Innovative antitumoral platinum (II) compounds as chemotherapeutic and immunotherapeutic agents

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Background: Platinum (II)-based drugs are widely used chemotherapeutic agents. However, as they have many side effects, numerous platinum (Pt) derivatives have been developed during the last years. Furthermore, some cancer treatments including Pt compounds are able to activate the antitumor immune response by inducing a particular cell death: the immunogenic cell death (ICD). This process is characterized by the exposure of the endoplasmic reticulum chaperone calreticulin (CRT) at the cell surface as well as the release of ATP and non-histone chromatin-binding protein high mobility group box 1 (HMGB1) which serve as immunostimulatory damage-associated molecular patterns (DAMPs) and increase the antitumor immune response. Based on these considerations, we decided to focus on N-heterocyclic carbene Pt complexes associated with the transfection agent polyethylenimine (PEI) to create multivalent cationic platinum compounds (NHC-Pt(II)-PEI).

Materials and methods: We investigated the cytotoxic activity of our derivatives in vitro by flow cytometry and in vivo in different mouse models. Then, we evaluated by an IFN- γ ELISpot assay the potential implication of the immune response on the NHC-Pt(II)-PEI in vivo effect in immunocompetent mice bearing tumors treated with Pt particles. Moreover, we assessed if NHC-Pt(II)-PEI were able to induce ICD by analysing the exposure of CRT at the cell surface by flow cytometry. We also combined our Pt derivative with immune danger signals, like polyinosinic: polycytidylic acid (polyI:C), to enhance this effect.

Results: Our conjugate displayed a good cytotoxic activity in vitro on several cancer cell lines as well as an antitumor effect in vivo in immunodeficient [1] and immunocompetent mice, in the same range than clinical used Pt drugs, but with fewer side effects. First results showed exposure of CRT at the cell surface of cancer cells treated with NHC-Pt(II)-PEI, suggesting the induction of ICD. To improve the antitumor immune response, we associated NHC-Pt(II)-PEI with polyI:C and found that both compounds formed a complex and we are now evaluating its cytotoxicity and effect on the immune response.

Conclusions: Altogether our results reveal the possibility of creating Pt derivatives that can be used as chemotherapeutic agents by killing tumor cells and as immunotherapeutic agents by triggering the antitumor immune response.

Reference

1. Chekkat N, Dahm G, Chardon E, Wantz M, Sitz J, Decossas M, Lambert O, Frisch B, Rubbiani R, Gasser G, Guichard G, Fournel S, Bellemin-Lapomnaz S. N-heterocyclic carbenepolyethylenimine platinum complexes with potent in vitro and in vivo antitumor efficacy. *Bioconjug Chem.* 2016; 27: 1942-1948

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