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Overview of Development and Formulation of ^{177}Lu-DOTA-TATE for PRRT

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Abstract: Peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs has become an established procedure for the treatment of patients suffering from inoperable neuroendocrine cancers over-expressing somatostatin receptors. Success of PRRT depends on the availability of the radiolabeled peptide with adequately high specific activity, so that required therapeutic efficacy can be achieved without saturating the limited number of receptors available on the target lesions. Specific activity of the radionuclide and the radiolabeled somatostatin analog are therefore important parameters. Although these analogs have been investigated and improved, and successfully applied for PRRT for more than 15 years, there are still many possibilities for further improvements that fully exploit PRRT with ^{177}Lu-DOTA-TATE.

The summarized data presented herein on increased knowledge of the components of ^{177}Lu-DOTA-TATE (especially the purity of ^{177}Lu and specific activity of ^{177}Lu) and the reaction kinetics during labeling ^{177}Lu-DOTA-TATE clearly show that the peptide dose and dose in GBq can be varied.

Here we present an overview of the development, formulation and optimisation of ^{177}Lu-DOTA-TATE, mainly addressing radiochemical parameters.

Keywords: ^{177}Lu-DOTA-TATE, DOTANOC, DOTATOC, DOTA-TATE, PRRT, radiochemistry, formulation.

INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) employing radiolabeled somatostatin analogs has become an established procedure for the treatment of patients suffering from inoperable neuroendocrine tumors (NET) over-expressing somatostatin receptors [1-10]. The use of several radiolabeled peptides such as, ^{177}Lu-DOTA-TATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid coupled Tyr^3-octreotate, Fig. **1**), ^{177}Lu-DOTATOC (DOTA coupled Tyr^3-octreotide) and ^{177}Lu-DOTANOC (DOTA coupled Nal^3-octreotide) have been investigated and reported for this purpose [1-12]. The clinical results obtained with ^{177}Lu-DOTA-TATE are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild [6, 13, 14], and the median duration of the therapy response for these radiolabeled analogs of octreotide is 30 - 40 months [15]. The patients' self-assessed quality of life increases significantly after treatment with ^{177}Lu-DOTA-TATE. There is a benefit in overall survival of several years from the time of diagnosis in patients treated with ^{177}Lu-DOTA-TATE in comparison to historical controls (*e.g.* treatment with Sandostatin®) [15]. Balancing benefits (clinical response to radionuclide therapy) *vs.* risks (normal organ radiotoxicity) is a significant challenge [16]; and careful assessment of biodistribution, dosimetry, and toxicity is thus essential, preferably on a personalized basis [16, 17]. The first clinical phase III study to evaluate safety and tolerability of ^{177}Lu-DOTA-TATE and compare therapeutic responses after ^{177}Lu-DOTA-TATE with those after treatment with a high dose of the unlabeled octreotide analog LAR (Novartis) is currently underway in several countries (http://clinicaltrials.gov/ct2/show/NCT01578239?term=NCT01578239&rank=1) [18].

Among other factors, success of PRRT depends on the availability of the radiolabeled peptide with adequately high specific activity (SA), so that required therapeutic efficacy can be achieved without saturating the limited number of available receptors on target lesions [19-21]. This, in turn, directly depends on the SA of the radionuclide and the radiolabeled somatostatin analog. Here we present an overview of the development of ^{177}Lu-DOTA-TATE, mainly addressing radiochemical parameters.

HISTORY OF RADIOLABELED PEPTIDES

G-protein-coupled receptors like somatostatin receptors are frequently overexpressed on human tumor cells [22, 23]. Somatostatin receptor–targeted imaging, initially with Tyr^3-octreotide and later with [^{111}In-DTPA^0]octreotide (OctreoScan), was important for imaging and diagnostics of NET in nuclear medicine [8, 24]. Radiolabeled peptides targeting G protein–coupled receptors with DOTA as the bifunctional chelator were developed and have shown *in vivo* stability, favourable pharmacokinetics (PK), and high and specific receptor-mediated tumor uptake [8, 24-26]. The uptake kinetics of radiolabeled-DOTA-peptides such as DOTATOC, DOTANOC and DOTA-TATE are rapid [25-27]. These desirable PK properties are required for PRRT.

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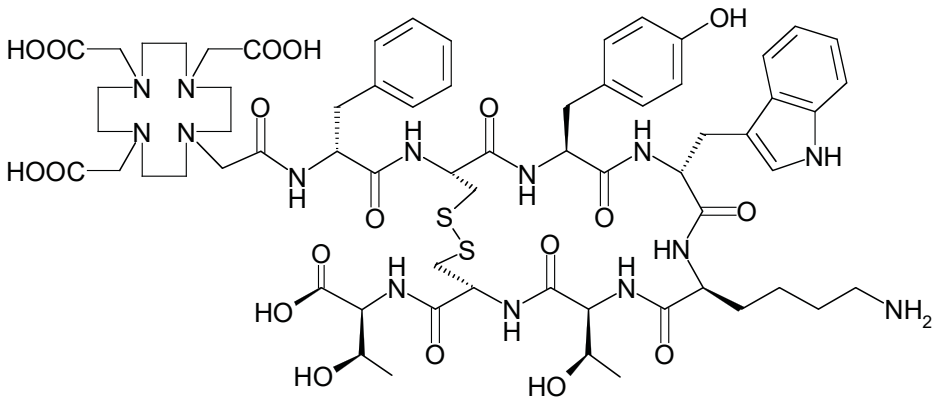

DOTA-DPhe-Cys-Tyr-DTrp-Lys-Thr-Cys-Thr
DOTA-DF-C-Y-DW-K-T-C-T

Fig. (1). Structural formulae of DOTA-TATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid coupled Tyr^3-octreotate). Molecular formulae, $C_{65}H_{90}N_{14}O_{19}S_2$, molecular weight is 1435.6.

DOTATOC, DOTANOC OR DOTA-TATE?

These radiopeptides (DOTATOC, DOTANOC, DOTA-TATE) have the highest affinity to the subtype 2 of the somatostatin receptor family [28], which is also most commonly expressed by most NET [19, 23]. Esser *et al*. reported a longer tumor residence time for ^{177}Lu-DOTA-TATE compared to ^{177}Lu-DOTATOC. Despite a longer residence time in kidneys after ^{177}Lu-DOTA-TATE, tumor dose will always be higher. Therefore, these authors concluded that the better peptide for PRRT is ^{177}Lu-DOTA-TATE [28]. Wehrmann *et al.* compared the biodistribution of ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTANOC in patients, and concluded that tumor uptake and absorbed dose were comparable for both radiopeptides, whereas whole-body retention was lower for ^{177}Lu-DOTA-TATE, and therefore the authors advocate the use of ^{177}Lu-DOTA-TATE [15, 29].

Recently Das *et al.* reported accumulation of ^{177}Lu-DOTANOC and ^{177}Lu-DOTA-TATE in cancerous lesions. Qualitative analyses of the scans showed higher retention and slower clearance of activity in case of ^{177}Lu-DOTANOC compared to that of ^{177}Lu-DOTA-TATE [30].

For this overview it should also be mentioned that for diagnosis of NET, ^{68}Ga-DOTANOC has been reported to have the highest sensitivity and specificity, while for PRRT ^{177}Lu-DOTANOC has unfavourable pharmacodynamics (PD) and PK [30].

Most peptide analogs are rapidly cleared from the body *via* the kidneys and partly re-absorbed in the tubuli of these organs leading to a high absorbed radiation dose [31, 32]. A possibility to improve the results of ^{177}Lu-DOTA-TATE or treatment with other radiolabeled somatostatin analogs is to reduce activity uptake in critical normal tissues, such as kidneys [4, 5]. In clinical practice, PRRT with radiolabeled somatostatin analogs should always be administered with renal protective agents, *e.g*., lysine and arginine or a commercially available mixture of amino acids. These amino acids cause a reduced renal uptake of radioactivity in the

SPECIFIC RADIOACTIVITY (SA) OF DOTA-PEPTIDES

The SA has many different definitions, *e.g*. SA can be expressed as the activity per mass of the nuclide, or as activity per mass of the ligand. Moreover, dimensions of SA also vary. As an example, activity can be expressed in Ci or Bequerel, or the mass in nmoles or mg. For a recent overview, see [33].

There are many factors that influence the interaction of a radioligand with its receptor. In a saturable regulatory peptide binding processes (*i.e*., *in vitro* radioimmunoassay and receptor binding), the signal-to-background ratio is often improved by increasing the SA (expressed as activity units per mass units of ligand, *e.g*. MBq per nmol) of the ligand. In *in vivo* experiments it was shown that, contrary to what was expected, the percentage uptake of radiolabeled somatostatin analogs in somatostatin receptor–positive tissues is not optimal at the lowest dose of maximum SA; rather, the uptake is a bell-shaped function of the injected mass, initially increasing followed by a decreased uptake. These findings might be the result of 2 opposing effects, first a positive effect of increasing ligand concentrations on the rate of internalization by ligand-induced receptor clustering and secondly a negative effect because of saturation of the receptor at increasing ligand concentrations [19]. This implies that the sensitivity of detection of somatostatin receptor-positive tumors by peptide receptor scintigraphy (PRS) might be improved by administration of an optimized dose of radioligand, as was found for other radioligands [19, 34-38]. These findings have been confirmed in patients for [^{111} In-DTPA^0]octreotide [19, 39, 40] and led to improved quality of imaging with a significant increase in tumor uptake.

Jonard *et al.* [41] presented data on tissue distribution after the administration of ^{86}Y-DOTATOC, labeled with various amounts of DOTATOC (range of 50-500 μg); with higher peptide amounts the kidney dose was not affected, however, tumor dose decreased. Velikyan *et al.* also investigated the impact of peptide mass on binding to NET somatostatin receptors *in vivo* by using ^{68}Ga-DOTATOC as tracer at a constantly high SA, preceded by injection of 0, 50, 250,

Table 1. Physical characteristics and constants from reactor-produced ^{177}Lu from enriched ^{176}Lu (n, γ) ^{177}Lu.

Target	^{176}Lu
Decay product of ^{177}Lu	^{177}Hf
t½ [days]	6.71
nmoles per GBq ^{177}Lu pmoles per 37 MBq ^{177}Lu	1.39 51.3
Ci ^{177}Lu per mg GBq per mg ^{177}Lu	110 4070
Maximal achievable SA of ^{177}Lu-DOTA-peptide [GBq.nmol^{-1}]	
in Theory	0.72[a]
in Practice	0.12[b], 0.42[c] 0.5[d]

[a]: Since, in theory 1 nmol of a DOTA-peptide can incorporate 1 nmol nuclide, this number indicates the maximal theoretical SA of ^{177}Lu-DOTA-peptides
[b]: data from (n, γ) reactor-produced ^{177}Lu from enriched ^{176}Lu [19].
[c] :^{177}Lu reactor-produced *via* (n, γ) from enriched ^{176}Y [86, 87]. In theory, the SA of this ^{177}Lu is 0.72 GBq per nmol, however in practice, the highest achieved and reported SA was 0.42 GBq ^{177}Lu per nmol DOTA-peptide [33] (see also **SA of ^{177}Lu-DOTA-TATE)**
[d]: at high thermal neutron flux (*e.g.* 1.5*10^{15} neutrons cm^{-2} s^{-1}) as in the High Flux Isotope Reactor at Oak Ridge National Laboratory (ORNL), after 4 days of irradiation 80% of all the Lu atoms can be in the form of ^{177}Lu [47, 51]. DOTA-TATE was successfully radiolabeled with this material, up to a SA of 0.5 GBq nmol^{-1} [33].
Table is adapted from Ref [33].

10 minutes before the tracer [42]. Nine patients with gastro-enteropancreatic NET were included. Accumulation of activity in the tumors varied and depended on the total amount of the pre-administered octreotide. In 5 of 6 patients, the highest tumor- to-normal tissue ratio was found when 50 µg of octreotide was preadministered. Thus again, optimizing mass improved image contrast. However, 1 patient showed a continuously increasing tumor uptake even with higher octreotide pre-administered. The application of ^{68}Ga-labeled ligand for optimizing therapeutic applications of concordant radiotherapeutic labeled ligand needs further dosimetric studies. A relation (such as in PK and clearance) between the ligands labeled with ^{68}Ga versus the therapeutic radionuclide (*e.g.* ^{90}Y or ^{177}Lu) at early time points also needs to be established [42].

Beauregard *et al*. suggested that tumor sequestration of ^{68}Ga-DOTA-TATE is a major factor leading to a sinkeffect that decreases activity concentration in healthy organs such as the kidney. Compared with a fixed-dose PRRT protocol, an adjusted-dose regimen tailored to tumor burden, body habitus and renal function may allow greater radiation dose to individual lesions without substantially adding to toxicity in normal tissues [43]. On the other hand, Kletting *et al.* prefers to avoid the introduction of unnecessary inaccuracy in dosimetry, and therefore recommended using the same substance along with the same amount for pretherapeutic measurements and therapy [44].

From the above-mentioned arguments it can be concluded that the highest SA does not always result in the highest target uptake, and the amount of administered radio-

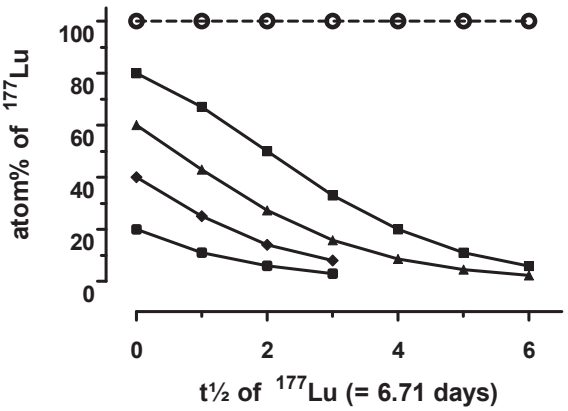

Fig. (2). Atom% of ^{177}Lu as f(t½) of ^{177}Lu. Atom% are expressed as % of 4070 GBq per mg Lu (4070 GBq per mg Lu is theoretical maximum, see Table 1), or 5.13 *10^{-11} moles per 37 MBq ^{177}Lu (see Table 1 and in text above **SA of ^{177}Lu**).

applied for optimizing personal patient peptide dose in PPRT. SA of ^{177}Lu and ^{177}Lu-DOTA-TATE are therefore important radiochemical and clinical parameters and are addressed separately, in **SA of ^{177}Lu, SA of ^{177}Lu-DOTA-TATE** and **FAQ's**.

SA OF ^{177}LU

As mentioned earlier, SA has many different definitions [45, 46]. In theory 1 nmol of a DOTA-peptide can incorporate 1 nmol Lu^{3+}, this number indicates the maximal theoretical SA of ^{177}Lu-DTPA- or DOTA-peptides, see Table **1**. The highest achievable SA of radioligands, *e.g.* ^{177}Lu - DOTA-TATE can be radiolabeled in theory at a level of 0.72 GBq ^{177}Lu per nmol ligand (see Table **1**). However, there are several factors influencing SA, such as ^{177}Lu from (n, γ) reactor-produced from enriched ^{176}Lu contains ^{175}Lu and ^{176}Lu, and in variable amounts. For recent overviews, consult Refs [47-50]. The presence of ^{176}Lu reduces the maximally achievable SA in practice to 0.12 GBq ^{177}Lu per nmol ligand (see Table **1**). ^{177}Lu from (n, γ) reactor-produced from enriched ^{176}Yb has a higher SA, and revealed a higher maximal achievable SA: 0.42 GBq ^{177}Lu per nmol DOTA-TATE [33] (see Table **1**).

Another possibility to express SA of ^{177}Lu is in atom%, expressed as % of theoretical value 4070 GBq per mg Lu, or 5.13 *10^{-11} moles per 37 MBq ^{177}Lu (see Table **1**). In Fig. (**2**) the atom% of ^{177}Lu as f(t½) of ^{177}Lu are shown. To illustrate this, suppose SA of ^{177}Lu is 100 atom%, after 1 half-life of ^{177}Lu the activity has decreased to 50%, whereas the corresponding mass has decreased also 50%, thus the ratio hasn't changed and remains 100 atom%. Fig. (**2**) also shows another frequently encountered misunderstanding, *e.g.* suppose a SA of ^{177}Lu of 80 atom% (*e.g.* from ORNL, see legend of Table **1** and [51]), after 1 half-life SA hasn't decreased to 40 atom%. Indeed, the activity halved, but the mass of Lu has changed also.

To illustrate and clarify this, after 1 half-life the atom% has decreased to 67 atom%, after 2 half-lives to 50 atom% *etc.* (Fig **2**). Thus in contrast to 40 and 20 atom%, resp., that is frequently suggested.

In short, correction for the transformation of ^{177}Lu to

To illustrate the high SA of ORNL-produced ^{177}Lu was confirmed as the highest achieved SA of ^{177}Lu -DOTA-TATE was 0.5 GBq per nmol DOTA-TATE.

SA OF ^{177}LU-DOTA-TATE

In daily practice ^{177}Lu -DOTA-TATE is produced at a SA of 40 MBq per nmol. Unfortunately, the need for high SA is often compromised by conflicting practical parameters, such as the pH and solubility of the radionuclide during radiolabeling. The pH determines reaction rates and yields, *i.e.* the rate of formation of the metal-DOTA complexes increases with pH, but on the other hand the solubility of Lu^{3+} decreases when pH is increased [52]. Moreover, reaction kinetics differ for each radionuclide and reactions can be hampered by contaminants, including contaminants from target material and decay products, see Table **1** [20]. Fortunately, $^{177}Hf^{4+}$ (decay product of ^{177}Lu, see Table **1**) does not interfere with the incorporation of ^{177}Lu in the DOTA-moiety under these conditions [21]. Eventually the highest achievable SA of ^{177}Lu-DOTA-TATE is determined by the SA of ^{177}Lu (Table **1**) [46].

It should also be noticed that the specifications mentioned on the datasheet of vendors frequently state that metal ions like Zn and Fe will not exceed 20 µg per Ci ^{177}Lu (1 Ci ^{177}Lu equals $5.13*10^{-8}$ moles, see Table **1**), however, when it reaches this level, and expressed in molar ratio *vs*. Lu, it would be 12 and 7 times higher, respectively, and this will certainly affect the highest achievable SA of ^{177}Lu-DOTA-TATE.

LABELING OF LU-DOTA-TATE AND QUALITY CONTROL

A typical reaction mixture for radiolabeling is 37 GBq (1 Ci, for 4 patients) $^{177}LuCl_3$ in 1 mL 0.05 M HCl with 1 mg DOTA-tate in 2.5 mL 50 mM sodium-ascorbate and gentisic acid and a final pH of 4 [38, 53-55]. Reaction kinetics for labeling DOTA-peptides differ per radionuclide, *e.g.* ^{177}Lu, reactions at pH 4–4.5 were completed after 20 min at 80°C [20]. After radiolabeling and cooling the reaction mixture to room temperature a chelator, such as DTPA is added. There are several reasons for this addition. First, it is difficult to take a representative sample from a solution containing DOTA-conjugated analogs labeled with radionuclides that are known to form colloids. For example, in the accurate determination of unchelated ^{177}Lu during the standard quality control by ITLC (0.1 M Na-citrate, pH 5 as mobile phase) or HPLC, the unchelated will be rapidly bound to the origin of the ITLC or to HPLC column [56]. This will result in a false identification of the incorporation or RadioChemical Purity (RCP), respectively [56], see **Quality Control by HPLC**, below. The addition of a chelator solves this problem, and the addition is therefore necessary (see **RCP and Quenchers**, below). Second, the free ionic fraction of radionuclide in radiolabeled DOTA-peptides can effectively be complexed by the addition of chelator *in vitro*, and this results in an efficient complexation of the free ionic fraction of radionuclide and excretion as such [57]. Since the free ionic fraction of radionuclide in radiolabeled DOTA-peptides can be complexed and rerouted *in vivo* effectively the specification for the % of incorporation (measured by ITLC) was lowered to 97 % at our Institution [57].

QUALITY CONTROL BY HPLC

Since radiolysis products of radiopeptides often differ in charge and shape *vs.* structure of the intact radiolabeled peptide, radiolysis of radiolabeled peptide can be quantified by HPLC. Typically RCP of radiolabeled DOTA-peptides is measured by HPLC and expressed as % of radiodetected peak area (*e.g.* $\mu V.sec^{-1}$) of the intact radiolabeled peptide *vs.* all radio peaks measured during the same HPLC-analyses [33, 58]. There are reports on the determination of peaks by HPLC, including accuracy, linearity, precision, repeatability and detection limit [33, 58]. To our knowledge, there are no criteria to qualify a HPLC separation method *plus* radiodetection in the field of nuclear medicine as perfect, good or good enough. Therefore, we suggested a set of standardized requirements to quantify RCP by HPLC for radiolabeled DTPA- or DOTA-peptides, including a base-to-base separation of metal-DOTA-peptide *vs*. DOTA-peptide [33, 58].

In our opinion, RCP values are currently expressed in Arbitrary Units. The requirements to standardize RCP measurements would open standardization to compare RCP quantifications between different systems and laboratories.

The following items on Quality Control (QC) are items to ″enable and optimize″ intra- and inter-laboratory comparisons of QC of ^{177}Lu-DOTA-TATE:

i. ITLC is for monitoring incorporation of the radionuclide

ii. ITLC cannot replace HPLC.

iii. Radiodetection and software for determination of peak areas are currently not standardised.

In addition, incorporation is not identical to RCP, thus ITLC is not a correct technique to monitor RCP.

Asti *et al.* [59] reported base-to-base chromatographic separations by UPLC (Ultra HPLC) of DOTA-TATE labeled with different non-radioactive metal ions. How this new chromatographic technique will affect radiodetection (*e.g.* balance between sensitivity of the detector and resolution by HPLC and UPLC) is currently under investigation.

1. The tools in analytical chemistry are constantly improving and applied in nuclear medicine: *e.g.* we are now able to quantify peptide content and purity of DOTA-TATE and other DOTA-peptides [45], including,
2. Quantification and identification of metal impurities already present in the DOTA-moiety of DOTA-TATE and other DOTA-peptides [45], and to
3. Quantify SA of ^{177}Lu [45] and eventually.
4. Improve SA of the radioligand.

RCP AND QUENCHERS

Measuring and quantification of RCP is not standardized, and therefore comparison of radiolabeling and RCP of regu-

latory peptides between different HPLC-systems and between laboratories, is cumbersome. De Blois *et al*. presented an overview in measuring and quantification of radiolysis RCP of radiolabeled regulatory peptides, including ^{177}Lu-DOTA-TATE [58]. To calculate the radiation dose in the reaction vials during radiolabeling and storage of the radiopeptides, a dosimetry model was developed. With this model RCP in the absence of quenchers can now be predicted and the effects of quenchers studied [58, 60, 61].

The conclusion was that maintaining high RCP requires a combination of quenchers [33, 58, 60, 61].

It would be desirable to radiolabel, store and transport a ready-for-use one-vial liquid formulation (for PRS and PRRT) of radiolabeled peptides. The use of ethanol, in combination with a mixture of gentisic- and ascorbic acid, has superior effects on stabilizing radiolabeled somatostatin analogs [60]. As a consequence, ^{177}Lu-DOTA-TATE can now be stored and transported in a single-vial ready-for-use liquid formulation up to 7 days after radiolabeling.

Although not fully within the scope of this "Overview of the development, formulation and optimising of ^{177}Lu-DOTA-TATE, mainly addressing radiochemical parameters", there are several practical items addressed here which are strongly related with the application of ^{177}Lu-DOTA-TATE: 1st is the trend of applying robotics for radiolabeling and, 2nd is the ^{177m}Lu-containing waste.

APPLICATION OF ROBOTICS

Maus *et al.* investigated the current trend to include a C_{18} solid phase extraction (SPE) post-radiolabeling in order to remove unwanted components such as HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) and non-incorporated ^{177}Lu from the injection solution [62]. However, with the introduction of SPE purification, quenchers such as gentisic acid and ascorbic acid were also removed from the injection solution. As a result, there was a concordant dramatic drop of the RCP of ^{177}Lu-DOTA-TATE. Maus *et al*. therefore concluded that re-addition of ascorbic acid post C_{18} SPE purification is required to maintain the RCP of ^{177}Lu-DOTA-TATE [62].

^{177M}LU-CONTAINING WASTE

As in most cases in Nuclear Medicine departments radioactive waste streams are based on the half-lives of the used radionuclides, *e.g*. waste containing ^{177}Lu is mixed with ^{131}I-containing waste.

The level of clearance of radioactive waste is country- and t½-dependent, *e.g*. in European Union, the clearance level of radionuclides with t½ > 100 days is 10 Bq per g. However, within the European Union there are countries with more restrictive levels: *e.g*. 1 Bq per g. It is obvious, the reduction of the clearance level of radionuclides (10 → 1 Bg per g) will take an extra 3-4 half- lives of ^{177m}Lu (480-640 days) of storage to reach that level of 1 Bg per g. As an example, suppose the ^{177m}Lu activity is 0.01% of the ^{177}Lu activity. After 14 half-lives of ^{177}Lu (± 13 weeks) ^{177m}Lu activity equals the ^{177}Lu activity. The ratio in activity of ^{177m}Lu the irradiation time [48, 63]. ^{177m}Lu content from reactors such as HFR in the Netherlands and BR2 in Belgium is 0.05 kBq ^{177m}Lu per MBq ^{177}Lu (0.005% [64] and <0.05% (according to specifications for GMP-produced ^{177}Lu, IDB, Baarle Nassau, the Netherlands), and 0.015% from the Dhruva reactor (Mumbai, India)[6].

The presence of ^{177m}Lu in ^{177}Lu should not be ignored, therefore Bakker *et al*. advised to collect high-activity ^{177}Lu- and ^{177m}Lu-containing waste separately [64].

FUTURE ASPECTS

Although DOTA-peptides can be labeled with therapeutic radionuclides at high SA, the SA (expressed as activity per mass of ligand), may be too low for PRS or PRRT. In short, delivery of sufficient amounts of radioactivity to these targets may not be high enough for PRS or PRRT. There are various reasons for this, *e.g*. the amounts of available receptor is too low (receptor density in tissue is in the range of 10^{-13} and 10^{-9} M [21, 65-68]. There may be several other ways to circumvent this limitation, such as different ways of administration influencing PK of the radioligand, such as long-lasting infusions of the radioligand, fractionating the dose or combinations hereof [40, 69, 70] intra-arterial [71-73] or intratumoral administration [18, 74].

Studies in patients have thus far been performed with somatostatin receptor agonists (DTPA-octreotide, DOTA-TOC, DOTANOC, and DOTA-TATE), because such agonists are internalized in the (tumor) cells and radioactivity is retained in the cell. Another approach is the use of an antagonist of the ligand [75-78]. Receptor antagonists are not internalized and, therefore, thought to be inappropriate for imaging and therapy, as we reported for DTPA- and DOTA-bombesin agonists [35]. However, ligands labeled with short-lived radionuclides might be possible, especially with α-emitters [71, 72, 79-81], since these radionuclides have a high Linear Energy Transfer (high energy deposition within a short range), consequently the cell kill probability is high, but only if the target (*e.g*. DNA) is within range. For a recent overview, consult other sources [18, 43].

An important item for the success of PRRT is implementing knowledge from radiobiology, like the research on radiosensitivity of tumor (and within types of tumor) and normal tissue. Moreover, there is a myriad of combinations, including pharmacological options, such as the tyrosine kinase inhibitor Sunitinib [82], mTOR inhibitor Everolimus [83], and a variety of combinations of chemotherapeutics such as Capecitabine and Temolozomide in pancreatic NET [17, 84].

With all the above-mentioned possibilities in mind and although radiolabeled somatostatin analogs have been investigated and successfully applied for PRRT for more than 15 years, there are still many possibilities to improve and fully exploit PRRT with ^{177}Lu-DOTA-TATE, as discussed in detail in Refs [8, 10, 18, 73].

FAQ's

Hofman and Ricks recently raised the question whether PRRT with ^{177}Lu-DOTA-TATE should be performed under standardized, randomized, or personalized conditions? [17]

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