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HIGHLIGHTS

Recent development of probes for radiotheranostics

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In recent years, the term “theranostics” has been used frequently in oncology. The term was coined by combining the words "therapeutics" and "diagnosis," indicating a comprehensive and efficient cancer diagnosis and treatment method that combines diagnostic imaging and molecular targeted therapy [1, 2]. In nuclear medicine, which uses radiopharmaceuticals for diagnostic imaging and cancer treatment, quantitative imaging is performed after administration of a diagnostic radiopharmaceutical, and subsequent image analysis provides detailed information on the pharmacokinetics of the radiopharmaceutical in the body [3]. Namely, if a diagnostic radiopharmaceutical and a corresponding therapeutic radiopharmaceutical that show equivalent pharmacokinetics are used in combination, the absorbed radiation dose can be calculated by each tissue during treatment. In other words, prior diagnostic imaging can predict the therapeutic effects and side effects. Furthermore, diagnostic radiopharmaceuticals can also be used to determine the therapeutic effect after treatment. The combination of molecular imaging and target therapy in nuclear medicine is theranostics using radioisotopes (RI), which is called radiotheranostics [4, 5].

Although the term "radiotheranostics" has only recently come into use, it is a concept that has been used in nuclear medicine for some time. It is used in nuclear medicine therapy in combination with nuclear medicine diagnostics, and there are diagnostic radiopharmaceuticals that correspond to therapeutic radiopharmaceuticals. [^{177}Lu]Lu-DOTATATE (lutetium oxodotreotide (^{177}Lu)), which is a ^{177}Lu-labeled octreotide analog, for the treatment of somatostatin receptor-positive neuroendocrine tumors and [^{131}I]I-MIBG (3-iodobenzylguanidine (^{131}I)) for the treatment of pheochromocytoma and paraganglioma, which were approved in Japan in 2021 [6, 7]. [^{111}In]In-DTPA-Octreotide (Indium pentetreotide (^{111}In)) and [^{123}I]I-MIBG (3-iodobenzylguanidine (^{123}I)) are the corresponding diagnostic radiopharmaceuticals. They are used for diagnostic imaging before therapy. Here, ^{177}Lu and ^{131}I are beta particle emitting radionuclides for therapy, and ^{111}In and ^{123}I are gamma ray emitting radionuclides for imaging.

In recent years, targeted alpha therapy (TAT) has attracted much attention due to the excellent therapeutic effects of alpha particles. In 2013, [^{223}Ra]$RaCl_2$ was approved by the U.S. Food and Drug Administration as the first therapeutic radiopharmaceutical with an alpha particle emitting radionuclide in the world (approved in Japan in 2016) after significantly prolonging overall survival in a phase III study for castration-resistant prostate cancer with bone metastases [8]. As [^{223}Ra]$RaCl_2$ accumulates in bone metastases, bone scintigraphy agents, such as [^{99m}Tc]Tc-MDP, are used for corresponding diagnostic radiopharmaceuticals. Meanwhile, the remarkable therapeutic effects of [^{225}Ac]Ac-PSMA-617, a prostate-specific membrane antigen (PSMA) ligand labeled with the alpha particles emitting radionuclide ^{225}Ac, in clinical studies have led to the development of radiopharmaceuticals for TAT [9]. However, ^{223}Ra has not been applied to labeling compounds because few chelates can be stably coordinated with ^{223}Ra. In addition, ^{225}Ac is not easy to obtain due to excessive demand for worldwide radioactivity.

Under these circumstances, ^{211}At has attracted attention as an alpha particle emitting nuclide. ^{211}At can be produced by the ^{209}Bi(α,2n)^{211}At reaction using a medium-sized cyclotron and is the only alpha particle emitting nuclide with an established production method and stable production in Japan. Astatine is also a halogen element and, thus, has the potential to be used in the same radiolabeling reaction as radioiodine, which is frequently used in nuclear medicine. Various ^{211}At-labeled compounds coupled with corresponding radioiodine-labeled compounds for radiotheranostics are currently investigated [10, 11]. Among them, phase I investigator-initiated clinical trials of [^{211}At]NaAt, a ^{211}At version of [^{131}I]NaI, which has long been used in thyroid cancer therapy (astatine is also taken up by thyroid cancer cells via

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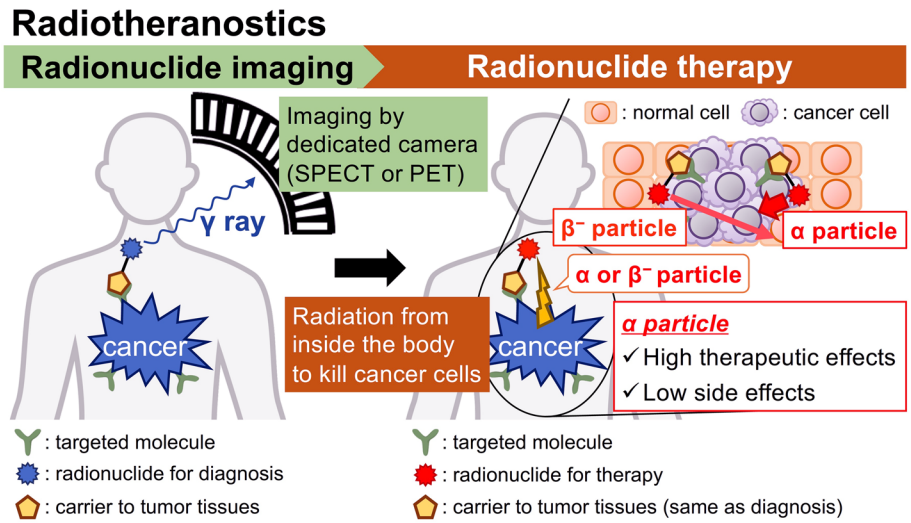
a NaI symporter), and [^{211}At]At-MABG (meta-astatobenzylguanidine), a ^{211}At version of [^{131}I]I-MIBG, were started in Japan in 2021 and 2022, respectively [12, 13].

Radiotheranostics containing TAT is innovative cancer theranostics and significantly contribute to personalized medicine.



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