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In vitro anticancer activity and neurotoxicity of novel heavy metal-based anticancer complexes.

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Cisplatin is one of the most effective metal-based anticancer agents, targeting a large number of solid tumours. Despite its efficacy, cisplatin treatment is still limited by severe side effects such as neuro-, hepato- and nephro-toxicity and by resistance phenomena, only partially overcome by the use of new platinum drugs (i.e. oxaliplatin and carboplatin). These problems have stimulated the research and development of alternative therapeutic strategies based on different heavy metals. In this work we investigated the in vitro activity and neurotoxicity of three anticancer complexes: [Cu(PTA)4]PF6, [Cu(thp)4]PF6 and [Au(PTA)4]PF6. Neurotoxicity was evaluated by embryonic rat dorsal root ganglia (DRG) organotypic culture model. Furthermore the extent of proteasome inhibition in rat embryonic DRG neurons was evaluated by fluorimetric assay. After 48 hours of treatment, both copper-based compounds were not neurotoxic even at higher concentrations with respect to the IC50 obtained in A549 and IGROV-1 human cancer cells while [Au(PTA)4]PF6 was neurotoxic at lower concentration than IC50 in cancer cell lines tested. Since the ubiquitin-proteasome system has been identified as molecular target in cancer cells for the heavy metal based-drug, we evaluated their ability to affect the proteasome machinery in DRG neurons. The copper-based compounds, that are not neurotoxic, do not inhibit proteasome activity in DRG neurons. On the contrary, the neurotoxic complex [Au(PTA)4] PF6, induces a significant inhibition of proteasome activity even at concentration lower than the IC50.

Furthermore, based on the content in heavy metal-based atoms, the complexes used in this study are suitable candidates for Photon Activation Therapy (PAT). Pretreatment of IGROV-1 cells with [Cu(PTA)4]PF6 induces an increase cell death with respect to drug or synchrotron (SR) alone. Furthermore the SR/[Cu(PTA)4]PF6 combinational treatment induced an increase in DNA damage with respect to single treatments.

Our results, together with the low IC50 of the copper compounds compared to the one observed for cisplatin, suggest them as promising compounds in anticancer treatment.

Keywords

Heavy metal-based complexes, neurotoxicity, proteasome inhibition, photon activation therapy.

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