

14th World Cancer & Anti-Cancer Therapy Convention

November 21-23, 2016 Dubai, UAE

Metavert for treating pancreatic cancer

Mouad Edderkaou, C Chheda, B Soufi, R Murali and S J Pandol
Cedars-Sinai Medical Center, USA

Background & Aim: Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease with no effective treatment. PDAC cells are highly proliferative and metastatic. We have developed a new drug called Metavert that targets at the same time the glycogen synthase kinase 3 beta (GSK-3 β) and histone deacetylase (HDAC), important mediators of cancer progression. The aim of this study was to test this agent for treatment of PDAC.

Methods: PDAC cell lines, patient-derived circulating tumor cells (CTCs), and normal cells were treated with different doses of Metavert and cell survival, apoptosis, epithelial to mesenchymal transition (EMT) markers, and invasion ability were measured. Treatments were performed alone and in combination with gemcitabine or exposure to irradiation. In vivo, KrasLSL-G12D/+; Trp53LSL-R172H/+; and Pdxcre (KPC) mice were intra-peritoneally injected with Metavert (5mg/Kg) 3 times per week from age 2 months until death. Survival and number of metastasis were determined. Pancreatic lesions and tumor grades as well as fibrosis and inflammation were measured by immunohistochemistry. Cytokine production and expression of cytokine receptors were measured in tumor cells and in cells present in the tumor microenvironment.

Results: Metavert significantly (at nano-molar concentrations) decreased cancer cell survival and increased apoptosis in several PDAC cells lines. The anti-cancer effect was stronger than the effect of the combination of HDAC and GSK-3 β inhibitors. The same doses of Metavert did not affect survival of normal hepatocytes and pancreatic ductal cells. Metavert decreased the survival of CTCs. Metavert increased histone acetylation, inhibited GSK-3 β activity, decreased expression of markers of EMT/ metastasis and cancer stemness, and prevented migration of the cancer cell lines and CTCs. Furthermore, Metavert sensitized PDAC cells and CTCs to gemcitabine and radiotherapy as well. Treatment with Metavert significantly increased KPC mice survival by ~50%. Histologic examination showed that Metavert treatment inhibited formation of both early pancreatic intraepithelial neoplasia (PanIN) lesions and late lesions (carcinoma) in the pancreas of these animals. Distal metastasis was decreased from 29% in control KPC mice to 0% in Metavert treated KPC mice. Fibrosis and M2 macrophages levels were decreased in Metavert treated mice.

Conclusion: We have designed and synthesized a novel drug that shows a significant anti-cancer effect in vitro in PDAC cells and CTCs and in the most aggressive mouse model of experimental PDAC. Importantly, Metavert increased the survival of KPC mice and prevented metastasis in vivo with no significant toxicity to normal cells. Pre-clinical toxicity studies are ongoing and the drug is expected to be approved for clinical testing within one year.

mouad.edderkaoui@cshs.org

Notes: