Tivantinib-Gemcitabine: Pharmacological Rational for a New Combination in Pancreatic Cancer

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Background: A trial on the combination of tivantinib with gemcitabine demonstrated manageable toxicity and anticancer activity (20% partial response and 46% stable disease), in different tumor types, including lung and pancreatic cancer (1). However, pharmacokinetics showed no differences in the concentration of tivantinib or gemcitabine, while circulating VEGF, HGF and c-Met failed to correlate with response. Our in vitro and in vivo studies on the combination of another c-Met inhibitor (crizotinib) with gemcitabine showed increased blood, cellular, and tissue concentrations of gemcitabine, through a cytidine deaminase (CDA)-mediated mechanism. Here we evaluated whether the tivantinib-gemcitabine combination might also affect this enzyme. Furthermore we evaluated microtubule disruption as a possible pharmacodynamic biomarker.

Methods: Four primary pancreatic cancer cell cultures were obtained from radically-resected patients. C-Met and phospho-c-Met were evaluated in the originator tumors and in the cells using specific monoclonal anti-human c-Met and anti-phospho-Y1003-c-Met antibodies. Cell growth inhibitory effects of tivantinib and gemcitabine were determined by SRB assay. CDA activity was evaluated by HPLC. Finally, perturbed microtubule dynamics was studied by FACS analysis.

Results: Cells and tissues showed a variable expression of c-Met, and cells with the highest c-Met levels were more sensitive to tivantinib and tivantinib-gemcitabine combination. Median drug-effect analysis revealed strong synergistic interaction. However this synergism was not associated to the increase in the accumulation of gemcitabine-nucleotides, as observed for crizotinib-gemcitabine. Furthermore no modulation of CDA activity was determined by direct interaction with tivantinib. Conversely, we observed a significant inhibition of tubulin polymerization both after tivantinib and gemcitabine-tivantinib exposure.

Conclusions: Tivantinib displays synergistic cytotoxic activity with gemcitabine, via molecular mechanisms that are independent from CDA, but affect tubulin polymerization. These notions might have an impact on the selection of patients for future trials.

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