A NEW POSSIBLE APPROACH FOR THERAPY AND FOLLOW UP OF BLADDER CANCER

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Introduction: The polymer PEI-MP (polyethylenimine, functionalised with methylphosphonate groups) that might be labelled with 188Re and 99mTc, have a strong potential for metabolic radiotherapy and diagnosis, respectively. The aim of this study was to evaluate the efficacy of 188Re-PEI-MP as therapeutic agent for bladder carcinoma and 99mTc-PEI-MP for its follow up.

Material and Methods: Cytotoxicity of PEI-MP was investigated 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), and flow cytometry for a concentration of 1000 µM of PEI-MP (24h). Radiochemical purity of 188Re-PEI-MP and 99mTc-PEI-MP was achieved using ascending microchromatography. Cellular uptake studies were performed using the complexes 188Re-PEI-MP, 99mTc-PEI-MP, Na188ReO4 and Na99mTcO4. Cell samples were collected during four hours, centrifuged to separate supernatant and pellet. Subsequently, the radioactivity of each portion was counted to determine percentage of uptake. The in vivo studies were performed using eight groups of Balb/c nu/nu mice: four normal groups injected with Na188ReO4, 188Re-PEI-MP, Na99mTcO4 and 99mTc-PEI-MP and four with bladder carcinoma xenotransplants injected with the same complexes. When tumour reached the appropriate volume, radiopharmaceuticals were administered by an intravenous injection in the tail vein (22-37MBq), with the animal anesthetized and previously placed on the gamma camera detector. After injection of the radiopharmaceuticals, were acquired dynamic and static images for 2 and 4 hours. 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 and flow cytometry tests showed that PEI-MP is not cytotoxic. The radiochemical purity of $^{188}$Re-PEI-MP and $^{99m}$Tc-PEI-MP was ≥85%. The uptake studies demonstrated that the uptake was higher for $^{188}$Re-PEI-MP and $^{99m}$Tc-PEI-MP in relation to their controls, and higher for $^{188}$Re-PEI-MP e relation to $^{99m}$Tc-PEI-MP. Biodistribution results, with Na$^{188}$ReO$_4$ and Na$^{99m}$TcO$_4$, showed a higher uptake by the thyroid, bladder and stomach, following a normal biodistribution. The biodistribution with $^{188}$Re-PEI-MP and $^{99m}$Tc-PEI-MP showed that the excretion of these complexes occurs primarily through the renal system, with a small fraction being eliminated by the hepatobiliary system. Tumour/muscle ratio for $^{188}$Re-PEI-MP was greater than 1.5.

**Conclusions:** Considering the results, $^{188}$Re-PEI-MP seems to be promising in the treatment of bladder cancer. Following the same biodistribution as $^{188}$Re-PEI-MP, $^{99m}$Tc-PEI-MP seems to be optimal for diagnosis and follow up of therapy.

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