Selenium selenite presents a great antitumor activity against pancreatic cancer by AIF activation and potentiates gemcitabine by p38 pathway: in vitro and in vivo study

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BACKGROUND AND AIMS

Sodium selenite is a selective cytotoxic agent for tumor cells. This cytotoxicity is due to the depletion of reduced glutathione and thioredoxin, leaving the cell devoid of defense mechanisms against oxidative stress. Pancreatic cancer is the ninth most frequent and the fourth deadliest. One of the main causes of its high mortality is the low response to treatment (chemotherapy), which makes it necessary to develop new therapeutic strategies. The objective of this study is to demonstrate the in vitro and in vivo antitumor capacity of sodium selenite, as well as its chemosensitizing character when used together with gemcitabine (GMZ).

METHODS

The methodology was based on the use of pancreatic adenocarcinoma cell lines PANC-1 and Pan02 (in vitro studies), which were exposed to selenite and selenite + GMZ in monolayer culture. In vivo studies were performed by generating tumors in C57BL mice after subcutaneous inoculation of the Pan02 line. In addition, immunofluorescence, Western-Blot and migration studies were performed to elucidate the molecular mechanisms by which sodium selenite acts. Finally, the effect of the treatment on cancer stem cells (CSCs) derived from tumor lines was assessed.

RESULTS

IN VITRO

Figure 1. Graphs of cell viability and IC50 values of sodium selenite and GMZ in PANC-1 and Pan02 cells. These tumor cells were exposed to sodium selenite and GMZ at different doses for 72 h.

Figure 2. Combination index (CI) of sodium selenite and GMZ in PANC-1 and Pan02 cells (CI < 1, antagonists; CI > 1, synergistic). GMZ (gemcitabine), SEL (sodium selenite). It can be seen a synergistic relationship between selenite and GMZ in the majority of studied combinations.

Figure 3. Survival index (SI) of sodium selenite and GMZ in PANC-1 and Pan02 cells (100% viability, 0% viability). At 24 h, the combination of both can be observed a great increase in phospho-p38 expression in combined therapy respect to monotherapies, which indicates an important role of the activation of p38 in tumors treated by combined therapy.

Figure 4. Western blot results for the expression of phospho-p38 in PANC-1 and Pan02 cells with sodium selenite (SEL) alone, GMZ and with the combination of both. It can be observed a great increase in phospho-p38 expression in combined therapy respect to monotherapies, which indicates an important role of the activation of p38 in tumors treated by combined therapy.

Figure 5. Migration studies with wound healing assay in PANC-1 and Pan02 cells with selenite and GMZ at different doses. Selenite depletion tumor cell migration in both PANC-1 and Pan02 cells. GMZ in monotherapy paradoxically increases tumor cell migration in monotherapy.

IN VIVO

Figure 6. Studies with cancer stem cells (CSCs) spheroids treated with sodium selenite (SEL), GMZ and combinations of both in PANC-1 and Pan02 cells. The combination of SEL and GMZ induces in a significant way the formation of CSCs spheroids in both PANC-1 and Pan02 tumor cells.

Figure 7. Graphical representation of pancreatic tumor volume growth (PANC-1) in C57BL/6 mice. Mice were treated with sodium selenite, GMZ and sodium selenite + GMZ. Control animals were used as controls. Data are presented as mean ± SD (n = 6). ** Significant inhibition of tumor volume growth comparing treatments among them and comparing treatments with controls (p<0.01).

Figure 8. Kaplan-Meier curves of mice from different treatment groups. Survival data was analyzed according to mice survival in each group. Comparison between groups of treatment was performed using the log-rank test.

Figure 9. H&E histopathological analysis of mice after different treatment protocols (5 and 10 cycles). Images were obtained 6 h after injection of panitumab.

CONCLUSIONS

In conclusion, sodium selenite is a potential agent for the improvement of pancreatic cancer treatment and could be considered for future clinical trials in humans.

REFERENCE


No conflicts of interest to declare