Targeted alpha therapy of cancer: Evaluation of [^{211}At] AAMT targeting LAT1†

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L-type amino acid transporter 1 (LAT1) is an isoform of the system L, which is Na^+-independent neutral amino acid transport agency. LAT1 is expressed in primary human cancers originating in various organs such as the brain, lung, thymus, and skin, it is a well-known specific cancer marker. Amino acid tracers containing radioactive halogen have attracted attention for use as probes in single photon emission computed tomography (SPECT) and positron emission tomography (PET). L-3-[^{18}F]- α-methyl-tyrosine (^{18}F-FAMT) has higher potential for tumor specificity than 2-deoxy-2-[^{18}F] fluoroglucose (^{18}F-FDG), which is widely employed as a PET probe for cancer staging. Further FDG has the potential for false-positive accumulation within inflammation related to high glucose metabolism in macrophages or neutrophils, whereas ^{18}F-FAMT accumulates in tumors via LAT1, which is expressed only in cancer cells.[1] In contrast, ^{18}F-FAMT is not transported by other isoforms of the system L (*e.g.*, LAT2, LAT3, and LAT4), that are expressed in normal tissues.[2,3] Therefore, our L-3-[^{211}At] - α-methyl-tyrosine (^{211}At-AAMT) is expected to exhibit LAT1 specificity and to have the potential to be used as a targeting alpha therapy (TAT) treatment.

Methods

The ^{209}Bi$(\alpha, 2n)^{211}$At reaction using the AVF Cyclotron at the Research Center for Nuclear Physics, Osaka University (Ibaraki, Japan) was used to produce ^{211}At.[4] Further ^{211}At was produced with the same nuclear reaction at the Nishina Center for Accelerator-Based Science, RIKEN, and it was then transported to the Osaka University.

PANC-1 cells were cultured at 37°C in D-MEM containing 10% fetal bovine serum and 1% antibiotics in a humidified incubator with 5% CO2. Cultured cells were washed in PBS (-) and harvested with trypsin. Tumor xenograft models were established by the subcutaneous injection of 1×10^7 cells in 0.2 mL of serum-free medium and Matrigel (1:1) into female BALB/c-nu/nu mice. PANC-1 xenograft mice (10 weeks old; body weight = 19.3 ± 1.4 g) were used when the tumor size reached approximately 50 mm^3 on average.

The mice were divided into two groups according to the injected dose [0.4 MBq ($n = 4$, 4.0 ± 0.2 MBq/mL); control ($n = 4$)]. The control group only received solvents.

Tumor sizes and body weights were measured three times per week. Mice were sacrificed when the tumor size reached more than 10% of the total weight. The mice were observed for 40 days. Uptakes were normalized by the injected dose (MBq) and body weight (g).

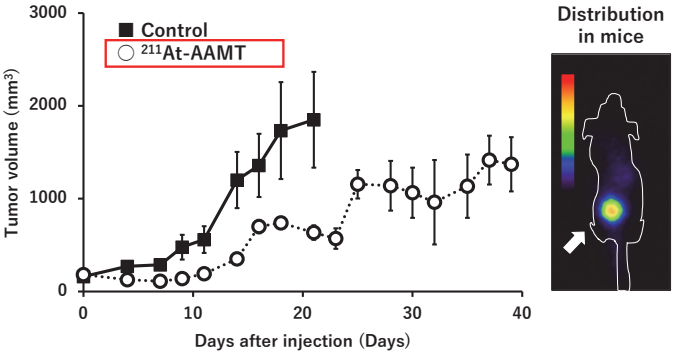

Fig. 1. Efficacy of ^{211}At-AAMT using the PANC-1 xenograft model. Tumor growth inhibition by ^{211}At-AAMT (Left). Coronal images of ^{211}At-AAMT in tumor-bearing model (Right).

Results

In the PANC-1 model, the control mice were injected only with solvents (0.2 w/v% AcOH and 1 w/v% ascorbic acid solution) and the ^{211}At-AAMT treatment group received i.v. injections of the 0.4 MBq/mouse ^{211}At-AAMT solution. No inflammation or abnormalities were observed around the injection site. In the ^{211}At-AAMT treatment group, the tumor growth was clearly inhibited and the body weight was not significantly decreased compared to the control group (Fig. 1).

Conclusion

^{211}At-AAMT may be considered a novel anti-cancer drug. While ^{211}At-AAMT could inhibit tumor growth with a single treatment, the tumor was not completely abolished, and therefore, a single injection was insufficient to decrease the tumor size continuously. Multiple doses may be necessary to exploit the high anti-tumor effect of ^{211}At-AAMT. In conclusion, ^{211}At-AAMT may be an effective anti-cancer drug when administered multiple times or in combination with existing anti-cancer drugs.

References
1) A. Achmad *et al.*, BMC Med. Imaging **17**, 66 (2017).
2) L. Wei *et al.*, J. Pharmacol. Sci. **130**, 101 (2016).
3) L. Wei *et al.*, Cancer Sci. **107**, 347 (2016).
4) T. Watabe *et al.*, J. Nucl. Med. **60**, 1301 (2019).

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