Targeted alpha therapy of thyroid cancer: Evaluation of [^{211}At]NaAt treatment in the xenograft model†

T. Watabe,[*2,*3] K. Kaneda-Nakashima,[*3,*4] Y. Liu,[*2] Y. Shirakami,[*3] K. Ooe,[*1,*2] A. Toyoshima,[*1,*3] E. Shimosegawa,[*2] M. Fukuda,[*3,*5] A. Shinohara,[*3,*4] and J. Hatazawa[*3,*5]

Radioactive iodine has long been used clinically for patients with differentiated thyroid cancer.[1] ^{131}I is used for the ablation of thyroid remnants or treatment of metastatic thyroid cancer.[1] However, some patients with multiple metastases are refractory to repetitive 131I treatment, despite the targeted regions showing sufficient iodine uptake.[2] In such patients, beta-particle therapy using ^{131}I is inadequate, and another strategy using a more effective radionuclide targeting the sodium/iodide symporter (NIS) is required.

^{211}At is an alpha emitter with chemical properties similar to those of iodine and is used in targeted alpha therapy. In the present study, we added ascorbic acid (AA) to ^{211}At solution to increase the radiochemical purity of astatide and evaluated its efficacy against differentiated thyroid cancer, which is characterized by the expression of NIS.

Methods

^{211}At was procured from the Research Center for Nuclear Physics at Osaka University and RIKEN via the short-lived RI supply platform. Upon procurement, ^{211}At was separated and purified via dry distillation from a bismuth target and finally collected in distilled water.

Crude ^{211}At solution (AA(−) solution) and ^{211}At solution treated with AA (AA(+) solution) were prepared. Thyroid uptakes were compared between the two solutions in normal male Wistar rats ($n = 6$). Cellular uptake analysis in K1-NIS cells was performed under the AA(+) and AA(−) conditions. The AA(+) solution was injected at three doses into K1-NIS xenograft mice: 1 MBq ($n = 6$), 0.4 MBq ($n = 6$), and 0.1 MBq ($n = 6$). The vehicle was injected into control mice ($n = 6$). The treatment effects were compared among the four groups. Planar and SPECT images were acquired using a gamma camera system (E-cam, Siemens) with a low-energy all-purpose collimator.[3] The energy window was set at 79 keV ± 20%, targeting the X-rays emitted from the daughter nuclide of ^{211}Po.[4]

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.

Results

Thyroid uptake was significantly enhanced in rats injected with the AA(+) solution as compared to those injected with the AA(−) solution. Cellular uptake analysis showed a significantly increased uptake of ^{211}At by the K1-NIS cells under the AA(+) condition as compared to the AA(−) condition. In the mouse xenograft model, the K1-NIS tumors showed a significant accumulation of ^{211}At 3 and 24 h post administration (22.5 ± 10.4% ID and 12.9 ± 6.8% ID, respectively). Tumor growth was immediately inhibited in a dose-dependent manner after the administration of ^{211}At. In the survival analysis, the ^{211}At groups (0.1, 0.4, and 1 MBq) showed significantly better survival than the control group.

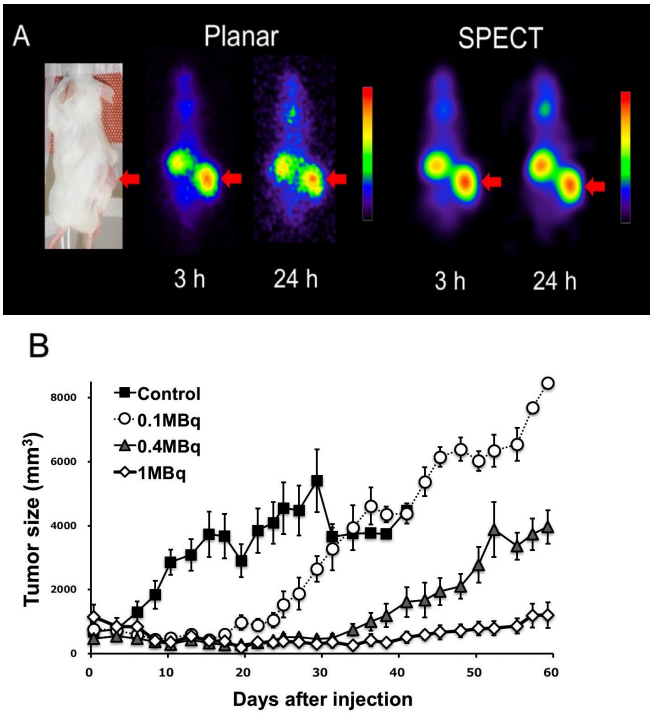

Fig. 1. (A) Planar and SPECT images of the mouse K1-NIS xenograft model after the injection of the AA(+) solution. High uptake was observed in the xenografts (arrows). (B) Change in the tumor size and body weight after the administration of AA(+) solutions.

Conclusion

The uptake of ^{211}At was enhanced in differentiated thyroid cancer cells as well as normal thyroid by using ^{211}At solution treated with AA. The solution also showed dose-dependent efficacy against the K1-NIS xenografts, suggesting its potential applicability to targeted alpha therapy.

References
1) T. Higashi *et al.*, Ann. Nucl. Med. **26**, 99 (2012).
2) M. Schlumberger, J. Endocrinol. Invest. **35**, 40 (2012).
3) J. T. Kuikka *et al.*, Nucl. Med. Commun. **19**, 457 (1998).
4) E. L. Johnson *et al.*, Nucl. Med. Biol. **22**, 45 (1995).

† Condensed from the article in J. Nucl. Med. **60**, 1301, (2019)

*1 RIKEN Nishina Center
*2 Graduate School of Medicine, Osaka University
*3 Institute for Radiation Sciences, Osaka University
*4 Graduate School of Science, Osaka University
*5 Research Center for Nuclear Physics, Osaka University