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Meeting Report | Oncology, Basic Science Track

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

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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 ^{213}Bi-labeled PSMA-targeting agents for prostate cancer treatment.

Methods Small-molecule inhibitor PSMA I&T and PSMA nanobody JVZ-008 were labeled with ^{213}Bi. In vitro, LNCaP cells were incubated for 20 min with ^{213}Bi-PSMA I&T, ^{213}Bi-JVZ-008, ^{213}Bi-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 ^{213}Bi-PSMA I&T (0.2 nmol + 10 nmol 2-PMPA for renal protection) or ^{213}Bi-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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