EFFECTS OF LIPOSOME-ENCAPSULATED PYRAZOLO-PYRIMIDINE DERIVATE ON THE GROWTH OF HUMAN THYROID CANCER CELLS

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Identification of effective systemic antineoplastic drugs against anaplastic thyroid carcinomas has particularly important implications. In fact, the efficacy of the chemotherapeutic agents presently used in these tumours, is strongly limited by their low therapeutic index. In this study, the effects of Si 34, a novel pyrazolopyrimidine derivative previously selected for its inhibitory activity toward the Src family tyrosine kinase, were evaluated against a human thyroid tumour cell line. ARO cells, derived from a thyroid anaplastic carcinoma, were exposed to different concentrations of the drug diluted in DMSO or entrapped within a pegylated liposomal delivery system to improve the drug antitumoral activity. Liposomes formulations were made up of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine/cholesterol/1,2-distearoyl-sn-glycero-3-phosphoethanolamine-MPEG 2000 (6:3:1 molar ratio). Cell growth was measured with cell counts and MTT test, and viability was assessed by trypan blue dye exclusion assay. Apoptosis in treated cells was determined by western blot analysis of PARP cleavage and immunofluorescent identification of apoptotic nuclei with Hoechst 33258.
In ARO cells, dose-response experiments showed a growth inhibitory effect of Si 34 which appeared at 5 μM and was maximal at 10 μM (25% and 75% reduction of cell counts compared with control cells treated with corresponding concentrations of DMSO alone). Treatment of ARO cells with Si 34 at 5 and 10 μM increased also cell mortality (compared to that observed in controls) approximately 4- and 7-fold, respectively. At concentrations that increased cell mortality, neither biochemical (evidence of PARP cleavage) or morphological characteristics of apoptosis (Hoechst 33258 staining) were detected in the cells treated with Si 34. When the compound was encapsulated in liposomes, a significant effect on both cell growth and mortality was observed by using earlier exposure time (24 h).
These results demonstrate the efficacy of inhibiting the growth of human thyroid tumor cells of these novel pyrazolopyrimidine compound. Moreover, the incorporation within liposomes enhances the drug cytotoxic effect with respect to free compounds, thus suggesting a more effective drug uptake inside the cells and the possibility to avoid the use of DMSO. If confirmed *in vivo*, such formulations of this compound may be tested in clinical trials for the treatment of human anaplastic thyroid tumors.