O07 225Ac-labeled girentuximab for targeted alpha therapy of CAIX-expressing renal cell cancer xenografts

Eur Urol Suppl 2019;18(8):e3045

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Introduction & Objectives: Despite progress in the treatment of clear cell renal cell carcinoma (ccRCC), the prognosis of patients with metastasized tumors remains poor, emphasizing the need to develop novel treatment options. A rapidly advancing field of interest is targeted radionuclide therapy using α-emitting radionuclides, such as actinium-225 (^{225}Ac). 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 radiolabel girentuximab with actinium-225 and assess its in vivo tumor targeting properties, therapeutic efficacy and toxicity in mice.

Materials & Methods: Girentuximab was conjugated with DOTA and labeled with ^{225}Ac and immunoreactivity 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 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 measurement up to 4 weeks post injection. Toxicity was monitored by measuring body weight. Furthermore, non-tumor bearing mice were used to analyze nephrotoxicity by immunohistochemistry and [^{99m}Tc]Tc-DMSA renal imaging, and blood samples were collected to assess hematotoxicity.

Results: Labeling efficiency exceeded 96% and the immunoreactive fraction of [225Ac]Ac-girentuximab was > 80%. 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 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.

Conclusions: Girentuximab can be efficiently labeled with actinium-225 and showed 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.