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REVIEW

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Perspectives for Concepts of Individualized Radionuclide Therapy, Molecular Radiotherapy, and Theranostic Approaches

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Abstract
Radionuclide therapy (RNT) stands on the delivery of radiation to tumors or non-tumor target organs using radiopharmaceuticals that are designed to have specific affinity to targets. RNT is recently called molecular radiotherapy (MRT) by some advocators in order to emphasize its characteristics as radiotherapy and the relevance of dosimetry-guided optimization of treatment. Moreover, RNT requires relevant radiation protection standards because it employs unsealed radionuclides and gives therapeutic radiation doses in humans. On the basis of these radiation protection standards, the development and use of radiopharmaceuticals for combined application through diagnostics and therapeutics lead to theranostic approaches that will enhance the efficacy and safety of treatment by implementing dosimetry-based individualization.

Keywords Radionuclide therapy · Theranostics · Radiopharmaceuticals

Overview of Radionuclide Therapy

Radionuclide therapy (RNT), i.e., targeted radionuclide therapy (TRT), nuclear medicine therapy, or therapy with radiopharmaceuticals, aims the specific delivery of radiation, which is emitted usually as beta or alpha particles from radiopharmaceuticals, to tumors or non-tumor target organs [1, 2]. Some advocators of RNT recently encourage us to call it molecular radiotherapy (MRT) in order to emphasize its characteristics of radiotherapy, in which standardization of the therapeutic procedures should be established by using radiation dosimetry methodologies [3, 4].

Therapy with iodine-131 (^{131}I) for the treatment of thyroid diseases has been one of the core RNT practices for a long time [5–7]. The dawn era of radioiodine therapy in hyperthyroidism and thyroid oncology begun around 1940, when radioiodine therapy came up for patients with hyperthyroidism or metastases of differentiated thyroid cancer by prescribing therapeutic dose of radioiodine. In a report on a practice of radioiodine therapy of these days, hyperthyroidism patients were treated with radioiodine using deliberately designed framework of studies that included calculation of radiation doses to tissues [8]. In terms of treatment of thyroid cancer, radioiodine including iodine-130 (^{130}I) and ^{131}I that were produced by a cyclotron constructed for medical purpose was given to a patient who had multiple lung and bone metastases [9]. Fortunately, the RNT method using radioiodine does not need a carrier substance for the delivery of the radionuclide to the target because radioiodine is taken in by the intrinsic mechanism of thyroid and thyroid cancer tissues. However, some RNTs have to employ high-affinity molecules as carriers for delivering radionuclides. Such molecules for radionuclide therapy are called therapeutic radiopharmaceuticals. When they reach their target, which is a target molecule on the surface of tumor cells or normal cells in some cases, they are supposed to bind directly to this target. Interestingly, some therapeutic radiopharmaceuticals are internalized into the target cells, and others stay on the surface membrane of the target cells. Among potential carrier molecules, monoclonal antibodies have proved to be efficacious for the radionuclides to reach the targets. Such therapy with radiolabeled antibodies is termed as radioimmunotherapy (RIT) and has been one of the major methods among various RNTs in laboratory and clinical studies. Many RIT radiopharmaceuticals were developed and tried in humans, and among them, yttrium-90 (^{90}Y)-ibritumomab tiuxetan, an anti-CD20 monoclonal antibody, was the first RIT pharmaceutical that was approved by Food

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and Drug Administration in the USA in 2002 for relapsed or refractory low-grade, follicular, or transformed B cell non-Hodgkin lymphoma (NHL) [10–12]. And this was followed in 2003 by ^{131}I-tositumomab, which is an anti-CD20 monoclonal antibody labeled with ^{131}I for B cell NHL [13]. The methods of RNT are lately being used more and more often for the treatment of various tumors along with the development of novel radionuclides, compounds, chelating agents, and application modes. Such recently developed methods that have successfully reached clinical application include lutetium-177 (^{177}Lu)-labeled peptides for therapy of neuroendocrine tumors. This emerging category of therapy is called peptide receptor radionuclide therapy (PRRT) [14] and ^{177}Lu-DOTATATE [15–17], approved in EU in 2017 and in the USA in 2018, is one of the representative pharmaceuticals. Another recent update among RNT pharmaceuticals is radium-223 (^{223}Ra) dichloride, which has recently been introduced in human use for the treatment of castration-resistant prostate cancer with bone metastases [18–20]. One of the most important features of ^{223}Ra is that it is the first alpha-emitting radionuclide that has demonstrated safety and efficacy in the treatment of malignancies. It received approval by regulatory authorities in 2013 in the USA and EU after well-designed multi-center clinical trials [20].

Radiation Protection and Safety in Radionuclide Therapy

Radiation protection in radionuclide therapy is incorporated in the entire frame work of radiation protection in medicine, which involves medical exposure, occupational exposure, and public exposure in radiological practices [21].

Medical exposure involves mainly patients and it also involves their comforters and carers, and volunteers in biomedical research. According to international standards on radiation protection [22–24], medical exposure of patients has interesting features on how the fundamental principles of radiation protection are implemented. The principle of dose limits, which is one of the fundamental principles of radiation protection in other fields, is usually not mandatory in medical exposure. The rationale for this situation is that uniform dose limits for all patients would sometimes do more harm than good in diagnosis and therapy of patients. The other two fundamental principles of radiation protection, justification, and optimization, function firmly in medicine, but in a different way from elsewhere. Justification in medical exposure is characteristic in that the very same subject receives the benefits and suffers the risks that come from a radiological procedure. Also, optimization of protection for medical exposure is characteristic because radiation therapy delivers radiation to patients for the sake of treatment, and diagnostic radiology should strike a good balance of benefit and risk to the patients. In this context, RNT requires well-designed radiation protection standards and countermeasures because it handles unsealed radionuclides in hospitals and delivers high radiation doses to tumor and normal tissues in humans.

From Empirical Therapy to Individualized Therapy

Prescriptions of dosage in RNT have often been based on a fixed amount of activity for patients, sometimes tailored to patient weight or body surface area [25]. Typically so far, established guidelines regarding radioiodine therapies still do not provide a clear recommendation on the amount of radioiodine that should be given through decades of treating thyroid cancer patients [26]. Guidelines and recommendations for RNT do not include advanced dosimetric evaluation, either. Analogous to circumstances in chemotherapy, fixed radioactivity doses or doses based on body weight or body surface area are considered sufficient in clinical practices [27]. In RNT, currently absorbed dose to the target volume cannot be accurately calculated in contrast to external beam radiation therapy [28]. For example, metastatic lesions may not be measurable because of too small size or indiscrete morphology. In such situations, there is no possible way for treatment optimization by using the absorbed dose to target tissues.

In this context, the next optimal alternative is to build therapy planning on the maximum tolerable absorbed dose (MTAD) to nontarget organs or tissues [28]. This concept of MTAD was established in early days' radioiodine therapy for thyroid cancer [29–32] and still clinically viable nowadays. During the development of PRRT for neuroendocrine tumors, on the basis of MTAD, long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE was conducted using dosimetric technologies for normal organs including the kidneys [33].

From Radionuclide Therapy to Theranostics

Theranostics means a concept of combining therapeutics and diagnostics that will reinforce the efficacy and safety of procedures in patient managements. Specifically, theranostics in nuclear medicine usually corresponds to a combination of imaging and RNT for oncological applications [34]. The use of the same or similar compounds both for imaging and RNT, which are labeled with photon-emitters for imaging and with beta or alpha emitters for RNT, has been one of the main streams in nuclear oncology. Such application of radiopharmaceuticals through imaging to therapy for enhancing the efficacy and safety of practices should be a typical example of theranostic approaches [3, 35, 36].

Established practices of imaging and therapy such as ^{131}I therapy for differentiated thyroid cancer and Zevalin therapy with indium-111 (^{111}In) antibody and ^{90}Y antibody for B cell non-Hodgkin's lymphoma are undoubtedly theranostic approaches in RNT. Moreover, the combination of ^{68}Ga-labeled somatostatin analogs and PRRT procedures with ^{90}Y- or ^{177}Lu-labeled counterparts for the treatment of neuroendocrine tumors [14] has proved to be a good theranostic application. Most recently, the combination of Ga-68 (^{68}Ga)-labeled PSMA (prostate-specific membrane antigen) ligands and ^{177}Lu-labeled or actinium-225 (^{225}Ac)-labeled counterparts for prostate cancer has been a very promising method in castration-resistant prostate cancer [37]. In terms of a theranostic approach in ^{223}Ra dichloride therapy for the treatment of castration-resistant prostate cancer with bone metastases, some researchers reported that the images of photons emitted from ^{223}Ra in patients were obtained and analyzed for calculation absorbed doses in normal tissues [38–42]. They emphasized this would enable customization of treatment from a present fixed protocol of 55 kBq/kg body weight up to six times with 4-week intervals to individually prescribed protocols in some upcoming years. Now, dosimetry-guided approaches in RNT will have significant contributions to achieve deliberate customization and individualization of treatment for patients (Fig. 1). This is the reason why some advocators for dosimetry-guided planning and practices have proposed the appellation of "molecular radiotherapy (MRT)" for RNT to emphasize the aspects of radiotherapy [43–45].

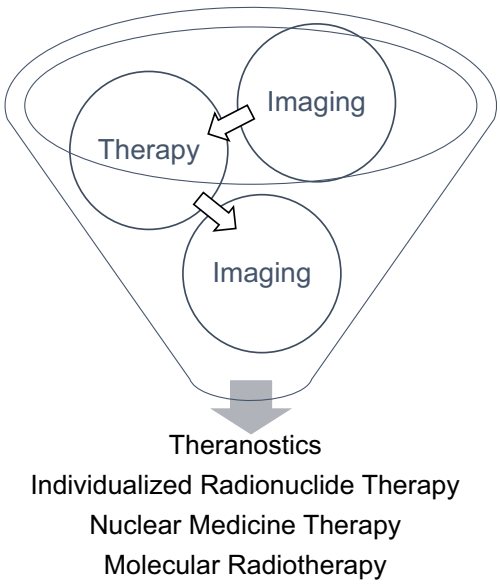

Fig. 1 Sequence of theranostic approach in radionuclide therapy. Initially imaging with diagnostic radiopharmaceuticals for staging of the diseases and dosimetry, then followed by administration of therapeutic radiopharmaceuticals, and imaging with photons emitted from radiopharmaceuticals

Pitfalls in Theranostic Approaches

When we take ibritumomab tiuxetan therapy as an example of application for theranostic approaches, the accumulation of ^{111}In antibody to B cell non-Hodgkin's lymphoma and that of ^{90}Y antibody [46] are not necessarily parallel. Rather, patients with negative ^{111}In antibody may reach a CR on ^{90}Y antibody therapy, which suggests that tumor response by ^{90}Y antibody therapy and absolute levels of ^{111}In antibody accumulation may not be correlated. This discordance of tumor response and absolute level of antibody accumulation might be well explained by homogeneity of intratumoral distribution of antibody instead of absolute level of antibody accumulation [47]. Lymphoma lesions that had homogeneous distribution of ^{111}In antibody showed better tumor response than those showing heterogeneous ^{111}In antibody distribution, which might imply that homogeneous distribution of antibody leads to effective irradiation to tumor tissues.

In a study that conducted treatment of neuroendocrine tumors by ^{90}Y-DOTATOC, the initial imaging finding was predictive for overall survival, whereas the initial kidney uptake was predictive for severe renal toxicity, also, response to ^{90}Y-DOTATOC was associated with longer survival, and somatostatin receptor imaging was predictive for both survival after treatment and occurrence of renal toxicity [48].

As of now, correlation of imaging findings and tumor responses in RNT using theranostic approaches are various among RNT methods. Imaging results are predictive for tumor response in some RNT methods, but not predictive for others. Evidences should be accumulated for each specific RNT procedures in order to define how the imaging findings can be used in the clinical circumstances including prediction of tumor response, patient selection, and individualization of protocols and dosage.

Conclusion

RNT is now enhancing its efficacy and safety by innovative technologies of radiopharmaceuticals and devices and experiencing a significant expansion across the globe. Theranostic approaches that fuse therapeutics and diagnostics involve dosimetry-based treatment procedures in clinical circumstances for conventional therapies as well as innovative therapies. In the future era of RNT, the concepts of individualization, molecular radiotherapy, and theranostic approaches will contribute so much to patient-centered care.

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Compliance with Ethical Standards

Conflict of Interest Makoto Hosono declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by the author.

Informed Consent For this type of study, formal consent is not required.

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