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225Ac-labeled girentuximab for targeted alpha therapy of CAIX-expressing renal cell cancer xenografts.

Authors: Robin Merkx, Annemarie Kip, Egbert Oosterwijk, Michael Wheatcroft, Alfred Morgenstern, Frank Bruchertseifer, Peter Mulders, Mark Rijpkema, Sandra Heskamp

Background: Despite progress in the treatment of clear cell renal cell carcinoma (ccRCC), the prognosis of patients with metastasized disease remains poor. Therefore, novel treatment options need to be developed. A rapidly advancing field of interest is targeted radionuclide therapy using α-emitting radionuclides, such as actinium-225 (225Ac). Carbonic anhydrase IX (CAIX) is over expressed in ccRCC and can be targeted effectively using the monoclonal antibody girentuximab. The aim of this preclinical study was to investigate the in vivo tumor targeting properties of 255Ac-labeled girentuximab, and assess the therapeutic efficacy and toxicity in mice.

Methods: Girentuximab was conjugated with DOTA and labeled with 225Ac and its binding to CAIX-expressing SK-RC-52 cells was determined in vitro. Immunodeficient mice bearing subcutaneous SK-RC-52 xenografts were injected intravenously with 30 ug [225Ac]Ac-DOTA-girentuximab (50 kBq). The biodistribution of [225Ac]Ac-DOTA-girentuximab was determined at 24, 72 and 168 hours post injection (p.i.). Subsequently, therapeutic efficacy was evaluated for different doses (3.7, 9.3 and 18.5 kBq) by measuring tumor growth using caliper measurements up to 4 weeks p.i. Toxicity was monitored by measuring body weight. Furthermore, non-tumor bearing mice were used to analyze nephrotoxicity by immunohistochemistry and [99mTc]Tc-DMSA renal imaging, and blood samples were collected to assess hematotoxicity.

Results: Labeling efficiency exceeded 96% and [225Ac]Ac-DOTA-girentuximab demonstrated specific binding to CAIX-expressing SK-RC-52 cells in vitro. In vivo, maximum tumor uptake was reached at 168 hours; 124.2 ± 28.8 %ID/g, while the corresponding blood level was 4.0 ± 2.2 %ID/g. The tumor to blood ratio was 35.5 ± 9.3 at 168 hours p.i. compared to 11.2 ± 3.1 at 72 hours p.i. Mean tumor volume doubling times were 22 ± 11, 33 ± 24 and 31 ± 20 days for 3.7, 9.3 and 18.5 kBq for treated groups respectively, compared to 17 ± 5 days for the control group. Tumor-bearing mice showed no weight loss after treatment. Assessment of nephro- and hematotoxicity is still ongoing.

Conclusion: Girentuximab can be efficiently labeled with actinium-225 and shows excellent tumor targeting. First data indicate that [225Ac]Ac-girentuximab may lead to tumor growth delay without short-term toxicity. However, future experiments in larger groups of animals should be performed to confirm these results and to monitor long term nephro- and hematotoxicity.

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Telix Pharmaceuticals

Email Address

Robin.Merkx@radboudumc.nl

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Primary author: Mr MERKX, Robin (Radboudumc, Nijmegen, The Netherlands)

Co-authors: Dr MORGENSTERN, Alfred (Joint Research Centre, Institute for Transuranium Elements); Mrs KIP, Annemarie (Radboudumc, Nijmegen, The Netherlands); Dr OOSTERWIJK, Egbert (Radboudumc, Nijmegen, The Netherlands); Dr BRUCHERTSEIFER, Frank (Joint Research Centre, Institue for Transuranium Elements); Dr

RIJPKEMA, Mark (Radboudumc, Nijmegen, The Netherlands); Mr WHEATCROFT, Michael (Telix Pharmaceuticals); Prof. MULDERS, Peter (Radboudumc, Nijmegen, The Netherlands); Dr HESKAMP, Sandra (Radboudumc, Nijmegen, The Netherlands)

Presenter: Mr MERKX, Robin (Radboudumc, Nijmegen, The Netherlands)