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A Unique Matched Quadruplet of Terbium Radioisotopes for PET and SPECT and for alpha- and beta-Radionuclide Therapy: An in vivo Proof of Concept Study with a New Receptor-Targeted Folate Derivative

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Background: Compared to other lanthanides, terbium (Tb) comprises clinically attractive radionuclides such as 152Tb and 155Tb with suitable decay properties for PET and SPECT imaging and 149Tb and 161Tb suitable for targeted alpha- and beta-radionuclide therapy. To evaluate these 4 radioisotopes we employed the folic acid/folate receptor (FR)-targeting strategy which has been thoroughly investigated over years by our group. Thus, the goal of this proof-of-concept study was to produce all 4 Tb-radioisotopes and assess their diagnostic and therapeutic features in vivo when labeled with a folate-based targeting agent.
Methods: 161Tb was produced by irradiation of 160Gd targets with neutrons at Paul Scherrer Institute or Institut Laue-Langevin. After neutron capture, the short-lived 161Gd decays to 161Tb. 149Tb, 152Tb, and 155Tb were produced by proton-induced spallation of tantalum targets, followed by an online isotope separation process at ISOLDE/CERN. The isotopes were purified by means of cation exchange chromatography at PSI. A long-circulating DOTA-folate conjugate (cm09) was radiolabeled with all four Tb-radioisotopes under standard labeling conditions. Biodistribution studies were performed over seven days using 161Tb-cm09. Diagnostic PET/CT (152Tb-cm09) and SPECT/CT (155Tb-cm09 and 161Tb-cm09) and therapy experiments with 149Tb-cm09 and 161Tb-cm09 were performed in KB tumor bearing mice.
Results: Carrier-free Tb-radioisotopes were obtained after purification, with activities ranging from approximately 6 MBq (for 149Tb) to approximately 15 GBq (for 161Tb). The radiolabeling of cm09 was achieved in >96% radiochemical yield for all 4 Tb-radioisotopes. The tissue distribution of 161Tb-cm09 resulted in a high tumor uptake (˜20% ID/g, 24 h p.i.) which was retained over several days. PET/CT and SPECT/CT studies allowed excellent tumor visualization in mice even 24 h after injection of the 152Tb-cm09 and 155Tb-cm09. Targeted radionuclide therapy studies performed with 149Tb-cm09 and 161Tb-cm09 revealed a significant inhibition of tumor growth and a prolonged survival (>1.7-fold and >2-fold) of treated mice compared to untreated controls.
Conclusions: This is the first comprehensive study with all 4 Tb-radioisotopes using one and the same targeting agent (Müller et al. J Nucl Med 2012, in press). Excellent in vivo tumor visualization was enabled with 152Tb-cm09 and 155Tb-cm09 using PET/CT and SPECT/CT. Thus, 152Tb and 155Tb could become ideal diagnostic matches for their therapeutic counterparts 149Tb and 161Tb providing identical chemical properties. Regarding the therapeutic approach, promising results were obtained after application of 149Tb-cm09 and 161Tb-cm09 with respect to a prolonged overall survival of the mice and an effective tumor growth inhibition.
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