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TITLE

Molecular Mechanisms Underlying the Synergistic Interaction of the Novel Anticancer Drug Ukrain with Gemcitabine in Preclinical Models of Pancreatic Cancer

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Introduction/Background: Current therapy for pancreatic ductal adenocarcinoma (PDAC) is surgery followed by adjuvant radiotherapy and chemotherapy for early-stage, and palliative chemotherapy for advanced disease. Gemcitabine is the standard drug in both adjuvant and palliative treatment, but yields a marginal impact on disease outcome. Several attempts to improve the efficacy of gemcitabine by addition of a second cytotoxic or targeted agent have not shown a significant survival advantage. A new drug, NSC-631570 (Ukrain), used, showed greater median survival in combination with gemcitabine compared to gemcitabine alone (10.4 months vs 5.2 months; $p<0.001$) in the palliative treatment of unresectable PDAC (Gansauge et al.; Langenbecks Arch Surg 2002). However, the authors did not study the interactions between ukrain and the molecular determinant expressions involved in the metabolism of gemcitabine. There is compelling evidence that gene transcripts of determinants of gemcitabine activity, such as hENT1, could be used to tailor chemotherapy in PDAC (Giovannetti et al., Cancer Res 2006). Therefore, the aim of present study was to evaluate the modulation of the expression of two pivotal genes (hENT1 and dCK) involved in gemcitabine activity.

Methods: In vitro studies were performed in 2 ATCC cell lines (PL45 and Mia PaCa-2) and 2 Primary Cell Cultures obtained from PDAC patients underwent surgical resections (PPTCC78 and PPTCC109). Cells were treated with Ukrain at IC50 concentration levels for 48h. The total RNA extraction was performed with Trizol protocol. All the amplifications were carried out with normalization of gene expression against the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) housekeeping control gene, and the quantitation of gene expression was performed using the direct ratio, the standard curve method and the ΔΔCT calculation, in which the amount of target, normalized to the endogenous control and relative to the calibrator (untreated control cells) was calculated as $2^{(-\Delta\Delta Ct)}$.

Results: Ukrain positively modulates the expression of hENT1 mRNA in all PDAC cell cultures treated with IC50 ($p<0.001$). The $2^{(-\Delta\Delta Ct)}$ analysis revealed a mean increase of 2.8 fold ($p=0.001$) with respect to untreated control cells. In PL45 and Mia PaCa-2 cells Ukrain positively affects mRNA expression of dCK gene as well.

Conclusions: To date a few options based on gemcitabine are available for treatment of PDAC. Most gemcitabine-based chemotherapy regimens resulted in a very limited disease control, and studies attempting to widen the therapeutic armamentarium against this disease are warranted. Based on the previous clinical data the Ukrain-gemcitabine combination appears a promising regimen and the results of the present study provide the experimental basis for the further clinical testing of the Ukrain-gemcitabine schedule in PDAC patients.