Establishment of nuclear medicine targeting LAT1, cancer type amino acid transporter

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Abstract

Our research group is a cross-disciplinary research group. We have a one-stop system from manufacturing nuclides to non-clinical trials, and we also work with affiliated hospitals that can conduct clinical trials. First, we produced astatine*1-211(^{211}At), a short-lived alpha-emitting nuclide, using an accelerator. Second, after separating ^{211}At, we established ^{211}At labeled α-methyl-L-tyrosine, which an amino acid, as a novel targeted radioisotope therapy, which an amino acid, with ^{211}At, an α-emitter, named ^{211}At-AAMT. ^{211}At-AAMT was effectively uptake into cancer cells by the amino acid transporter LAT1*2. α-emitter combines high linear energy transfer with minimal tissue penetration, thus damaging cancer cells lethally while sparing surrounding normal tissue. This strategy may prove a breakthrough in the management of intractable or advanced cancers.

Background & Results

It is well known that a cancer-specific L-type amino acid transporter 1 (LAT1) is highly expressed in several kinds of human cancer tissues. Inhibiting the function of LAT1 has been known to induce anti-cancer effects, such as growth inhibition and cell death. However, there had been limited progress in the development of agents targeted radioisotope therapy to LAT1 so far. Our multidisciplinary research team at Institute for radiation sciences in Osaka University has established a targeted α-therapy with a novel drug targeting LAT1.

We selected astatine-211(^{211}At) as labeled nuclides, it is because we have advanced technology about astatine-211 in Japan. Targeted α-therapy selectively delivers α-emitters to cancers; the advantage over conventional β-therapy is that alpha decay is highly targeted, and the high linear energy transfer causes double-strand breaks to DNA, effectively causing cell death. The short half-life and limited tissue penetration of alpha emitting nuclide ensures high therapeutic effects with few side-effects to surrounding normal cells.

Next, to deliver the astatine-211 into cancer cells, we labeled it to α-Methyl-L-tyrosine, which has high affinity for LAT1. ^{211}At-AAMT was uptake rapidly into the cancer cells as nutrition and injured these cells. ^{211}At-AAMT inhibited tumor growth in a PANC1 pancreatic cancer model (Fig.1). In addition, metastasis suppression was observed in a lung metastasis model of B16F10 melanoma (Fig.2).

Significance of the research and Future perspective

Adding to efficacy is dosing convenience. As an injectable short-range nuclear medicine, ^{211}At-AAMT may be administered in outpatient clinics, a huge advantage over conventional radiation protocols, and may even be an alternative to surgery in specific cancers. This approach has immense potential to revolutionize radionuclide therapy of not only pancreatic cancer but other malignancies that lack effective treatment including advanced or metastatic disease. Since LAT1 is expressed in many types of cancer, ^{211}At-AAMT may be applicable to various cancer types. It has the potential to become, so to speak, a "universal remedy".

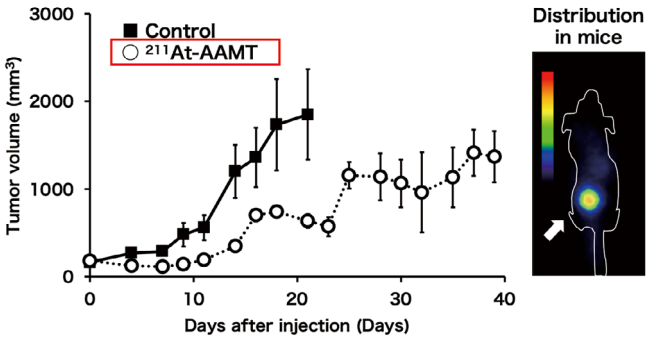

Fig. 1: The efficacy of ^{211}At-AAMT using the PANC-1 xenograft model. Tumor growth inhibition by ^{211}At-AAMT (Left). Coronal images of ^{211}At-AAMT in tumor-bearing model (right).

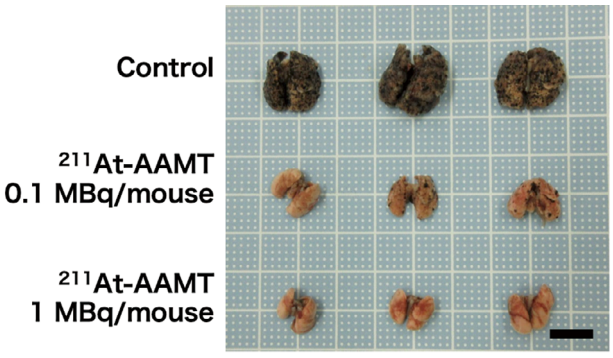

Fig.2: Tumor metastasis inhibition via ^{211}At-AAMT using a B16F10 model. Photos of experimental mice lung.

*1 Astatine: Atomic number 85, and group 17 (halogen). Chemical element with the symbol At. All of astatine's isotopes are short-lived. Naming after Greek astatos, meaning "unstable".

*2 LAT1: L-type amino acid transporter 1. LAT1 is a heterodimeric membrane transport protein that preferentially transports branched-chain (valine, leucine, isoleucine) and aromatic (tryptophan, tyrosine, phenylalanine) amino acids.

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Keyword nuclear medicine, alpha emitter, astatine-211, amino-acid, transporter