-1 may be a strategy to overcome drug resistance in chemotherapy of bile duct cancer.

Key word: Heme oxygenase-1, cholangiocarcinoma and gemcitabine