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Short Communication

Targeted alpha-particle therapy – possibilities of post-therapeutic imaging

Monika TULIK [1,ABCDEF*], Jolanta KUNIKOWSKA [1,ADEF]

[1]*Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland*
[*]*Corresponding author: Monika Tulik; monika.tulik@wum.edu.pl*

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Abstract

The article presents the physical foundations of targeted radioisotope therapy with alpha particles, difficulties of imaging after an administration of alpha emitters, as well as current research trends and possibilities of their post-therapeutic imaging.

Keywords: targeted alpha-particle therapy; alpha particles; imaging.

Introduction

Targeted radioisotope therapy (TRT) or radiopharmaceutical therapy (RPT) is a treatment with the use of a radioactive drug (radiopharmaceutical) binding to selected type of cells (often neoplastic). Predominantly, it is a systemic treatment, but it may also be given locoregionally or intra-arterially. The advantages of this type of therapy over others are, firstly, that the uptake of a therapeutic radiopharmaceutical can be monitored *in vivo* immediately after its administration (by planar scintigraphy/single photon emission computed tomography, SPECT, or positron emission tomography, PET). This is extremely important because the accumulation of the radiopharmaceutical at the target site (corresponding to the absorbed dose in targeted cells) is a strong predictor of the success of the applied therapy. Looking at it from another site, it is possible to label targeted molecules with radionuclides suitable for scintigraphy or PET imaging. This offers new options, especially to oncological patients, where an optional treatment is selected by corresponding imaging results. This approach is called “theranostics”, which means the use of a diagnostic tool to predict the efficacy of a therapeutic option.[1] Secondly, radionuclides labelled molecules as a delivery vehicle can accumulate in the primary tumour or each metastatic site, as long as targeted cells can bind a ligand (e.g. by a specific receptor or other mechanism of binding). On the other hand, healthy cells, which do not bind the targeted molecule, so are not directly irradiated, which translates into little exposure of healthy tissue to ionizing radiation. Low irradiation of healthy tissues should correspond to a low rate of post-therapeutic complications, as well as a lower probability of generation of secondary malignant neoplasms.[2,3] Thirdly, many radionuclides are now available emitting different types of radiation at different energies, which enables to selection of radioisotopes based on their physical properties for a specific purpose and individual patient's needs. A good example of such an approach is various uses of itrium-90 (^{90}Y) and lutetium-177 (^{177}Lu). It has been suggested that ^{90}Y is more suitable for bigger lesions of neuroendocrine neoplasms (NENs) compared to ^{177}Lu, because of the longer range of emitted β^- particles (negatrons) in tissue. Moreover, a combination of ^{90}Y and ^{177}Lu could be better than either radionuclide alone for peptide receptor radionuclide therapy (PRRT) in NENs, with an improved overall survival.[4,5]

From its very beginning, namely from the time of the first use of iodide-131 (^{131}I) for differentiated thyroid cancer and hyperthyroidism treatment and phosphate-32 (^{32}P) for polycythemia vera therapy, the focus of the nuclear medicine therapeutic community was paid on radioisotopes emitting negatrons. This was of course caused by relatively easy production and wide availability of radioisotopes decaying with β^- emission, as well as the development of radiopharmacy (synthesis of new target molecules and chelators, ensuring the stability of obtained vectors with radioisotopes emitting negatrons). Today, no one denies the proven clinical effect of using TRT in treatments of such diseases as hyperthyroidism, differentiated thyroid cancer, disseminated and inoperable NENs, neuroblastoma in children, bone pain, joint synovitis, metastatic liver cancer or metastatic prostate cancer. However, there are still many aspects of targeted radioisotope therapy that need to be optimized, and many ways for its further development.[6] One of the possibilities is to replace radioisotopes emitting negatrons with alpha particle-emitting radionuclides.

Authors’ contribution: A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

Basics of targeted alpha-particle therapy

Targeted alpha-particle therapy (TAT) is a relatively new therapeutic method. It can be a treatment option for patients resistant to conventional therapies, not only TRT with the use of β^- emitters.

Alpha particles are doubly ionized helium-4 nuclei (two protons and two neutrons) emitted during the decay of radioisotopes, usually with an atomic number Z greater than 82. They are more toxic to target cells than other types of ionizing radiation (e.g. negatrons). Their significant effectiveness results from their physical properties. They are characterized by high linear energy transfer (LET ≈ 100 keV/μm, ranging from 50 to 230 keV/ μm), so they deposit a lot of energy over a very short, linear track.[7] Indeed, alpha particles have a very short range in matter, on the order of < 100 μm. In practice, this limits their cytotoxic effect mainly to targeted cells. Alpha particles have a higher probability of causing double-stranded breaks to DNA structure, which can be irreparable. Cell death as a result of this type of damage is largely independent of the state of oxygenation and the phase of the cell cycle.[8] Relative biological effectiveness (RBE) of 5 was recommended for projecting the possible deterministic biological effects associated with an estimated alpha-particle absorbed dose.[9] All these features ultimately lead to the delivery of a substantial absorbed dose only to the target cells, while limiting damage to the surrounding healthy (non-targeted) tissues.[10]

Alpha-particle emitters for therapeutic applications, which have the potential for clinical use, are presented in **Table 1**.[11] Among several alpha-particle emitters suitable for use in TAT, actinium-225 (^{225}Ac) and bismuth-213 (^{213}Bi) have been particularly promising. The chemical properties of these metals, allow for obtaining a stable chemical connection with many molecules using the popular chelator DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). The chemical stability of the final compound (a connection of the radioisotope to the ligand via the chelator) is one of the key parameters because highly unstable molecules are not good candidates for effective radioisotope-labeled drugs. The unstable compound would disintegrate before the selected molecule could bind to f.e. a specific receptor, and as a result, alpha particles would deposit their energy not to the selected cancer cells, but to some healthy tissues.

Ultimately, the high relative biological effectiveness and cytotoxicity of this type of radiation explain why alpha particle emitters are gaining increasing importance in targeted radioisotope therapy (both in systemic and locoregional applications). At present TAT is mainly focused on neoplastic diseases and improving the quality of life of patients with multiple metastases. Until now, only radium-223 dichloride ([^{223}Ra]RaCl$_2$, "XOFIGO"®) has obtained marketing authorization in Europe and North America for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases without visceral metastases, based on data obtained from the ALSYMPCA trial.[12]

Other applications of alpha emitters for targeted radioisotope therapy described in the literature are preclinical and clinical studies conducted so far in a limited number of centres worldwide. More information about current studies with the use of alpha-emitters, including conducted clinical trials, can be found in the publications of Zhang et al.[13] and Jabbar et al.[14] It is worth mentioning that the Department of Nuclear Medicine, Medical University of Warsaw, Poland has been conducting research on TAT for the treatment of patients diagnosed with glioblastoma recurrence for more than a decade. The method is based on administering substance P (neurokinin type 1 receptor ligand, NK-1) labelled with ^{213}Bi or ^{225}Ac directly to the tumour or to the postoperative tumour bed.[15]

Table 1. α-radionuclides for potential clinical use (based on data published in [11]).

parent	daughter	$t_{1/2}$	emissions per decay
^{225}Ac		9.9 days	4α, 3β −
	^{213}Bi	46 min	1α, 2β −
^{211}At		7.2 h	1α, 1EC*
^{227}Th		18.7 days	5α, 2β −
	^{223}Ra	11.4 days	4α, 2β −
^{224}Ra		3.6 days	5α, 2β −
	^{212}Pb	10.6 h	1α, 2β −
	^{212}Bi	1.0 h	1α, 1β −
^{149}Tb		4.1 h	1α, β +

**EC, electron capture*

Difficulties with post-therapeutic imaging of α-radionuclides

The use of alpha-particle emitters in the clinical environment requires a new approach to imaging and dosimetry, compared to the well-known and quite detailed imaging protocols and calculation methods of absorbed dose for TRT with β^- particles. Post-therapeutic planar or SPECT imaging of the distribution of alpha particles in the patient's body, especially quantitative, seems to be possible, however extremely difficult. There are several reasons for that. Firstly, γ radiation and x-rays accompanying the decays of alpha-particle emitters have a low abundance. Detailed information about the intensities of gamma and X-ray lines for individual alpha-emitting radioisotopes can be found in [16]. Secondly, patients receiving alpha-particle emitters labelled compounds are typically injected with the activity of a few MBq. For comparison, standard PRRT of patients with NENs with [^{177}Lu]Lu-DOTATATE assumes the administration of several GBq of therapeutic activity. Thirdly, energies of most gammas emitted in the line with alpha decays lie in the suboptimal range for proper camera gamma performance (more than around 160 keV). One could observe a high contribution of down-scatter of higher energy photons. A

septal penetration could also be observed, even when high-energy (HE) collimators are used. All this together results in a very limited number of total counts in the image with a significant contribution of noise. Hence, in the case of alpha-particle emitters, it can limit not only the quantitative potential of images but also the positive, qualitative identification of lesions for analysis.

Some of the alpha-particle emitters could be imaged directly. An example of such a radioisotope is ^{213}Bi, which decays with the emission of one α particle of 8.4 MeV energy and the accompanying emission of gamma radiation of 440 keV. The gamma line of 440 keV gives an opportunity to simply track and localize molecules labelled with ^{213}Bi. However, some parent radioisotopes decaying with the emission of alpha particles do not generate gamma radiation during their decay, and the observed gamma lines come from their daughter radioisotopes from the decay chain. So, it is not possible to perform imaging of the distribution of the directly administered radioisotope; however, assuming that parent radioisotope and daughter radioisotopes stay in the same place, it is possible to use radiation accompanying the decay of daughter isotopes for imaging. This is the case of ^{225}Ac, for which francium-221 (^{221}Fr) and ^{213}Bi, emitting gamma radiation with an energy of 218 keV and 440 keV, respectively, could be imaged. Seo Y notes, however, that even if direct imaging of parent radionuclides and their decay chains is not practically feasible, surrogate radiopharmaceuticals with more imaging-friendly radionuclides instead of alpha-emitting radionuclides may be a compromise, and still may add valuable information for the development and implementation of TAT as long as there is a verification step to show similar biokinetics between a therapeutic alpha-emitting radiopharmaceutical and its surrogate imaging radiopharmaceutical.[16]

Experimental attempts at imaging distribution of α-radionuclides

Obtaining not only qualitative but, above all, quantitative images, allowing for the assessment of the absorbed dose in the selected area of interest, is a research challenge. Currently, there are only a few publications confirming the possibility of obtaining quantitative scintigraphic images of alpha-emitting radioisotopes. It should be highlighted that most of earlier studies rely on planar images. Previously, SPECT imaging of alpha emitters has been performed, and interest in its quantitative option has been observed for only about 5 years.

For imaging of ^{223}Ra and its progeny, three major photon peaks are of potential use (82 keV, 154 keV, and 270 keV).[17] Hindorf C et al. performed a phantom study showing that a planar quantitative imaging of ^{223}Ra is possible with a sufficient degree of accuracy for a clinical situation, with the camera equipped with either a medium- or high-energy collimators, and with a 20% wide energy window centered on 82 keV.[18] Further, several reports confirming the possibility of planar quantitative imaging of ^{223}Ra in clinical conditions were published. However, quantification of such images is difficult and has not become a part of the clinical routine for patients treated with ^{223}Ra.[19-22] It is worth noting that Murray I et al. showed the possibility of γ-camera quantification of thorium-227 (^{227}Th) and ^{223}Ra by using multiple energy window acquisitions.[23]

Few studies refer to qualitative and quantitative imaging after administration of ^{225}Ac and ^{213}Bi. Since ^{213}Bi is a radioisotope belonging to the ^{225}Ac decay chain, as mentioned earlier, imaging of ^{225}Ac can be performed, among others, by detecting photons emitted by ^{213}Bi. Therefore, the papers on imaging these isotopes will be discussed together.

Sgouros G et al. obtained one of the first quantitative images of a patient with relapsed acute myeloid leukaemia treated systemically with ^{213}Bi labelled to a monoclonal antibody HuM195.[24] Corrdier D et al. performed one of the first qualitative images of ^{213}Bi during locoregional treatment of patients with functionally critically located gliomas.[25] The first qualitative planar imaging of ^{225}Ac was performed in 2015, and SPECT in 2020.[26-28] Gosewisch A et al. published a short paper about the first effort to perform quantitative SPECT/CT imaging and dosimetry for [^{225}Ac]Ac-PSMA-I&T.[29] Delker A et al. demonstrate the clinical feasibility of quantitative low-count SPECT imaging for [^{225}Ac]Ac-PSMA-I&T therapy of advanced prostate cancer based on the ^{213}Bi peak and provide a first image-based estimate of the radiation absorbed dose in critical organs and lesions.[30] Benabdallah N et al. established that multiple-energy windows are recommended to provide higher count statistics and to improve the quality of ^{225}Ac SPECT images.[31] According to these authors, such an acquisition protocol could also be the basis for its quantification. Liubchenko G et al. perform quantitative SPECT/ CT of prostate cancer patients after [^{225}Ac]Ac-PSMA-I&T therapy, exploiting all available photopeaks, to compare the pharmacokinetics of the two ^{225}Ac daughters ^{213}Bi and ^{221}Fr.[32] The use of the ^{213}Bi or ^{221}Fr post-therapeutic scans resulted in comparable (within 8%) absorbed dose estimates for the kidneys and lesions. The authors concluded that this finding may offer the opportunity to simultaneously image both photopeaks for dosimetry purposes to improve the counting statistics. Quantitative results for the peak at 78 keV (the third of the major photopeaks in ^{225}Ac energy spectrum, originating from a few ^{225}Ac gamma lines of low abundance and bremsstrahlung X-rays from ^{209}Pb along with many scattering photons) have been comparable to those obtained for the photopeaks of ^{213}Bi and ^{221}Fr, suggesting that this signal could also be used to improve the signal strength for quantitative ^{225}Ac SPECT imaging. Tulik M et al confirmed the feasibility of quantitative SPECT imaging of ^{225}Ac with multiple energy windows, in a model reproducing specific conditions of TAT using substance P labelled with ^{225}Ac in the case of patients with recurrent glioblastoma.[33]

According to the knowledge of the author, for the remaining alpha particle emitters considered to have potential for future clinical applications (namely astatine-211 (^{211}At), terbium-149 (^{149}Tb), radium-224 (^{224}Ra) / lead-212 (^{212}Pb)), mostly phantom objects, Monte Carlo simulations or preclinical models (mice) have been studied so far to confirm the possibility of their quantitative imaging.[34-39] We could find only one study assessing the pharmacokinetics and imaging of ^{212}Pb-TCMC-trastuzumab after intraperitoneal administration in patients with HER-2-expressing malignancy.[40]

Conclusions

Targeted alpha-particle therapy is a relatively new form of TRT that offers hope to patients who have not benefited from previous, standard treatments. However, imaging of patients after the administration of alpha emitters, especially quantitative, still requires a lot of research effort.

Editor's comment

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