

Evaluation of the potential of ^{188}Re -PEI-MP for therapy of bladder carcinoma and $^{99\text{m}}\text{Tc}$ -PEI-MP for diagnosis and follow up

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Introduction: The development of water-soluble polymers such as PEI-MP (polyethyleneimine, functionalised with methylphosphonate groups) that might be labeled with ^{188}Re (emits of high energy beta particles) and $^{99\text{m}}\text{Tc}$ are recent approaches, with a strong potential for metabolic radiotherapy and diagnosis, respectively. The aim of this study was to evaluate the efficacy of ^{188}Re -PEI-MP as therapeutic agent for bladder carcinoma and $^{99\text{m}}\text{Tc}$ -PEI-MP for its diagnosis and follow up.

Material and Method: 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). Radiochemical purity of ^{188}Re -PEI-MP and $^{99\text{m}}\text{Tc}$ -PEI-MP was achieved using ascending microchromatography. Cellular uptake studies were performed with CRL-1472 cell line. ^{188}Re -PEI-MP, $^{99\text{m}}\text{Tc}$ -PEI-MP, $\text{Na}^{188}\text{ReO}_4$ or $\text{Na}^{99\text{m}}\text{TcO}_4$ were added to cell suspension (2 million cells/mL). 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 six groups of Balb/c nu/nu mice: four normal groups injected with $\text{Na}^{188}\text{ReO}_4$ (n=18), $^{188}\text{Re-PEI-MP}$ (n=17), $\text{Na}^{99\text{m}}\text{TcO}_4$ (n=10) and $^{99\text{m}}\text{Tc-PEI-MP}$ (n=10), respectively; two with bladder carcinoma xenotransplants injected with $\text{Na}^{188}\text{ReO}_4$ (n=8) and $^{188}\text{Re-PEI-MP}$ (n=12), respectively. When tumor reached the appropriate volume, $\text{Na}^{188}\text{ReO}_4$, $^{188}\text{Re-PEI-MP}$, $\text{Na}^{99\text{m}}\text{TcO}_4$ or $^{99\text{m}}\text{Tc-PEI-MP}$, 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 six groups was divided into two groups, of which one was imaged at 120 minutes, and the other at 240 minutes. For biodistribution purposes, mice were euthanized 2 and 4 hours after injection and organ samples were weighed and counted in a well-counter to obtain percentage injected activity per gram of organ (%ID/g).

Results and Discussion: The MTT assay showed that PEI-MP is not cytotoxic. The radiochemical purity of $^{188}\text{Re-PEI-MP}$ and $^{99\text{m}}\text{Tc-PEI-MP}$ was $\geq 85\%$. *In vitro* results demonstrated that the uptake was relatively higher for $^{188}\text{Re-PEI-MP}$ and $^{99\text{m}}\text{Tc-PEI-MP}$ than for $\text{Na}^{188}\text{ReO}_4$ and $\text{Na}^{99\text{m}}\text{TcO}_4$, respectively, remaining constant over time (4h). Biodistribution results, with $\text{Na}^{188}\text{ReO}_4$ and $\text{Na}^{99\text{m}}\text{TcO}_4$, showed a higher uptake by the thyroid, bladder and stomach, following a normal biodistribution. The biodistribution with $^{188}\text{Re-PEI-MP}$ and $^{99\text{m}}\text{Tc-PEI-MP}$ showed that the excretion of these complexes occurs primarily through the renal system, with a small fraction being eliminated by the hepatobiliary system. Tumor/muscle ratio for $^{188}\text{Re-PEI-MP}$ was greater than 1.5.

Conclusions: Given to its biodistribution and tumor/muscle ratio, $^{188}\text{Re-PEI-MP}$ seems to be promising in the treatment of bladder cancer. Following the same biodistribution as $^{188}\text{Re-PEI-MP}$, $^{99\text{m}}\text{Tc-PEI-MP}$ seems to be optimal for diagnosis and follow up of therapy.



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