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Evaluating the antitumor activity of selonsertib in pancreatic cancer cell lines

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a pathology that ranks seventh among the most common causes of cancer mortality worldwide [1]. Importantly, drug resistance is a major clinical problem for patients with PDAC. Unfortunately, few efficient therapeutic options are available for this type of resistant cancer, and the standard chemotherapy remains gemcitabine or gemcitabine combined with paclitaxel [2,3]. Our research group identified Chitinase-3-Like 1 (CHI3L1) as being involved in reducing PDAC drug response in vitro [4], suggesting that combining CHI3L1 inhibitors with conventional chemotherapy may overcome PDAC drug resistance. **Objective:** The main objective is to assess the antitumor and chemosensitising effect of selonsertib (a compound currently in phase III clinical trial for the treatment of diabetic nephropathy and kidney fibrosis) on PDAC sensitive and resistant cell lines. Methods: The effect of gemcitabine (positive control) and selonsertib in the PANC1 PDAC cell line was evaluated with the Sulforhodamine B (SRB) assay. Then, the GI50 concentrations (that inhibits 50% of cell growth) after 48 h incubation were determined from the drug response curves. The effect of selonsertib in a resistant counterpart cell line to PANC1 (PANC1-CDR resistant to gemcitabine, recently established in our laboratory, unpublished results) is being evaluated. **Results:** Our data demonstrated that gemcitabine inhibited the growth of PANC1 cells with a GI50 of 0.76±0.1 µM, which is in agreement with the literature. Interestingly, selonsertib efficiently inhibited the growth of PANC1 cells with a GI50 of 9.5±3.3 µM. The effect of selonsertib on the growth of the resistant PANC1-CDR cell line is being determined. **Conclusions:** In this work, we showed the antitumor potential of selonsertib in the PANC1 PDAC cell line (that harbors KRAS mutation and has an aggressive phenotype). Future work will evaluate the effect of selonsertib on other PDAC cell lines (with different genetic backgrounds) and on the PANC1-CDR resistant cell line. Moreover, we expect to disclose the chemosentitizing effect of selonsertib in PDAC sensitive and resistant cells.

Keywords: antitumor activity; CHI3L1; combination therapy; pancreatic cancer; selonsertib

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