Cytotoxic effect of Camptothecin nanosponges on anaplastic thyroid cancer cells *in vitro* and on orthotopic xenograft tumors *in vivo*

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Cancers of the thyroid 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*. In the present study, it has been evaluated 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*. It has been revealed that CN-CPT significantly inhibited cell viability, in the range of concentrations $2x10^{-10}$M - $6x10^{-8}$M, showing a faster and enhanced effect compared to free CPT. The inhibition of clonogenic capacity and cell cycle progression validates the previous obtained data. Migration, which allows cancer cells to metastazise to distant organs, is a key process in tumor progression and it is supported by cell ability to adhere to the endothelial cell layer and extravasate. CN-CPT demonstrated its anti-metastatic potential by inhibiting tumor cell adhesion to endothelial cells (10^{-11}M – 10^{-8}M) and migration ($6x10^{-8}$M – $6x10^{-9}$M). 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, *in vivo* obtained data show that CN-CPT, in comparison with the unencapsulated drug, significantly inhibited the growth and the volume of orthotopic ATC xenografts in SCID/beige mice without apparent toxic effects. This work extends those observations showing that β-cyclodextrin nanosponges appear to be a promising tool for the treatment of anaplastic thyroid cancers.

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