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Meeting Report | Oncology, Basic Science Track

²¹³Bi-labeled PSMA-targeting agents for alpha radionuclide therapy of prostate cancer

Kristell Chatalic, Julie Nonnekens, Frank Bruchertseifer, Alfred Morgenstern, Margret Schottelius, Hans Wester, Wytse van Weerden, Otto Boerman, Marion de Jong and Sandra Heskamp

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Abstract

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Objectives Prostate specific membrane antigen (PSMA) is a valuable target for specific delivery of diagnostic and therapeutic radionuclides to prostate tumors. Up to now, PSMA-targeted radionuclide therapy strategies have mainly focused on beta-emitting radionuclides. Potentially, the therapeutic efficacy could be significantly enhanced by using alpha-emitting radionuclides. Here we report on two novel ²¹³Bi-labeled PSMA-targeting agents for prostate cancer treatment.

Methods Small-molecule inhibitor PSMA I&T and PSMA nanobody JVZ-008 were labeled with ²¹³Bi. In vitro, LNCaP cells were incubated for 20 min with ²¹³Bi-PSMA I&T, ²¹³Bi-JVZ-008, ²¹³Bi-DTPA, or medium, and fixed at 1, 2, 4, 24, and 48 h after treatment. Mice engrafted with LNCaP tumors were injected with 5 MBq ²¹³Bi-PSMA I&T (0.2 nmol + 10 nmol 2-PMPA for renal protection) or ²¹³Bi-JVZ-008 (0.7 nmol + 4 mg gelofusin for renal protection) and their biodistribution was determined at 1 h after injection. In addition, tumors of treated and untreated mice were

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collected 1 h and 24 h post treatment. Fixed cells and tumors were stained for 53BP1 and H2AX to determine the presence of DNA double strand breaks (DSBs).

Results Treatment of LNCaP cells with ^{213}Bi -PSMA I&T and ^{213}Bi -JVZ-008 induced DSBs in vitro, as indicated by the presence of increased numbers of 53BP1 and H2AX nuclear foci. In vivo, tumor uptake of ^{213}Bi -PSMA I&T and ^{213}Bi -JVZ-008 at 1 h post injection was 5.75 ± 2.70 %ID/g and 2.68 ± 0.56 %ID/g, respectively. The two tracers showed similar tumor-to-kidney ratios. ^{213}Bi -PSMA I&T and ^{213}Bi -JVZ-008 both induced DSBs in LNCaP tumors at 1 h after injection, which were still observed 24 h after injection. At early time points, the DNA damage was visible as single foci and linear tracks, i.e. alpha-tracks. Alpha-tracks were no longer detectable 24 h post treatment.

Conclusions Preclinical evaluation of ^{213}Bi -PSMA I&T and ^{213}Bi -JVZ-008 revealed good tumor targeting and induction of DSBs in PSMA-expressing LNCaP xenografts. These promising preliminary results warrant further evaluation of the therapeutic efficacy and toxicity of ^{213}Bi -labeled tracers for treatment of metastasized PCa.

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