



Activities for the Development of Targeted Radionuclide Therapy in Japan

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Abstract

Targeted radionuclide therapy (TRT) is unique because of its efficacy and its theranostic feature in the era of precision medicine. So far, introduction of new TRT has not been going well in Japan due to several reasons including strict regulations, shortage of facilities for TRT, and insufficient reimbursement for TRT in clinic. Japanese community had several strategies to develop TRT in these 10 years, including the establishment of the National Conference for Nuclear Medicine Theranostics in which physicians, scientists, patients, people supporting patients, and industrial people gather. To promote TRT with supports from the government, the preparatory committee for the establishment of Japan Foundation of Medical Isotope Development (JAFMID) was launched. I would like to call TRT “Precision Nuclear Medicine.” When we can add genomic information here, we can put it to new stage of cancer therapy. It is time for us.

Keywords Targeted radionuclide therapy · Theranostics · Japan · Governmental support

Targeted radionuclide therapy (TRT) has been one of major interests in the nuclear medicine community because of its efficacy and its theranostic feature in the era of precision medicine. The demand for TRT has been also growing rapidly among physicians in many fields of not only thyroid diseases but also of neuroendocrine tumors, prostate cancer, etc. Consequently, the number of presentations at the occasion of international conferences has been increasing every year.

I have to say introduction of new TRT has not been going well in Japan for decades. Patients go abroad to Switzerland, Germany, Australia, and Malaysia to undergo treatments with ¹⁷⁷Lu-PRRT and ¹⁷⁷Lu-PSMA by their own expenses. This situation is caused by several reasons including strict regulations, shortage of facilities for TRT, and insufficient reimbursement for TRT in clinic. However, the situation has been gradually moving forward. Out-patient ablation for thyroid cancer with 30 mCi ¹³¹I was approved in 2010 [1]. ²²³Ra-chloride for patients with bone metastases of castration-resistant prostate cancer was approved in 2016 [2]. Currently, company-oriented clinical trials are running for

¹³¹I-MIBG [3] and ¹⁷⁷Lu-DOTATATE [4], and the introduction of ⁶⁸Ga/¹⁷⁷Lu-PSMA has been vigorously discussed. Phase I clinical trial has been initiated at the National Research Institute for Cancer for ⁶⁴Cu-ATSM which targets hypoxic tissues [5]. Development of ²¹¹At-MABG, an alpha emitter substitute for ¹³¹I-MIBG, is going on at the National Institute of Radiological Science [6] which will be transferred for clinical trial to Fukushima Medical University where GMP-certified facility for radiopharmaceuticals and medium-sized cyclotron of capacity to produce enough amount of ²¹¹At for clinical use.

In these 10 years, the Japanese Society of Nuclear Medicine, JSNM, has tried to change the situation. We had discussions on issues of TRT using various platforms in the Society such as the working group for alpha emitters established in 2009 and the strategy meeting group for TRT established in 2012. We met many officials at the Ministry of Health, Labour and Welfare (MHLW) and the Nuclear Regulatory Authority. Many symposiums were programmed at annual JSNM congresses to facilitate discussions.

During these activities, we recognized that voices of patients are essential to convince the authorities of the necessity to develop TRT. In 2016, we reformed the strategy meeting group for TRT to the National Conference for Nuclear Medicine Theranostics in which nuclear medicine physicians, scientists, patients, people supporting patients, and industrial

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people gather (<https://www.ncnm.jp/>). Physicians including endocrinologists, surgeons, urologists, pediatricians, radiation oncologists, and medical oncologists also participate in this. Pancreas Cancer Action Network Japan (<https://www.pancan.jp/>) and Cancer Support Community Japan (<http://www.csc-japan.org/>) work together with us. In 2017, the 10th international symposium on targeted alpha therapy, TAT-10, was hosted by the Japanese community in Kanazawa (<http://nucmed.w3.kanazawa-u.ac.jp/symposium/tat10/>). We had 225 participants of whom 110 were from abroad. Totally, 74 papers were presented. This symposium was surely good occasion for people working on alpha emitters in the world, and evoked motivation of Japanese researchers, both in academia and industry.

Perhaps the most important thing for the development of TRT is how we can involve the Government. Governmental bodies such as European Commission (http://ec.europa.eu/euratom/observatory_radioisotopes.html), Department of Energy in the US (<https://science.energy.gov/np/research/idpra/>), and Australia's Nuclear Science and Technology Organisation (<https://www.ansto.gov.au/>) are working together with the nuclear medicine communities to realize demands on radionuclide supply. Very recently, Prime Minister of Canada announced establishment of center for advanced medical isotope research and development (<https://www.triumf.ca/headlines/prime-minister-canada-announces-establishment-premier-centre-for-advanced-medical-isotope>). Learning from these previous instances, the preparatory committee for the establishment of Japan Foundation of Medical Isotope Development (JAFMID) was launched on October 1, 2018, led by Dr. Jun Hatazawa, the President of JSNM (<https://www.jafmid.or.jp/>). The idea of JAFMID is recognized by the officials of MHLW. Those of Ministry of Economy, Trade and Industry, Ministry of Education, Culture, Sports, Science and Technology, and Nuclear Regulatory Authority are expected to join the discussion for the domestic production of radioisotopes for medical use. Complicated and strict regulations for radioisotopes have been preventing Japanese researchers and physicians from bringing radiocompounds developed in laboratories to clinics. Thanks to two young nuclear medicine physicians, Dr. Tadashi Watabe of Osaka University and Dr. Anri Inaki of Kanazawa University, who served as assistant directors in MHLW, the regulatory scenario for developing radiopharmaceuticals is going to be revised for deregulation.

With this background, the number of articles in *Annals of Nuclear Medicine*, the official journal of JSNM, related to TRT or theranostic use of radioligands, has been increasing and consisted of 13% in these 2 years. Eight papers are on $^{68}\text{Ga}/^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE/DOTATOC [4, 7–13], 7 discuss $^{18}\text{F}/^{68}\text{Ga}/^{177}\text{Lu}$ -PSMA [9, 10, 14–18], and 1 is on a new target, CXCR-4 [19]. The article of Kunikowska et al. [7] on $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE was awarded the first best prize in

2018. Noteworthy, two papers reported domestic experience with ^{68}Ga -DOTATOC [12, 13]. Phase I/IIa clinical trial of ^{89}Zr -anti-PSMA minibody was reported by a Japanese group [20]. For the proper uses of ^{177}Lu -DOTATATE, JSNM released the manual guideline of it [4].

TRT is a real form of precision medicine. We can obtain precise information on confirmation of targeting of therapeutics, target quantification (dosimetry), prediction of therapeutic response, efficacy assessment, and possible adverse reaction. We can use these data to determine patient eligibility for therapy, performing precision medicine. I would like to call this “Precision Nuclear Medicine.” When we can add genomic information here, we can put it to new stage of cancer therapy. It is time for us.

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Compliance with Ethical Standards

Conflict of Interest Seigo Kinuya declares no conflict of interest.

Ethical Approval This is a kind of commentary that ethical approval is not required.

Informed Consent This manuscript does not contain any human study so informed consent should not be applied.

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