Anti-cancer effect of ^{211}At-labeled antibody on xenografted mice with intravenous injection

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Astatine-211 is a promising α emitter for targeted α therapy because of its simple decay scheme, which can avoid undesirable radiation from daughter nuclides. In a previous study, we investigated the radiolabeling method of ^{211}At on monoclonal antibodies using a stannyl compound (*m*-MeATE). The synthesis of ^{211}At-labeled IgG was successful, but we observed the detachment of ^{211}At 24 h after intravenous (IV) injection. To overcome the deastatination, the use of decaborane, a boron cluster compound, is a possible solution because its binding to astatine is more stable *in vivo*.[1)] However, as we have previously reported,[2)] the ^{211}At-decaborate moiety may increase hydrophobicity, which probably causes its poor bioavailability, resulting in the low tumor uptake by IV injection. In the present study, we introduced a PEG linker between decaborate and IgG to decrease the hydrophobicity. By using this conjugate, we investigated the anti-cancer effect of ^{211}At-labeled trastuzumab on HER2-positive cancer xenografted mice with IV injection.

The ^{211}At-decaborate (B10)-PEG5-trastuzumab was obtained through the 3-step synthesis (Fig. 1). We used 46 MBq of ^{211}At produced in the ^{209}Bi$(\alpha, 2n)^{211}$At reaction at the RIKEN AVF cyclotron for labeling 40 μg of the antibody-linker conjugate, and the mixture after the reaction was applied to filtration with G50 DNA-grade gel to remove free ^{211}At and replace it with physiological saline. The radioactivity yield was 65% (30.2 MBq was retained on the antibody), with the protein recovery rate being 64%. The specific radioactivity was 1.08 MBq/μg.

We first investigated the bio-distribution of the ^{211}At-labeled trastuzumab in xenografted mice 3, 24, and 48 h after IV injection. Figure 2 shows that ^{211}At-trastuzumab was in the blood at significant levels (around 15%ID/g) for 48 h and progressively accumulated in the target A431 tumor region (up to approximately 20%ID/g) during the same period. On the other hand, the control C6 tumor region did not show a significant accumulation from 24 to 48 h. This result was consistent with the typical outcome of a PET imaging study using ^{64}Cu-labeled trastuzumab.

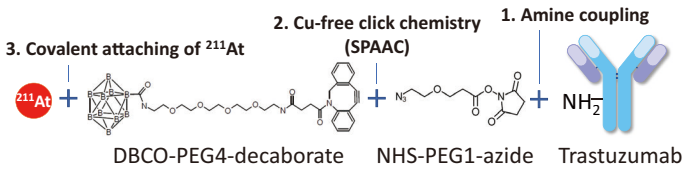

Fig. 1. Synthesis of ^{211}At-B10-PEG5-trastuzumab.

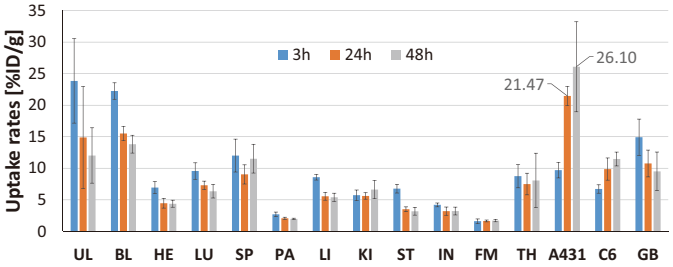

Fig. 2. Biodistribution in xenografted mice (n = 4). A431, HER2 positive; C6, HER2 negative.

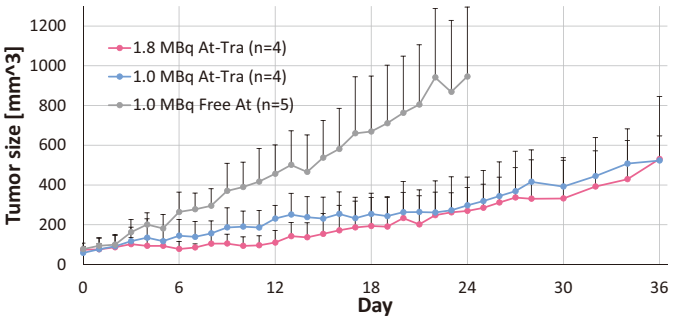

Fig. 3. Average tumor size of the mice after IV injection of ^{211}At-B10-PEG5-trastuzumab.

Subsequently, we proceeded to examine the anti-cancer effect of ^{211}At-trastuzumab via IV injection. Two groups of mice were administered 1.8 or 1.0 MBq of ^{211}At-trastuzumab (1.7 μg), while the control group was administered 1.0 MBq of free ^{211}At. The changes in the body weight and tumor size, as well as the survival rate were observed up to 36 days after the IV injection (Day 0) (the tumor size is shown in Fig. 3).

A larger dose (1.8 MBq) of ^{211}At-Trastuzumab caused a severe decrease in the body weight within a week, implying a serious side effect of the injection, and led to the euthanization of a mouse. The ^{211}At-trastuzumab in either dose successfully suppressed the growth of the tumor in size with only one shot of the IV injection, and no mice died because of the tumor. No adverse effects were observed in the 1.0 MBq At-Tra group. In contrast, the tumor grew much more rapidly in the control group, with no mice alive until Day 36. Thus, we successfully demonstrated the favorable anti-tumor effect of ^{211}At-B10-labeled trastuzumab conjugated with a PEG linker, which was probably supported by the improved biodistribution.

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References
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