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

Aim: The aim of this study was to evaluate the efficacy of ^{188}Re-PEI-MP, as therapeutic agent for osteosarcoma and bladder carcinoma using an *in vivo* model.

Material and Methods: To proceed with the *in vivo* studies, it was investigated the cytotoxicity of PEI-MP in osteosarcoma cell line (MNNG-HOS) and 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 (ITLC-SG/acetone and W3MM/citrate 1M). The *in vivo* studies were performed using six groups of Balb/c nu/nu mice: two normal groups were injected with Na^{188}ReO$_4$ (n=18) and ^{188}Re-PEI-MP (n=17) respectively; two with osteosarcoma xenotransplants were injected with Na^{188}ReO$_4$ (n=17) and ^{188}Re-PEI-MP (n=19) respectively; and two with bladder

carcinoma xenotransplants were 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. In mice with osteosarcoma tumor/muscle ratio was greater than 1.0, and for mice with bladder carcinoma the tumor/muscle ratio was greater than 1.5.

Conclusions: The ^{188}Re-PEI-MP seems to be promising in the treatment of both types of cancer, but with a greater potential for bladder cancer.

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