CISPLATIN NEUTRON ACTIVATED FOR GLIOMA TREATMENT

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Gliomas are the most common and most deadly primary tumours found in the brain and carry a particularly poor prognosis. This neoplasm infiltrates diffusely into regions of the normal brain rendering total surgical extirpation impossible. Because of its location beyond the reach of locai control when it is first detected, these tumours have frustrated almost every attempt at successful therapy. The identification of novel therapeutic agents able to inhibit the growth of these tumours is therefore essential to improve the prognosis of glioma patients. The antitumor activity of cis-dichlorodiamineplatinum(II) (CDDP, cisplatin) was discovered by Rosenberg et al [1]. However the effectiveness of cisplatin against recurrent tumours is less than that against primary tumours [2], probably because of the presence of a population of cisplatin resistant cells. Additionally, in spite of its strong anticancer potency, chemotherapy with cisplatin associates many serious side effects, such as nephrotoxicity. An increase of anticancer potency has been observed by concomitant combination of irradiation and chemotherapeutic agents, including cisplatin [3,4]. This synergy enables the reduction of cisplatin dose, diminishing the side effects. Ionising radiation interacts with tissue, thereby damaging DNA and other chemical structures. One of the methods of radiosensitisation of tumour cells is concomitant application of chemotherapeutic agents that alter DNA sensitivity to irradiation. Cisplatin, likewise other platinum-based anticancer drugs, appear to be excellent radiosensitizer [5]. By introducing radionuclides into the cells during the treatment with cisplatin, internal radiation and chemotherapy are possible at a low rate of toxicity. Because of its insertion into DNA, cisplatin itself is a optimal carrier molecule for the radionuclide once cisplatin and the radioactivity will act on the specific target. The proposal of this work was to investigate the antitumoral effect of neutron activated cisplatin at the TRIGA MARK-I IPR-RI and verify if the low-dose continuous internal radio-chemotherapy produces additive effects on malignant glioblastoma cells.

Neutron activation was done on cisplatin as described by Leal et al.[6]. Briefly, cisplatin was irradiated at 100kW during 8 hours into polyethylene flasks carried out on a TRIGA MARK-I IPR-R1 nuclear reactor at the Centro de Desenvolvimento da Tecnologia Nuclear - Comissão Nacional de Energia Nuclear (CDTN-CNEN), Brazil. Chemical stability after neutron activation was evaluated on gel filtration chromatography. Antitumoral activity was assessed by in vitro cytotoxicity and proliferation assays on malignant glioblastoma cells. Glioblastoma cells were incubated with different concentrations of non-radioactive or radioactive cisplatin (cisplatin *). Cytotoxicity and apoptosis were evaluated after 48 h treatment and anti proliferative effect was evaluated by clonogenic assay.

The final specific activity for cisplatin* after neutron activation was of approximately 87kBq mg^{-1}. Native cisplatin was cytotoxic for glioblastoma cells in a dose dependent manner (IC_{50}= 4.9 x10 $^{-6}$M). Treatment with neutron activated cisplatin (IC_{50}= 1.8 x10 $^{-6}$M) proved to be more potent than native cisplatin, and irradiation alone (IC_{50} ~ 6 Gy).

The results obtained in the present work indicate that cisplatin* kept its chemical stability upon neutron activation and was a very potent radiosensitizer evoking a supra additive effect. Treatment with internal radio-chemotherapy based on neutron activated cisplatin became possible a significant reduction of the cisplatin concentration required for effective inhibition of glioblastoma growth. Therefore production of radioactive cisplatin based on neutron activation may constitute a good strategy for the preparation of novel therapy for malignant glioblastoma.

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