A preclinical evaluation on the radiohybrid tandem [^{18}F]La- and [^{225}Ac]Ac-rhPSMA-10.1 for targeted alpha therapy of prostate cancer

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Background: Prostate-specific membrane antigen (PSMA)-targeted alpha therapy emerged as a promising treatment option for advanced metastatic castration-resistant prostate cancer. Imaging and dosimetry of ^{225}Ac-PSMA ligands remain challenging because of suboptimal decay properties for SPECT. Radiohybrid (rh) ligands can be labelled with a radiometal for therapy or ^{18}F for imaging. The ^{18}F-labelled ligand, complexed with the natural metal, displays the identical chemical structure and pharmacokinetics compared to the therapeutic agent. In the present study, we therefore evaluated a rh ^{225}Ac-labelled PSMA-targeted ligand ([^{225}Ac]Ac-rhPSMA-10.1). [^{18}F]La-rhPSMA-10.1, complexed with natural lanthanum, mimicking the complex structure of ^{225}Ac, was investigated as a corresponding PET imaging agent.

Methods: Cell studies (affinity, internalization, externalization) of [^{225}Ac]Ac-rhPSMA-10.1 and [^{18}F]La-rhPSMA-10.1 were performed on LNCaP and PC3Pip cells in comparison to the references [^{225}Ac]Ac-PSMA-I&T and [^{225}Ac]Ac-PSMA-617. For evaluation of the efficacy, LNCaP tumour-bearing mice (groups n=6) received a single injection of different doses of [^{225}Ac]Ac-rhPSMA-10.1 (20, 30 and 40 kBq; 0.2-0.4 nmol), [^{225}Ac]Ac-PSMA-I&T (20 kBq; 0.2 nmol), versus non-radioactive rhPSMA-10.1 (control; 1 nmol) and were followed for 60 days. The pharmacokinetics of [^{18}F]La-rhPSMA-10.1 were determined via PET-imaging and ex-vivo biodistribution analysis (10 min-4 h p.i.).

Results: [^{225}Ac]Ac-rhPSMA-10.1 (4-7 MBq, 0.1-0.2 MBq/nmol) and [^{18}F]La-rhPSMA-10.1 (1-4 GBq, 50±4% radiochemical yield, 10-30 MBq/nmol) were prepared with ≥95% radiochemical purity. [^{225}Ac]Ac-rhPSMA-10.1 and [^{18}F]La-rhPSMA-10.1 displayed nearly identical cellular uptake and retention, falling in a similar range as the references. For all injected activities, tumour volumes declined in a similar way from day 7 p.i. onwards. At day 28, mean tumour volume relative to baseline had decreased by 39±17% for [^{225}Ac]Ac-PSMA-I&T; and 44±25%, 54±21%, 54±12% for 20, 30 and 40 kBq [^{225}Ac]Ac-rhPSMA-10.1, respectively. Median survival was 12 d in the control group and was not reached for the 20 and 30 kBq [^{225}Ac]Ac-rhPSMA-10.1 groups. In the 20 kBq [^{225}Ac]Ac-PSMA-I&T and 40 kBq [^{225}Ac]Ac-PSMA-rhPSMA10.1 groups, two and three mice, respectively, had to be sacrificed due to low body condition scores, resulting in median survival of 59 and 60 days. [^{18}F]La-rhPSMA-10.1 demonstrated fast clearance from background tissues via renal excretion and tumour uptake of 12.8±4.2%ID/g at 10 min, which was maintained over 4 h (12.7±3.1%ID/g).

Conclusion: [^{225}Ac]Ac-rhPSMA-10.1 revealed high anti-tumour efficacy with low side effects at 20 and 30 kBq, highlighting its potential for targeted alpha therapy of prostate cancer. [^{18}F]La-rhPSMA-10.1 showed favourable pharmacokinetics for PET-imaging and further studies on its suitability as a PET-surrogate for [^{225}Ac]Ac-rhPSMA-10.1 have been initiated.

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