



Meeting Report | Oncology: Basic, Translational & Therapy: Radiopharmaceutical Therapy

[¹³¹I]MIP-1375, a small molecule prostate-specific membrane antigen (PSMA) inhibitor for targeted therapy of prostate cancer (PCa)

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Abstract

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Objectives [¹²³I]MIP-1072, (S)-2-(3-((S)-1-carboxy-5-(4-[¹²³I]iodobenzylamino)pentyl)ureido)pentanedioic acid is a high affinity ligand for PSMA (*Can Res* 2009) which has been shown to localize to radiologically-proven metastatic PCa in man. The high expression of PSMA in PCa has led us to evaluate the ¹³¹I analog of MIP-1072, MIP-1375, for therapeutic efficacy in human PCa tumor model.

Methods High specific activity MIP-1375 was prepared with Na¹³¹I via iododestannylation. LNCaP spheroids were treated with 0-37 MBq/mL MIP-1375 for 0-8 hours. Mice with PSMA(+) (LNCaP and transfected PC3-PSMA) or PSMA(-) (PC3-vector) xenografts were administered 35 MBq as a single dose or two doses one week apart. To determine whether PSMA binding was specific, a cohort of mice were co-injected with 10 mg/kg PMPA to block

PSMA binding. Radiotherapy was initiated when tumors reached 300 mm³. Tumor growth and body weight were monitored three times per week. LNCaP tumors were stained for KI-67, a marker of cellular proliferation.

Results MIP-1375 was synthesized to a radiochemical yield of 67%, a radiochemical purity of >98% and specific activity of >75 GBq/mmol. MIP-1375 inhibited the growth of LNCaP spheroids in a dose and time dependent manner, and significantly delayed the growth of PSMA(+) tumors as compared to controls. MIP-1375 treated LNCaP tumors exhibited decreased KI-67 staining compared to controls. PSMA-dependent efficacy was evident since tumors in mice co-injected with MIP-1375 and PMPA or PSMA(-) tumors grew at a rate equivalent to the vehicle groups. No significant change in body weight was observed in any group.

Conclusions MIP-1375 inhibited the growth of tumor xenografts in a PSMA-specific manner at ¹³¹I doses that are clinically relevant. These data support further investigation of MIP-1375 as a targeted radiotherapeutic for treatment of PCa in man

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