Innovative targeted alpha therapy for prostate cancer: preclinical evaluation of [^{211}At]PSMA5†

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Prostate cancer is currently the most prevalent cancer among men (92,021 new cases/year in Japan). After surgery and radiation therapy, hormone therapy is performed for recurrent lesions. However, the prognosis is poor if the hormone therapy becomes resistant with multiple metastases.

In recent years, prostate-specific membrane antigen (PSMA), which is a membrane marker expressed in prostate cancer, has received significant attention. PSMA is expressed in more than 90% of prostate cancers.[1] Targeted α-therapy (TAT) for PSMA is a promising treatment for metastatic castration-resistant prostate cancer (CRPC).[2] Astatine is an α-emitter (half-life $T_{1/2}$ = 7.2 h) that can be produced by a 30 MeV cyclotron. In this study, we evaluated the treatment effect of ^{211}At-labeled PSMA compounds in mouse xenograft models.

^{211}At was procured from RIKEN via the short-lived RI supply platform. Upon procurement, dry distillation was used to separate and purify ^{211}At. ^{211}At-labeled PSMA1, PSMA5, and PSMA6 were synthesized by the substitution reaction of ^{211}At with the dihydroxyboryl groups.[3]

Tumor xenograft models were established by subcutaneous transplantation of human prostate cancer cells (LNCaP) in NOD/SCID mice.[4] [^{211}At]PSMA1, [^{211}At]PSMA5, or [^{211}At]PSMA6 was administered to LNCaP xenograft mice to evaluate biodistribution at 3 and 24 h. The treatment effect was evaluated by administering [^{211}At]PSMA1 (0.40 ± 0.07 MBq), [^{211}At]PSMA5 (0.39 ± 0.03 MBq), or saline. Histopathological evaluation was performed for the at-risk organs at three and six weeks after administration.

All the animal experiments were performed in compliance with the guidelines of the Institute of Experimental Animal Sciences. The protocol was approved by the Animal Care and Use Committee of the Osaka University Graduate School of Medicine.

[^{211}At]PSMA5 resulted in higher tumor retention compared to [^{211}At]PSMA1 and [^{211}At]PSMA6 (30.6 ± 17.8, 12.4±4.8, and 19.1±4.5%ID/g at 3 h versus 40.7± 2.6, 8.7±3.5, and 18.1±2.2%ID/g at 24 h, respectively), whereas kidney excretion was superior in [^{211}At]PSMA1 compared to [^{211}At]PSMA5 and [^{211}At]PSMA6. The administration of [^{211}At]PSMA5 had an excellent treatment effect on tumor growth. [^{211}At]PSMA1 also showed a substantial treatment effect; however, the tumor size was relatively more prominent than in the case of [^{211}At]PSMA5. In the histopathological evaluation, regenerated tubules were detected in the kidneys at three and six weeks after administering [^{211}At]PSMA5. No abnormality was found in the histology of the thyroid.

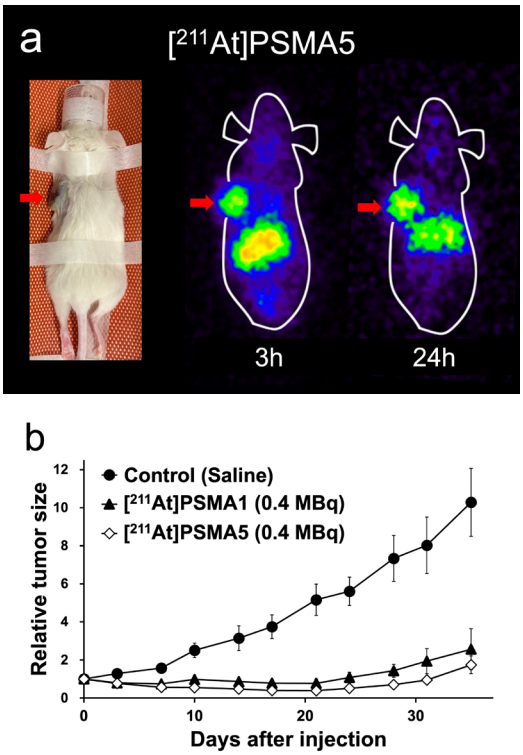

Fig. 1. (a) Planar images of [^{211}At]PSMA5 in LNCaP xenograft mice. High uptake was observed in the xenografts (arrows). (b) Change in the tumor size after administering [^{211}At]PSMA1 (0.4 MBq, n = 5), [^{211}At]PSMA5 (0.4 MBq, n = 12), or control (saline, n = 10).

TAT using [^{211}At]PSMA5 resulted in excellent tumor growth suppression with minimal side effects in the normal organs. [^{211}At]PSMA5 should be considered as a new possible TAT for metastatic CRPC. An investigator-initiated clinical trial will start at the Osaka University after tox studies.

References
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