

Immunomodulatory and cytotoxic effects of palladium(II) complexes in Ehrlich ascites tumor

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Inorganic compounds are used in cancer chemotherapy. Cyclometallated Pd(II) are reactive inorganic complexes used in studies to investigate their antitumor potential and interaction with the immune system. In this study, cytotoxic and immunological response induced by two organopalladated complexes [Pd(dmba)(π -NCS)]₂ (1), [Pd(dmba)(NCS)(dppp)] (2), and *cis*-platin, as standard, were investigated in mice bearing Ehrlich Ascites Tumor (EAT). Previously, their cytotoxic potential and IC₅₀ were evaluated towards EAT cells and on macrophage culture. The tumor-bearing mice were divided into five groups of eight animals, and inoculated intraperitoneally with 1 mL of the organopalladated compounds (1) or (2) at the concentration of 1x10⁻³ M, diluted in PBS/DMSO 0.3%, or 10 mg/kg (LD₅₀) of *cis*-platin or 1 mL of DMSO 0.3% (vehicle control) or 1 mL of PBS (tumor control). The following parameters were evaluated: percentage of tumor cells in the peritoneal exudate, nitric oxide (NO) (Griess reagent after nitrate reductase treatment) and tumor necrosis factor-alpha (TNF- α bioassay) released in mice serum, and increase in life span. All data suggest that structural differences between complexes (1) and (2) influence the cytotoxic and immunological activities. The compound that contains the dppp ligand (2) demonstrated antitumoral properties based on *in vitro* cytotoxic effects on EA7 cells (IC₅₀ = 5.29 \pm 3.89 μ M) and *in vivo* (tumor cells in

the peritoneal exudate = $24.86 \pm 4.26\%$) when compared with cis-platin (IC50 = 33.77 ± 2.29 and tumor cells percentage = $27.14 \pm 4.10\%$). Concerning immunomodulatory response, we observed production of NO (9.18 ± 1.06 $\mu\text{mol/mL}$) whereas TNF- α was decreased (67.27 ± 5.89 units/mL of serum) in mice serum. The life span was increased, similarly to the group treated with *cis-platin*. The complex (2) has a potential role as an antitumor agent because it showed synergic effect between cytotoxic and immunomodulatory activities of the host.

Key words: PD (II) complexes, *cis-platin*, Ehrlich ascites tumor, macrophages, nitric oxide, tumor necrosis factor- α