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Pre-clinical evaluation of DOTA-conjugated PSMA-inhibitors and their comparison with standard reference Glu-urea-Lys-(Ahx)-HBED-CC

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New theranostic radiopharmaceuticals for rapid visualisation of prostate cancer and the highly effective radioendotherapy are of utmost clinical interest. Since the Prostate-specific membrane antigen (PSMA) is upregulated in nearly all prostate cancers compared with the rather low expression levels in normal tissue, PSMA can be considered as an attractive target for the diagnosis and therapy of prostate cancer. This project is focused on the development and evaluation of a series of linker variations of DOTA conjugated ⁶⁸Ga-PSMA-PET imaging agents. These ligands consist of three principle components: the PSMA binding motif (Glu-urea-Lys pharmacophore), a variable linker and the DOTA chelator. The combination of DOTA with the PSMA targeting inhibitors might open the possibility of using the same vector molecule for imaging and therapeutic purposes due to the similarity of the coordination chemistry of ⁶⁸Ga and that of therapeutic radionuclides such as ⁹⁰Y or ¹⁷⁷Lu. All studied compounds were compared with the clinically used reference Glu-NH-CO-NH-Lys-(Ahx)-HBED-CC. It was reported that the chelator HBED-CC seems to interact advantageously with the binding pocket. The here aimed linker region is designed in order to elucidate the structure-activity relationships (SAR) and to compensate binding potential of HBED-CC. After the formation of the resin immobilized Glu-urea-Lys, the further synthesis of the PSMA binding motif and linker region was performed by solid-phase peptide chemistry. The resulting product was coupled by using the active ester of DOTA. All compounds were analysed using RP-HPLC, MALDI-MS, and NMR. Subsequent ⁶⁸Ga-labeling resulted in a radiochemical yield (RCY) of >97% after 15 minutes at 95 °C for DOTA-conjugated compounds and in a RCY of more than 99% in less than 2 min for the HBED-CC-based compound. In order to select the most promising precursors, in vitro cell binding properties (competitive binding affinity and specific internalization) were studied using the PSMA expressing cell line LNCaP. The tumor-targeting and pharmacokinetic properties were further investigated through in vivo biodistribution studies and dynamic small animal microPET imaging. PET scans and biodistribution data were obtained 1 or 2 hours after injection in BALB/c nu/nu mice bearing LNCaP tumor xenografts. All prepared compounds revealed a high affinity for PSMA on the human prostate cancer cell line LNCaP. Of the library of 25 targeted probes synthesised two were found to bind the cells with low subnanomolar affinity (K_i = 0.07 ± 0.02 nM, and 0.49 ± 0.09 nM, respectively) which was significantly improved in comparison with the HBED-CC-based standard compound (K_i = 12.1 ± 2.1 nM). The inhibition potency investigated by the enzyme-based NAALADase assay confirmed these results. Both mentioned DOTA-conjugated imaging agents showed a higher specific internalisation of up to 48 % ID/10⁶ cells which is crucial in respect to the tumor targeting properties. Taken together, these two substances showed improved cellular uptake compared to the reference Glu-urea-Lys-(Ahx)-HBED-CC. In addition, differences between the HBED-CC and the DOTA derivatives were observed also in the in vivo organ distribution studies. The lower kidney, liver and spleen values together with the higher tumor uptake were in favor of the DOTA compounds. Time-activity curves obtained from dynamic PET measurements showed prolonged tumor uptake and a faster clearance from the kidneys. Finally, the interaction with the binding pocket and the in vivo tumor-targeting and the pharmacokinetic properties of the DOTA-conjugated compounds were significantly optimized by modification of the linker region. This approach could lead to an improved management of recurrent prostate cancer with one and the same precursor for diagnostic and therapeutic

purpose.

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