An *in vivo* study to analyse the potential of ^{188}Re-PEI-MP for metabolic radiotherapy of bladder carcinoma

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Introduction: ^{188}Re is a promising radionuclide for metabolic therapy because of the emission of high energy beta-particles. The development of water-soluble polymers such as PEI-MP (polyethyleneimine, functionalised with methylphosphonate groups) that might be labeled with ^{188}Re are recent approaches, with a strong potential for metabolic radiotherapy. The aim of this study was to evaluate the efficacy of ^{188}Re-PEI-MP, as therapeutic agent for bladder carcinoma.

Material and Methods: To proceed with the *in vivo* studies, it was investigated the cytotoxicity of PEI-MP in bladder carcinoma cell line (CRL-1472) using the MTT test for different concentrations of PEI-MP (1 µM to 1000 µM) and incubation times (24h, 48h, 72h and 96h). Radiochemical purity of ^{188}Re-PEI-MP was achieved using microchromatography. The *in vivo* studies were performed using four groups of Balb/c nu/nu mice: two normal groups injected with Na^{188}ReO$_4$ (n=18) and ^{188}Re-PEI-MP (n=17) respectively; two with bladder carcinoma xenotransplants injected with Na^{188}ReO$_4$ (n=8) and ^{188}Re-PEI-MP (n=12) respectively. When tumor reached the appropriate volume, Na^{188}ReO$_4$ and ^{188}Re-PEI-MP were administered by an intravenous injection in the tail vein (22-37MBq), with the animal anesthetized and previously placed on the gamma

camera detector. Immediately, a dynamic acquisition followed, with a 128x128 matrix for 10 min (20 frames, 30 seconds). Static images (2 min) were performed with a 256x256 matrix, where each of the four groups was divided into two groups, of which one was imaged at 120 minutes, and the other at 240 minutes. For biodistribution proposes, mice were euthanized 2 and 4 hours after injection and organ samples where weighted and counted in a well-counter to obtain percentage injected activity per gram of organ (%ID/g).

Results: The MTT assay showed that PEI-MP is not cytotoxic. The radiochemical purity of ^{188}Re-PEI-MP was ≥90%. Biodistribution results, with $Na^{188}ReO_4$, showed a higher uptake by the thyroid, bladder and stomach, following a normal biodistribution. The biodistribution with ^{188}Re-PEI-MP showed that the excretion of this complex occurs primarily through the renal system, with a small fraction being eliminated by the hepatobiliary system. Tumor/muscle ratio was greater than 1.5.

Conclusions: ^{188}Re-PEI-MP seems to be promising in the treatment of bladder cancer.

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