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Effect of Camptothecin nanosponges on anaplastic thyroid cancer models

Thyroid cancers are the most common tumors of endocrine origin and, over the past 10 years, their incidence has increased globally. Anaplastic carcinoma of the thyroid (ATC) is one of the most lethal human malignant cancers with a median survival of 6 months from the diagnosis. To date there is no treatment that can successfully change the course of the ATC. Nanomedicine has enormous potential to improve the accuracy of cancer therapy, by enhancing drugs availability and stability, decreasing their effective dose and by reducing their side effects. Camptothecin (CPT) is an inhibitor of DNA Topoisomerase-I with a wide spectrum of anticancer activities. The use of CPT has been hampered by a poor aqueous solubility and a high degradation rate. Previously, we have reported that CPT encapsulated in β-cyclodextrin-nanosponges (CN-CPT) has an increased solubility, is protected from degradation and displays an enhanced inhibitory effect on the prostate tumor cells both *in vitro* and *in vivo*. The aim of this study was to evaluate whether β-cyclodextrin nanosponges carriers can display their antitumoral efficacy on two anaplastic thyroid carcinoma cell lines (Cal-62 and BTH-101) and on a thyroid tumor model *in vivo*. Cell proliferation was evaluated by MTT assay and obtained data revealed that CN-CPT significantly inhibited cell viability, with a very significant effect of 60% of inhibition at the concentrations $2x10^{-9}$M and 10^{-9}M after 72h, compared to 25% displayed by free CPT on BTH-101 and similar results were obtained on Cal-62 ($p<0,05$). The inhibition of clonogenic capacity and cell cycle progression validates previous data. CN-CPT demonstrated its anti-metastatic potential by inhibiting tumor cell adhesion to endothelial cells (10^{-8}M – 10^{-11}M), with a 60% of inhibition compared to 20% displayed by the free drug at 10^{-9}M on both cell lines, and migration ($2x10^{-8}$M – $2x10^{-9}$M), with a 60% of inhibition compared to 6% exhibited by free CPT at $2x10^{-8}$M on BTH-101 ($p<0,05$). The effects on intracellular signalling were assessed by Western blot analysis and they revealed an inhibition of the Rho family activator β-PIX expression and of the MAPK Erk1,2 phosphorilation. Finally, the effects of CN-CPT were evaluated *in vivo,* on an orthotopic model of the tumor obtained by injecting Cal-62 cells into the thyroid lobe of female NSG mice. Mice were injected with PBS (n=5), 1 mg/kg CPT (n=7) or CN-CPT (n=7) at day 10 after tumor challenge. The median survival period for PBS, CPT and CN-CPT groups were 28, 25 and 38 days, respectively. The differences in survival between the CN-CPT group compared with the control group were statistically significant when compared by log-rank test ($p<0,05$). Only CN-CPT inhibited the growth of orthotopic anaplastic thyroid carcinoma xenografts and produced statistically significant differences in mean tumor volume when compared with the control group. Only CN-CPT was able to inhibit the development of lung metastasis. In the majority of tumors from CN-CPT-treated mice, the pattern of Ki67 positive nuclei was heterogeneous, featuring low percentage of positive cells in the core of the lesion and high levels in the peripheral area on the invasive edge. By contrast, tumors from PBS- and CPT-treated mice showed homogeneously distributed Ki-67 staining on the tumor area.

This work extends those observations showing that β-cyclodextrin nanosponges appear to be a promising tool also for the treatment of anaplastic thyroid cancers.

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