Radiation protection in therapy with radiopharmaceuticals

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ABSTRACT

Purpose: Radionuclide therapy (RNT) involves the selective delivery of radiation, emitted from radionuclides to tumors or target organs. The techniques of RNT are increasingly being used for the treatment of various tumors. The purpose of this article is to report on the current state of RNT, to clarify the issues of radiation protection associated with RNT, and to show future prospects.

Results and conclusions: Medical exposure of patients has unique features; application of dose limits is not undertaken, and justification and optimization do apply but in a different way from in other exposures. The expanding use of RNT has raised concern regarding potential carcinogenic and leukemogenic effects and research on second primary cancer after RNT have been developing. RNT combined with imaging and dosimetry and featuring a theranostic approach is undergoing a significant expansion, and such dosimetry-based treatment planning leads to individualization, or personalization, which is likely to improve the effectiveness and safety of patient management in RNT.

Introduction

Radionuclide therapy (RNT), also named targeted radionuclide therapy (TRT) or nuclear medicine therapy, involves the selective delivery of radiation, emitted from radionuclides, to tumors or target organs (Chatal and Hoefnagel 1999; Zukotynski et al. 2016). RNT is lately called molecular radiotherapy (MRT) by some researchers to stress its characteristics of irradiation therapy and the necessity of radiation dosimetry (Eberlein et al. 2017; Stokke et al. 2017). One of the most representative radionuclide therapies is that using iodine-131 (131I) for the treatment of thyroid diseases (Bonnema and Hegeduš 2012; Pryma and Mandel 2014; Luster et al. 2017). The earliest practices of radioiodine therapy in oncology were undertaken in the 1940s, when physicians started treating patients with metastases of differentiated thyroid cancer by administering therapeutic dose of radioiodine. In a report on an application of radioiodine therapy early years, radioiodine comprising iodine-130 (130I) and 131I that were produced by a cyclotron dedicated to medical purpose (Seidlin et al. 1946; Siegel 1999). In contrast with the RNT method using radioiodine which does not need a carrier for the delivery of the radionuclide, some RNTs use high-affinity molecules as carriers for the delivery of radiation, and such radiolabeled compounds for radionuclide therapy, or therapeutic radiopharmaceuticals, are usually administered orally, intravenously, intra-arterially, or even intracavitarily, and reach their target, that is, a target molecule on the surface of tumor cells or sometimes normal cells, and directly interacts with these cells. Some radiopharmaceuticals enter inside the cells and others remain on the surface of the cells. Monoclonal antibodies have thought to be efficient carrier molecules for the radionuclides to be delivered to the targets. Therapy with radiolabeled antibodies, also named radioimmunotherapy (RIT), has been a mainstream of RNT in preclinical and clinical studies for a long time. Among RIT agents that were tried to clinical application, yttrium-90 (90Y)-ibritumomab tiuxetan, a radiolabeled anti-CD20 monoclonal antibody, was the first RIT agent to receive Food and Drug Administration approval in the USA in 2002 for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma (NHL) (Wagner et al. 2002; Wiseman et al. 2003; Witzig et al. 2007). This 90Y-ibritumomab tiuxetan was followed in 2003 by 131I-tosiatumomab, which is also a radiolabeled anti-CD20 monoclonal antibody for the treatment of B-cell NHL (Kaminski 2007).

Recently, the techniques of RNT are increasingly being used for the treatment of various tumors using novel radionuclides, compounds, chelating agents, and application. Examples of recently developed methods that are in clinical practice include lutetium-177 (177Lu)-labeled peptides for therapy of neuroendocrine tumors (Bodei et al. 2010), includ-
2018. Radium-223 (223Ra) dichloride has been recently introduced in clinical practices for the treatment of castration-resistant prostate cancer with bone metastases (Parker et al. 2013; Parker et al. 2018). Importantly, 223Ra is the first alpha-emitting radionuclide that has shown safety and efficacy for the treatment of cancer patients, and received approval in 2013 in the USA and EU.

Features of radiation protection in medicine

Radiation protection in medicine covers in principle, medical exposure, occupational exposure, and public exposure in association with various clinical circumstances. Medical exposure involves not only patients but also their comforters and carers, and volunteers in biomedical research. Medical exposure of patients has unique features that affect how the fundamental principles are applied (ICRP 2007a, 2007b). Application of dose limits, which is one of the fundamental principles of radiation protection elsewhere, is not undertaken in medical exposure. This is because, such dose limits would often do more harm than good in the course of treating patients. Two fundamental principles of general radiation protection, justification, and optimization apply in medicine in a different way. Justification in radiation protection of patients is unique in that the very same subject enjoys the benefits and suffers the risks associated with a radiological procedure. Optimization of protection for patients is also unique in that radiation therapy gives intentional radiation for the purpose of treatment, and diagnostic procedures give the benefit and the risk to the same subjects. Therapy with radiopharmaceuticals, namely RNT, requires deliberate radiation protection standards as it uses unsealed radionuclides and gives therapeutic radiation doses in humans.

Second primary cancer in radionuclide therapy

The expanding use of RNT has raised concern regarding potential carcinogenic and leukemogenic effects (Hakala et al. 2016; Martinez et al. 2017). Research on second primary cancer after RNT has been developing especially on 131I therapy for hyperthyroidism and differentiated thyroid cancer. To date, 131I therapy for hyperthyroidism has not been associated with an elevated risk of cancer mortality, while evidence has been accumulated that 131I therapy for differentiated thyroid cancer is associated with an elevated risk of solid cancers and hematological malignancies.

The conclusions reported in a study involving 35,593 hyperthyroid patients (Ron et al. 1998) are a consensus on the safety of 131I therapy regarding potential second malignancy. The study reported that 131I therapy did not result in a significantly increased risk of total cancer mortality, while there was an elevated risk of thyroid cancer mortality. However, the excess number of deaths was small and underlying thyroid disease appeared to play a role. And, the authors concluded 131I therapy appeared to be a safe therapy for hyperthyroidism.

In contrast to 131I therapy for hyperthyroidism, that for differentiated thyroid cancer appeared to be associated with a statistically elevated risk of malignancies (Rubino et al. 2003). The dose-response relationships were linear, which illustrated that a treatment of 3.7 Gbq of 131I could theoretically induce an excess of 53 solid malignant tumors and 3 leukemias, in 10,000 patients during 10 y of follow-up. However, another study reported that there was no statistical difference in risk of second primary cancer between high- and low-doses of 131I for the treatment of differentiated thyroid cancer (Ko et al. 2015). As of now, the general consensus on the risk associated with 131I therapy seems that the evidence of serious risks associated with the therapy is weak and contradictory, and then, the potential risk of adverse effects must be weighed against the risk of dying from recurrent thyroid cancer (which is >8% in a 30-year follow-up period of patients not treated with 131I therapy) (Blumhardt et al. 2014).

From radionuclide therapy to theranostics

Theranostics means generally a method of combining diagnosis and therapy and enhancing the efficacy and safety of procedures to an individual patient. In nuclear medicine, theranostics usually refers to a combination of imaging and RNT in oncological nuclear medicine (Moek et al. 2017). The use of radiopharmaceuticals for imaging and therapy, consisting of novel radionuclides, including alpha emitters, conjugated with compounds or probes, has been increasing for the management of various tumors. Such application of radiopharmaceuticals is considered as an example of theranostic approaches (Choudhury and Gupta 2017; Eberlein et al. 2017; Nitipir et al. 2017). Conventional imaging and treatment of 131I therapy for differentiated thyroid cancer, and Zevalin therapy with indium-111 (111In) antibody and 90Y antibody to B-cell non-Hodgkin’s lymphoma can be examples of theranostics. And nowadays, the combination of 68Ga-labeled somatostatin analogs and the 90Y- or 177Lu-labeled counterparts for neuroendocrine tumors (Bodei et al. 2010) is an effective theranostic approach and the combination of Ga-68 (68Ga)-labeled PSMA (prostate-specific membrane antigen) ligands and 177Lu-labeled or actinium-225 (225Ac)-labeled counterparts for prostate cancer (Kratochwil et al. 2018).

Dosimetry-guided personalized therapy

Such theranostic procedures are currently attracting attention in nuclear medicine. The implementation of a series of somatostatin receptor imaging and PRRT (peptide receptor radionuclide therapy) for neuroendocrine tumors have proved to be promising, and a large-scale clinical trial of 177Lu-DOTATATE against neuroendocrine tumors has been conducted (Strosberg and Krenning 2017; Hosono et al. 2018), which lead to the approval of the radiopharmaceuticals in 2017 as above. However, imaging with 68Ga-labeled PSMA ligands and RNT with 177Lu-labeled PSMA ligands in the management of prostate cancer are currently being
conducted at an increasing number of hospitals across the globe. A study of clinical application of alpha-emitting $^{225}$Ac-labeled PSMA ligand, reporting good tumor response in advanced prostate cancer, gave a great impact to the world (Kratochwil et al. 2018). RNT using alpha emitters (Targeted Alpha Therapy, TAT) has attracted much attention due to high linear energy transfer and relative biological effectiveness of 3–5 (Sgouros et al. 2010). From the viewpoint of radiation protection, the radiation weighting factor for alpha particles is 20 (ICRP 2007a). In these procedures, dosimetry based on imaging is critical in the research and development of procedures and also in clinical applications by guiding subsequent RNTs. Moreover, dosimetry for alpha-emitter therapy requires studies on the microscopic distribution of emitters due to a short range of a few cell diameter. Methods of micro-dosimetry should be established by considering the distribution and kinetics of the alpha-emitting radiopharmaceuticals (Sgouros et al. 2011). Dosimetry-guided practices will have significant implications for the evolution of RNT (Figure 1). And such dosimetry-guided approach enhances the aspects of RNT as radiotherapy, which will lead to diffusion of the concept of molecular radiotherapy (MRT). The European directive on basic safety standards (Council directive 2013/59 Euratom) mandates dosimetry-based treatment planning for radiation therapies including radiopharmaceutical therapies, and the directive came into operation in February 2018. There are arguments on the role of dosimetry in RNT. The board of European Association of Nuclear Medicine stressed that although dosimetry is an undisputed aspect of radiopharmaceutical development, its clinical use to tailor the administered activity to an individual patient should be clarified through further evidence (Giammarile et al. 2017). Whatever is the role of dosimetry, the methodologies of dosimetry by means of imaging techniques need to be established for the sake of development and clinical application of RNT (Flux et al. 2017; Stokke et al. 2017).

Conclusions

RNT combined with imaging and dosimetry and featuring a theranostic approach is undergoing a significant expansion, and such dosimetry-based treatment planning is already an established standard in some clinical circumstances. The processes of individualization, or personalization, are likely to improve the effectiveness and safety of patient management in RNT (Stokke et al. 2017).
Flux GD, Verburg FA, Chiesa C, Bardies M, Gleisner KS, Hertz B, Konijnemberg M, Lassmann M, Ljungberg M, Luster M, et al. 2017. Comparison of Empiric Versus Dosimetry-Guided Radioiodine Therapy: The Devil Is in the Details. J Nucl Med. 58:862.

Giammarile F, Muylle K, Delgado Belmont R, Kunikowska J, Haberkorn U, Oyen W. 2017. Dosimetry in clinical radionuclide therapy: the devil is in the detail. Eur J Nucl Med Mol Imaging. 44:1–3.

Hakala TT, Sand JA, Jukkola A, Huhtala HS, Metso S. Kellokumpu-Lehtinen PL. 2016. Increased risk of certain second primary malignancies in patients treated for well-differentiated thyroid cancer. Int J Clin Oncol. 21:231–239.

Hosono M, Ikebuchi H, Nakamura Y, Nakamura N, Yamada T, Yanagida S, Kitaoka A, Kojima K, Sugano H, Kinuya S, et al. 2017. Manual on the proper use of lutetium-177-labeled somatostatin analogue (Lu-177-DOTATATE) injectable in radionuclide therapy (2nd ed.). Ann Nucl Med. 32:217–235.

ICRP. 2007a. The 2007 recommendations of the international commission on radiological protection. ICRP publication 103. Ann ICRP 37:1–332.

ICRP. 2007b. ICRP Publication 105. Radiation protection in medicine. Ann ICRP 37:1–63.

Kaminski M. 2007. Bexxar, iodine I 131 tositumomab, effective in B-cell non-Hodgkin lymphoma. Cancer Biol Ther. 6:996–997.

Ko KY, Kao CH, Lin CL, Huang WS, Yen RF. 2015. (131)I treatment for thyroid cancer and the risk of developing salivary and lacrimal gland dysfunction and a second primary malignancy: a nationwide population-based cohort study. Eur J Nucl Med Mol Imaging. 42:1172–1178.

Kratochwil C, Bruchtseder F, Rathke H, Hohenfellner M, Giesel FL, Haberkorn U, Morgenstern A. 2018. Targeted α-therapy of metastatic castration-resistant prostate cancer with 225ac-psma-617: swimmer-plots analysis suggests efficacy regarding duration of tumor control. J Nucl Med. 59:795–802.

Luster M, Piestroff A, Hanscheid H, Verburg FA. 2017. Radioiodine therapy. Semin Nucl Med. 47:126–134.

Martinez A, Martinez-Ramirez M, Martinez-Caballero D, Beneit P, Clavel J, Figueroa G, Verdu J. 2017. Radiopharmaceuticals. 14:71.

Moek KL, Giesen D, Kok IC, de Groot DJA, Jalving M, Fehrmann RSN, Lub-de Hooge MN, Brouwers AH, de Vries EGE. 2017. Theranostics using antibodies and antibody-related therapeutics. J Nucl Med. 58:838–905.

Nitipir C, Niculae D, Orlov C, Barbu MA, Popescu B, Popa AM, Pantea AMS, Stanciu AE, Galateanu B, Gheorghe O, et al. 2017. Update on radionuclide therapy in oncology. Oncol Lett. 14:7011–7015.

Parker C, Heidenreich A, Nilsson S, Shore N. 2018. Current approaches to incorporation of radium-223 in clinical practice. Prostate Cancer Prostatic Dis. 21:37–47.

Parker C, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, Fossa SD, Chodacki A, Wiechno P, Logue J, Seke M, et al. 2013. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 369:213–223.

Pryma DA, Mandel SJ. 2014. Radioiodine therapy for thyroid cancer in the era of risk stratification and alternative targeted therapies. J Nucl Med. 55:1485–1491.

Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, Harris BS, III HDA, McConahay WM, Maxon HR, et al. 1998. Cancer mortality following treatment for adult hyperthyroidism: cooperative thyrototoxicosis therapy follow-up study group. JAMA. 280:347–355.

Rubino C, de Vathaire F, Dottorini ME, Hall P, Schwartz C, Couette JE, Dondon MG, Abbas MT, Langlois C, Schlumberger M. 2003. Second primary malignancies in thyroid cancer patients. Br J Cancer. 89:1638–1644.

Seidlin SM, Marinelli LD, Oshry E. 1946. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. J Am Med Assoc. 132:838–847.

Sgouros G, Hobbys RF, Song H. 2011. Modelling and dosimetry for alpha-particle therapy. Curr Radiopharm. 4:261–265.

Sgouros G, Roeseke JC, McDevitt MR, Palm S, Allen BJ, Fisher DR, Brill AB, Song H, Howell RW, Akabani G, et al. 2010. MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. J Nucl Med. 51:311–328.

Siegel E. 1999. The beginnings of radioiodine therapy of metastatic thyroid carcinoma: a memoir of samuel m. seidlin, m. d. (1895–1955) and his celebrated patient. Cancer Biotherapy and Radiopharmaceuticals. 14:71–79.

Stokke C, Gabina PM, Solny P, Cicone F, Sandstrom M, Gleisner KS, Chiesa S, Spezi E, Papini M, Konijnemberg M, et al. 2017. Dosimetry-based treatment planning for molecular radiotherapy: a summary of the 2017 report from the internal dosimetry task force. EJNMMI Phys. 4:27.

Strosberg J, Krenning E. 2017. 177Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 376:1391–1392.

Wagner HN Jr, Wiseman GA, Marcus CS, Nabi HA, Nagle CE, Fink-Bennett DM, Lamonica DM, Conti PS. 2002. Administration guidelines for radioimmunotherapy of non-Hodgkin’s lymphoma with (90)Y-labeled anti-CD20 monoclonal antibody. J Nucl Med. 43:267–272.

Wiseman GA, Kormmehl E, Leigh B, Erwin WD, Podoloff DA, Spies S, Sparks RB, Stabin MG, Witzig T, White CA. 2003. Radiation dosimetry results and safety correlations from 90Y-Ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin’s lymphoma: combined data from 4 clinical trials. J Nucl Med. 44:465–474. eng.

Witzig TE, Molina A, Gordon LI, Emmanouilides C, Schilder RJ, Flinn IW, Darif M, Macklis R, Vo K, Wiseman GA. 2007. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. Cancer. 109:1804–1810.

Zukotynski K, Jadvar H, Capala J, Fahey F. 2016. Targeted radionuclide therapy: practical applications and future prospects. Biomark Cancer. 8:35–38.