IN VITRO AND IN VIVO ANTINEOPLASTIC EFFECTS OF A NOVEL PLATINUM BIOCONJUGATE USING A BIOCOMPATIBLE POLYMERIC MATRIX

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Cisplatin is one of the most effective anticancer agents. However, drawbacks such as the poor selectivity between malignant and normal cells, leading to severe toxic effects, and the presence of intrinsic or acquired resistance severely limit the efficacy of platinum-based chemotherapy. Recently, it has been shown that "drug targeting and delivery" methods, based on drug conjugation to agents with selective access to tumors, may be a interesting strategy to improve the therapeutic index of platinum derivatives. In the present study, a water-soluble, biocompatible polymer, suitably modified for Pt coordination, was used as selective carrier for a cytotoxic Pt-fragment $K[PtCl_3NH_3]$, previously selected from a series of charged Pt-complexes. A nanosphere (ZN2) core-shell-like bioconjugate was obtained from a poly-metacrylate (PMMA) with a shell with positively charged quaternary ammonium groups, which form ionic couples with the negatively charged $[PtCl_3NH_3]^-$. The effects of the free complex and of the resulting polymer conjugate(PtZN2) were assessed on an *in vitro* model, represented by the B16 murine melanoma cell line, and an *in vivo* model, obtained by the subcutaneous injection of B16 cells in C57BL76 mouse, and compared with the effects of cisplatin. Cytotoxicity studies, performed by the MTT assay, indicate that PtZN2 and cisplatin exert similar cytotoxic effects on B16 cells, with IC_{50} values of 0.83 ± 0.14 μM and 0.41 ± 0.14 μM (mean±s.e.m) respectively, while the free $[PtCl_3NH_3]^-$ was significantly less toxic (IC_{50} = 10.47 ± 1.31 μM). *In vivo* studies showed that PtZN2 (25 and 50 mg/Kg/die for 5 days) is able to decrease tumor growth to a similar extent as cisplatin (5 mg/Kg/die for 5 days) and significantly more effectively than $K[PtCl_3NH_3]$. *In vivo* efficacy was found to correlate with Pt intratumor accumulation, as evaluated by ICP-MS following tumor mineralization. Survival curves indicate a 100% of survival in PtZN2-treated mice, while the survival rate for cisplatin-treated mice was 40%. PtZN2-treated mice did not show any signs of nephrotoxicity, as evaluated by the measure of creatinine plasma levels. Overall, our results indicate that PtZN2 has a better therapeutic index as compared to cisplatin and thus could be the starting point for the development of novel platinum bioconjugates.