Overcoming nephrotoxicity in peptide receptor radionuclide therapy using $[^{177}\text{Lu}]$Lu-DOTA-TATE for the treatment of neuroendocrine tumours

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Abstract

Article history:
Received 4 February 2021
Received in revised form 21 June 2021
Accepted 21 June 2021
Available online xxxx

Keywords:
$[^{177}\text{Lu}]$Lu-DOTA-TATE
PRRT
GEP-NETs
Kidney
Nephrotoxicity
Renal protection

Peptide receptor radionuclide therapy (PRRT) is used for the treatment of patients with unresectable or metastasised somatostatin receptor type 2 (SSTR2)-expressing gastroenteropancreatic neuroendocrine tumours (GEP-NETs). The radiolabelled somatostatin analogue $[^{177}\text{Lu}]$Lu-DOTA-TATE delivers its radiation dose to SSTR2-overexpressing tumour cells, resulting in selective cell killing during radioactive decay. While tumour control can be achieved in many patients, complete remissions remain rare, causing the majority of patients to relapse after a certain period of time. This raises the question whether the currently fixed treatment regime (4 × 7.4 GBq) leaves room for dose escalation as a means of improving therapy efficacy. The kidneys have shown to play an important role in defining a patient’s tolerability to PRRT. As a consequence of the proximal tubular reabsorption of $[^{177}\text{Lu}]$Lu-DOTA-TATE, via the endocytic megalin/cubilin receptor complex, the radionuclides are retained in the renal interstitium. This results in extended retention of radioactivity in the kidneys, generating a risk for the development of radiation nephropathy. In addition, a decreased kidney function has shown to be associated with a prolonged circulation of $[^{177}\text{Lu}]$Lu-DOTA-TATE, causing increased irradiation to the bone marrow. This can on its turn lead to myelosuppression and haematological toxicity, owing to the marked radiosensitivity of the rapidly proliferating cells in the bone marrow. In contrast to external beam radiotherapy (EBRT), the exact absorbed dose limits for these critical organs (kidneys and bone marrow) in PRRT with $[^{177}\text{Lu}]$Lu-DOTA-TATE are still unclear. Better insights into these uncertainties, can help in optimizing PRRT to reach its maximum therapeutic potential, while avoiding severe adverse events, like nephropathy and hematologic toxicities. In this review we focus on the nephrotoxic effects of PRRT with $[^{177}\text{Lu}]$Lu-DOTA-TATE for the treatment of GEP-NETs. If the absorbed dose to the kidneys can be lowered, higher activities can be administered, enlarging the therapeutic window for PRRT. Therefore, we evaluated the renal protective potential of current and promising future strategies and discuss the importance of (renal) dosimetry in PRRT.

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Peptide receptor radionuclide therapy (PRRT) is a class of systemic cancer therapy that has gained increasing importance in the management of patients with unresectable or metastasized neuroendocrine tumours (NETs) overexpressing the somatostatin receptor type 2 (SSTR2). Lutathera® was the first-in-class PRRT drug to be approved (by the EMA in 2017 and the FDA in 2018) for the treatment of gastroenteropancreatic NETs (GEP-NETs). The radiopharmaceutical is comprised of the beta-emitting radionuclide lutetium-177 coupled to the somatostatin analogue (SSA) Tyr(3)-octreotate (TATE) through the bifunctional chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) ([177Lu]Lu-DOTA-TATE). As such, [177Lu]Lu-DOTA-TATE selectively delivers its radiation dose to tumour cells by high-affinity binding to the overexpressed SSTR2 (Fig. 1) [1]. While initially the beta-emitter yttrium-90 was used to radiolabel SSA, its greater energy (934 keV compared to 147 keV for lutetium-177) and longer path length causes a larger radiation dose to the radiosensitive glomeruli, resulting in a higher risk of developing nephrotoxicity [2,3]. GEP-NETs represent the most common subtype of NETs, which are a heterogeneous group of malignancies arising from the diffuse endocrine system. Although GEP-NETS are rare by incidence (around 3.6/100,000/year in the USA and 1.8/100,000/year in Europe), their slow-growing nature generates a large number of patients living with the disease (estimated prevalence of 48/100,000 in the USA and 38/100,000 in Europe) [4,5]. For patients with localized disease, surgery remains the preferred approach. However, metastatic disease is observed in approximately 30% of patients at diagnosis, requiring systemic treatments, of which PRRT is the most promising option [6].

1. Introduction

Market authorization was granted following the promising results of the NETTER-1 randomized phase 3 clinical trial. Significant survival and quality of life benefit was shown for patients treated with [177Lu]Lu-DOTA-TATE compared with high-dose octreotide LAR (the long acting repeatable unlabelled compound at twice the normal dosage), which represented the standard of care. [177Lu]Lu-DOTA-TATE treatment was associated with a higher overall response rate (18% versus 3%) and a longer median progression free survival (28.4 months versus 8.5 months) [7]. In addition, time to quality of life deterioration (TOD) was significantly longer in the [177Lu]Lu-DOTA-TATE group versus the control group [8]. Its capacity to kill tumours while largely sparing healthy tissues, makes PRRT with [177Lu]Lu-DOTA-TATE appear to be a magic bullet for targeted cancer treatment. However, this statement should be taken with some caution. While tumour control can be achieved in many patients, complete remissions remain rare, causing the majority of patients to relapse after a certain period of time. In addition, treatment is limited by potential side effects of the kidneys and the bone marrow, hindering the use to its full potential [9,10]. Results from the NETTER-1 trial showed 29 patients (26%) in the [177Lu]Lu-DOTA-TATE treatment group suffered a serious adverse event (SAE), of which 10 (9%) were related to the treatment. In the control group, 26 patients (24%) suffered a SAE of which 1 (1%) was treatment related. It can be concluded that there were no significant differences in the overall number of SAE between the [177Lu]Lu-DOTA-TATE group and the control group, but there were significantly more SAE related to the [177Lu]Lu-DOTA-TATE treatment. The majority of the grade 3 or 4 adverse events in the treatment group were 18 patients (17%) with gastrointestinal disorders, with significant higher incidence of nausea and vomiting than in the control group. Grade 3 or 4 blood disorders were observed in 14
patients (13%), with significantly higher incidences of thrombocytopenia and lymphopenia. The median follow-up time of the patients of 14 months in the initial NETTER-1 report, was most probably too short to observe nephrotoxicity [7].

1.2. Theragnostics

$^{[177}\text{Lu}]$Lu-DOTA-TATE is part of a theragnostics pairing, the same molecular targeting compound that is radiolabelled with lutetium-177 (therapeutics), can similarly be labelled with gallium-68 (diagnostics). Before starting PRRT with $^{[177}\text{Lu}]$Lu-DOTA-TATE, SSTR2 imaging (positron emission tomography (PET)) with $^{[68}\text{Ga}]$Ga-DOTA-TATE can be performed to examine the overexpression of these receptors in the tumour tissue. For patients to benefit from PRRT, tumour uptake should preferentially be higher or at least as high as normal liver uptake [11]. This pairing process prevents useless treatment of patients with insufficient SSTR2 tumour expression, as low maximum standardized uptake values (SUVmax) ($<$16–18) of $^{[68}\text{Ga}]$Ga-DOTA(0)-Phe(1)-Tyr(3)-octreotide ($^{[68}\text{Ga}]$Ga-DOTA-TOC) have shown to be a predictor of therapeutic failure [12].

1.3. Standard fixed treatment regime

The recommended treatment regime of $^{[177}\text{Lu}]$Lu-DOTA-TATE is fixed and consists of 4 infusions of 7.4 GBq each, with a recommended interval between each administration of 8 weeks, as used in the NETTER-1 trial. Distribution and dosimetry studies, based on full body (planar) and 3D SPECT scans, show a rapid uptake of the radiopptide in kidneys, tumour lesions, liver and spleen. Its elimination is primarily mediated by renal excretion. Within 24 h, approximately 60% of $^{[177}\text{Lu}]$Lu-DOTA-TATE is eliminated via the urine (65% within 48 h) [13]. For renal protection purpose, an intravenous infusion with the positively charged amino acids lysine and arginine is started 30 min prior to the beginning of the $^{[177}\text{Lu}]$Lu-DOTA-TATE infusion and maintained for at least 3 h after administration. This co-infusion reduces tubular reabsorption of the radiopptide by approximately 40% and thus reduces radiation exposure, limiting potential renal toxicities. However, adequate renal function is essential for this strategy to be effective. Therefore, PRRT with $^{[177}\text{Lu}]$Lu-DOTA-TATE is contraindicated in patients with kidney failure, as indicated by a glomerular filtration rate (GFR) lower than 30 mL/min. Patients with inferior renal function (GFR < 50 mL/min) have been identified to be at risk of increase in absorbed dose to the kidneys and bone marrow due to a longer circulation time of $^{[177}\text{Lu}]$Lu-DOTA-TATE, this also lead to an increase in hematologic toxicities [14]. For these reasons, renal function (together with liver function and haematology) tests are required before, during and after each administration. These are used to assess the patient’s condition and to adapt the therapeutic protocol if necessary (dose, infusion interval, number of infusions) [15].

1.4. Long-term follow-up

Because NETs are slow-growing and patients are expected to be treated for longer periods, life expectancy is long (median of 41 months), compared to other cancer types once metastasized [16]. That is why it is particularly important to ensure an expanded follow-up period to detect potentially long-term nephrotoxicity. The joint International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging practical guidance on PRRT in NETs recommends follow-up examinations every 8–12 weeks for the first 12 months, and thereafter twice a year [17]. Follow-up results of up to 3 years were reported in an evaluation of the kidney function in 323 patients treated with $4 \times 7.4$ GBq $^{[177}\text{Lu}]$Lu-DOTA-TATE, with only 1 patient developing grade 3 renal toxicity, which was not treatment related [13]. In another study 200 patients were followed after 1–10 cycles of $^{[177}\text{Lu}]$Lu-DOTA-TATE (maximizing the kidney dose to 23 Gy) over 3 years and longer, without any grade 3 toxicity and 1 grade 4 toxicity, again unrelated to the treatment [18]. However, while results from toxicity studies mainly focus on severe toxicity events (grade 3 or 4), persisting moderate toxicity (grade 1 or 2) can as well have a significant impact on the quality of life in this setting of a long-term treatment [19,20]. Therefore, it is essential to obtain a thorough understanding of the effect of PRRT on the kidneys, in order to minimize the gradual loss in renal function caused by radiation nephropathy.

1.5. Objectives

Although PRRT with $^{[177}\text{Lu}]$Lu-DOTA-TATE has proven its clinical benefit, approximately 15–30% of patients show disease progression during therapy and another 10–15% will progress early (6 months to 1 year) after treatment, indicating there is still room for improvement of PRRT efficacy. Even though PRRT with $^{[177}\text{Lu}]$Lu-DOTA-TATE is generally well tolerated, adverse events include haematological toxicity (10% grade 3 or 4), myelodysplastic syndrome (2–4%) and renal failure (<1% grade 4) [9]. These finding show that, despite several protective efforts, the kidneys and bone marrow remain the main dose-limiting organs to PRRT, as they pose an important limitation to the amount of radioactivity that can be safely administered to patients. In this review, we focus on the nephrotoxic effects of PRRT with $^{[177}\text{Lu}]$Lu-DOTA-TATE for the treatment of GEP-NETs. If the absorbed dose to the kidneys can be lowered, higher activities can be administered, enlarging the therapeutic window for PRRT. This statement is on the condition that there is no increase in bone marrow related toxicity. Therefore, we evaluated the renal protective potential of current and promising future strategies and discuss the importance of (renal) dosimetry in PRRT.

2. Renal handling and retention of radiopptides

2.1. Megalin/cubilin receptor complex

The kidneys are exposed to ionizing radiation while clearing the radiopptides from the body. Proteins and peptides with a molecular weight of less than 25 kDa (such as synthetic SSA) are freely filtered from the plasma through the glomeruli, ending up in the ultrafiltrate. After glomerular filtration, the ultrafiltrate (containing the radiopptides) is partly reabsorbed by the proximal tubular cells, as part of the normal renal physiological process preventing excessive loss of water and nutrients [3]. The megalin/cubilin receptor complex plays a key role in the reabsorption of radiopptides. These endocytic receptors are highly expressed on the apical side of proximal tubule cells. After interaction with these receptors, the radiopptides are internalized and transferred to the lysosomal cell compartment where...
degradation by proteolytic enzymes occurs. The metabolites are retained in the renal interstitium, situated between basement membranes of epithelia and vessels, resulting in extended retention of radioactivity in the kidneys (Fig. 2) [22].

2.2. Renal SSTR₂ expression

In addition to their active reabsorption, renal uptake and retention of radiolabelled SSA can also occur as a consequence of the basal expression of SSTR₂ in kidney tissue [23]. All five SSTR subtypes have shown abundant expression in human kidneys [22]. More specifically, SSTR₂ is expressed in the glomeruli and all SSTR subtypes are expressed in the tubuli (both distal and proximal convoluted tubules and loop of Henle) [20,24,25]. While proximal tubular reabsorption covers the major part of renal uptake, binding to SSTR₂ can contribute to the total renal uptake of radiolabelled SSA [21]. Interestingly, a recent study showed that treatment with unlabelled long-acting SSA prior to injection of [⁶⁸Ga]Ga-DOTA-TATE did not change the uptake in tumour tissue, but did reduce uptake in normal liver leading to an increased tumour-to-liver ratio. It can be assumed that SSTR₂ in normal tissues are saturated earlier than those of tumour tissue. If the same is true in the therapeutic setting with [¹⁷⁷Lu]Lu-DOTA-TATE, remains to be tested. However these findings put into question the current recommendation of withdrawing long-acting SSA 3–4 weeks prior to PRRT [26].

3. Renal function measurement

3.1. Glomerular filtration rate (GFR)

Different renal function tests have been documented in literature, varying from basic tests to more sophisticated methods. Most commonly the clearance of creatinine, an endogenous amino acid/metabolite that is freely filtered by the glomerulus, is measured. Based on serum and/or urine creatinine levels, a person’s glomerular filtration rate (GFR) can be estimated. Nephrotoxicity caused by PRRT is observed by a continuous decrease in GFR. Depending on the extent of the decrease in GFR or the corresponding increase in serum creatinine, different grades (1–5) of nephrotoxicity can be distinguished, according to the Common Terminology Criteria for Adverse Events (CTCAE) (Table 1). A recent systematic review evaluated short- and long-term nephrotoxicity after PRRT with yttrium-90- and lutetium-177-radiolabelled SSA in patients with different types of NETs [27]. The analysis included 34 studies, comprising 5386 participants, and a follow-up from 12 up to 191 months. They describe a mean annual decrease in estimated GFR between 2 and 4 mL/min/1.73 m², suggesting different grades of nephrotoxicity after PRRT. A higher median GFR decline was...
observed after treatment with yttrium-90-radiolabelled SSA (7.3%), compared to solely lutetium-177-radiolabelled SSA (3.8%). 17.4% of the total number of patients developed grade 1 or 2 nephrotoxicity, while grade 3 or 4 side effects (2.4%) were observed almost exclusively in patients treated with yttrium-90-radiolabelled SSA. An explanation for the reduced occurrence and severity of renal toxicity with lutetium-177 compared to yttrium-90, can be found in the combination of its shorter tissue penetration range (2 mm vs. 12 mm) and its lower $\beta$-energy (147 keV vs. 934 keV) [3]. Together, this results in limited cross-fire effects, causing less additional damage to the functional subunits (glomeruli) in close vicinity of the radiopeptide-accumulating cells (proximal tubuli) of the kidneys [28, 29].

3.2. Clearance of radiopharmaceuticals

It should be taken into account that different methods for monitoring renal function might render different results, varying in precision and accuracy. Because serum creatinine levels are affected by several factors such as diet, age and muscle mass, its measurement provides limited reliability. A more accurate renal function assessment is provided by measuring plasma clearance of radioactive substances, for example technetium-99m-labelled diethylene triamine pentaacetic acid ($^{99m}$Tc-DTPA). This method is preferably used for patients with pre-existing risk factors for long-term nephrotoxicity. In addition, gallium-68-labelled EDTA ($^{68}$Ga-Ga-EDTA) seems to have good potential in the assessment of renal function because it allows 3D PET imaging and quantification of the distribution of the tracer [20]. GFR is a measure of glomerular function and does not evaluate tubular function. After the radiopeptide has been filtered by the glomeruli, it is reabsorbed by the proximal tubuli and retained in the interstitium, where it exerts its effects for a longer period of time. Therefore, measurement of renal function using tracers such as technetium-99m-labelled diethylene triamine pentaacetic acid ($^{99m}$Tc-Tc-DTPA). This method is preferably used for patients with pre-existing risk factors for long-term nephrotoxicity. In addition, gallium-68-labelled EDTA ($^{68}$Ga-Ga-EDTA) seems to have good potential in the assessment of renal function because it allows 3D PET imaging and quantification of the distribution of the tracer [20].

5. Risk factors for PRRT nephrotoxicity

A wide variation exists on the reporting of nephrotoxicity in patients after PRRT with $^{177}$Lu-DOTA-TATE. For example, the nephrotoxicity assessment of Sabet et al., showed a mean reduction in GFR of 2.1 ± 13.1 mL/min/m$^2$ per year among 74 patients [30]. This large variability might be the consequence of patient and treatment heterogeneity, making certain groups more likely to experience renal side effects than others. Risk factors associated with the development of renal damage can be categorized as patient-related (e.g., age, pre-existing renal disease, hypertension, diabetes mellitus) or treatment-related (e.g., choice of radionuclide, time interval between cycles, cumulative radiation dose to kidneys) [27].

Bodei et al. evaluated the predictive effect of several clinical parameters for long-term toxicity in NET patients who underwent PRRT with $^{177}$Lu-DOTA-TATE [38]. It showed that mainly hypertension followed by lesions involving the kidneys were most significantly associated with nephrotoxicity following PRRT with $^{177}$Lu-DOTA-TATE, making these individuals more presumable and more markedly to suffer from renal toxicity. These results align with a study of Svensson et al., showing patients with inferior renal function to be exposed to higher renal absorbed doses [14]. These patients also experienced longer residence time of $^{177}$Lu-DOTA-TATE in the whole body, which showed a significant correlation with grade of haematological toxicity. However, the study of Bergsma et al. investigating nephrotoxicity after PRRT with $^{177}$Lu-DOTA-TATE, could not detect any significant association between assumed renal risk factors and loss of renal function over time [13]. They concluded that with the standard fixed regime (4 × 7.4 Gbq), nephrotoxicity is low. From a group of 323 patients, only 3 (1%) developed grade 2 renal toxicity and no grade 3 or 4 renal toxicity occurred. This data suggests that for PRRT with $^{177}$Lu-DOTA-TATE, higher radiation doses can be applied.

6. Renal dose limits

6.1. The biologically effective dose (BED)

Because data about nephropathy caused by PRRT were limited, experiences from EBRT were initially used to determine kidney dose limits. A renal dose tolerance limit of 15–18 Gy has been derived from EBRT, which is associated with a 5% likelihood of developing severe kidney damage within 5 years [39]. However, type and mode of radiation deposition of PRRT differs significantly from EBRT; radiation from the radiophosphate is not homogenously distributed within the organ, dose rates are much lower and not constant as they exponentially decrease with time (related to effective half time) and lastly, exposure is not acute but protracted from hours to days [20]. Therefore, the concept of the biologically effective dose (BED) might be more of interest, as it indicates the absorbed dose with the same...
biological effect, independent from the irradiation source [40]. For patients without associated risk factors, a 40 Gy BED is considered the renal upper limit. For patients with abovementioned risk factors a threshold less than 28 Gy is recommended [41]. The study of Löser et al. revealed an estimated total absorbed kidney dose of 20.7 ± 8.5 Gy following the standard therapy regime of 4 cycles with 7.4 GBq $^{[177]}$Lu-DOTA-TATE [42]. However, Garske-Román et al. states that 50% of patients might be undertreated and able to receive more than 4 × 7.4 GBq of $^{[177]}$Lu-DOTA-TATE before reaching 23 Gy to their kidneys [18]. Another drawback of the empiric regime is that the absorbed doses per injected activity (IA), in both tumours and healthy tissues, are highly variable between patients. Therefore, instead of administering a “maximum safe fixed activity”, an individual dosimetry-based approach might be preferable. This would allow the determination of a patient-specific activity to be injected in order to obtain an effective tumour treatment, while limiting severe side effects [43].

6.2. Personalized PRRT with $^{[177]}$Lu-DOTA-TATE based on renal dose

A personalized approach for PRRT with $^{[177]}$Lu-DOTA-TATE has been proposed in a study by Del Prete et al., in which the IA was adjusted to deliver a prescribed absorbed dose of 23 Gy to the kidney using quantitative SPECT/CT-based dosimetry [44]. The median per-cycle personalized IA was 8.9 GBq (range 0.7–32.4 GBq), representing a median 1.24-fold (and a maximum up to 4.38-fold) increase in IA over the currently used fixed-IA regime. The first results showed promising response rates and favourable tolerance profiles, suggesting the protocol to be safe to increase tumour irradiation in the majority of patients. Nonetheless, 51.9% of patients showed lymphocytopenia, which is remarkably higher than previously reported for empiric PRRT with $^{[177]}$Lu-DOTA-TATE (22.3%) [11]. This probably reflects the increased systemic and bone marrow irradiation resulting from the personalized protocol. Even though no clinical consequences (such as opportunistic infections) were observed during 3 months of follow-up, subacute haematological toxicities are associated with an increased occurrence of myelodysplasia and leukaemia [45,46]. Therefore, a personalized protocol in which the IA is adjusted not only to the absorbed dose to the kidneys, but also to the bone marrow, might be of greater value for improving patient outcomes. However, such an approach is not straightforward, as it would be more complex to determine the optimal dose for each patient and more difficult to draw any joint conclusions from clinical trials.

6.3. Salvage/relapse PRRT with $^{[177]}$Lu-DOTA-TATE

In another study, the safety of repeated PRRT cycles with $^{[177]}$Lu-DOTA-TATE (median of 9 cycles, range 8–13 cycles) in patients with recurrent NETs was assessed [47]. It was shown that therapy with 8 or more cycles of $^{[177]}$Lu-DOTA-TATE (mean administered activity of 7.6 GBq per cycle) was well tolerated and led to survival benefit, compared to patients who received only baseline treatment, consisting of 4 cycles of $^{[177]}$Lu-DOTA-TATE. No significant changes in the mean values of thrombocytes, leucocytes and serum creatinine were observed in comparison with baseline data. However, this was a small retrospective study, wherefore safety results cannot easily be transferred to the general NET population. Therefore, larger prospective trials are needed to determine the safety and survival advantage of this relapse therapy. For example, a recent study by van der Zwan et al., retrospectively analysed the efficacy and safety of salvage PRRT with $^{[177]}$Lu-DOTA-TATE in patients with progressive bronchial NETs or GEP-NETs [48]. A cumulative dose of up to 60.5 GBq salvage PRRT (obtained by adding 4 additional cycles of 7.4 GBq to the initial treatment) was shown to be safe and effective. Salvage therapy resulted in a significant longer overall survival compared to the control group. Safety appeared to be similar to that of initial $^{[177]}$Lu-DOTA-TATE treatment, with a total incidence of acute myeloid leukaemia and myelodysplastic syndrome of 2.2% and no observations of grade 3 or 4 nephrotoxicity. In this study, treatment dosing relied on the usual follow-up parameters of bone marrow and renal function. No personal dosimetry was used, which calls into question its added value, especially when comparing the reported survival of 81 months [48] to 54 months in the 23 Gy kidney dosimetry guided therapies [18]. In addition, a recent meta-analysis revealed a similar safety profile of NET patients re-treated with $^{[177]}$Lu-DOTA-TATE compared to initial treatment [49].

7. Nephroprotective strategies

Much research has already been conducted to reduce radiation damage to the kidneys during PRRT. This has revealed various important factors that play a role in the development of radiation nephropathy, which can be focused on in the development of protective strategies. These include modifying the characteristics of the radiopeptide, inhibiting renal uptake of the radiopeptides and reducing the harmful effects of radiation to the kidneys (Fig. 3). These strategies all aim to reduce the absorbed dose to the kidneys and/or increase the kidneys radiation tolerance [3].

7.1. Modifying the characteristics of the radiopeptide

7.1.1. Structural changes of the radiolabelled peptide

One approach to reduce renal uptake and retention of radiopeptides, is to bring structural changes to the peptide. Increasing its size or decreasing its affinity for renal transporters can result in reduced glomerular filtration and tubular reabsorption, respectively. Furthermore, substitution, addition, or deletion of certain amino acids can have an influence on the renal uptake of peptides. The pharmacokinetics of the radiopeptide might also be altered by coupling to other molecules e.g. polyethylene glycol (PEG) groups or albinum binding sequences. Nevertheless the affinity of the peptide for the SSTR2 receptor should remain intact, to ensure its uptake in the tumours. In addition, structural modifications resulting in an increased circulatory half-life, might increase the radiation dose to the bone marrow and subsequently increase the risk for hematologic toxicities [3].

7.1.2. Choice of the radionuclide

Over the past two decades, different radionuclides have been studied for their efficacy and safety in the treatment of NETs. These studies have revealed the more favourable toxicity profile of lutetium-177 over yttrium-90 [50]. Different radiolabelled SSA were tested in a preclinical setting. It was demonstrated that $^{[177]}$Lu-DOTA-TATE had the highest tumour uptake together with the best tumour-to-kidney ratio [51]. A smaller median decline in creatinine clearance and a lower mean cumulative renal dose were observed in patients treated with lutetium-177 compared with yttrium-90-DOTA-Phe(1)-Tyr(3)-octreotide (TOC) [52]. These findings are consistent with the results of a long-term evaluation of renal toxicity after PRRT showing a more marked, constant and progressive loss of renal function after $^{[90]}$Y-DOTA-TOC treatment [41].

Over the past few years, alpha-emitters, such as actinium-225 and bismuth-213, have gained increasing interest in therapy of NETs. With a path length of 40–100 μm (equivalent to the thickness of 1–3 cell widths), energy is delivered within a very short range to target sites causing even less radiation damage to adjacent cells. This short path length together with a higher particle energy (5–8 MeV) leads to a higher linear energy transfer (LET) of alpha particles compared to beta particles (~100 keV/μm vs. 0.2 keV/μm) [53]. This results in more severe and less reparable cell damage, which is beneficial in tumours but not in kidneys and other healthy tissues. Whether alpha-emitters are better candidates for PRRT remains to be investigated. Anecdotal clinical studies have shown that they might be more efficacious than beta-emitters [54], but the extent of the associated renal tubular damage and other possible healthy organ damages is presently still unclear.

7.2. Inhibiting renal uptake of the radiopeptides

7.2.1. Lysine and arginine amino acid infusion

The discovery that co-administration of an amino acid solution comprised of L-lysine and L-arginine with PRRT significantly reduces renal toxicity, has been the biggest success in nephroprotection so far. These cationic amino acids inhibit proximal tubular reabsorption of the radiopeptides, by competing for negative charges on the tubule cell membrane. As a consequence, recirculation of the radiopeptides is limited and the renal dose is reduced by 9–53%. This large range might be the consequence of the large diversity in absorbed dose between patients along with their renal function [50]. However, this strategy does not come without consequences. A hyperosmolar amino acid solution can cause nausea and vomiting, putting the patient in need for antiemetic treatment. Moreover, solutions containing a high amount (75 g) of lysine have shown to cause metabolic changes including hyperkalaemia, potentially resulting in (fatal) cardiac arrhythmias [55]. Gelofusine is commonly applied in critical emergencies and in the post-surgical setting as a plasma expander. It consists of bovine bone derived heat-treated succinylated gelatine. The exact mechanism by which it reduces renal uptake of radiopeptides is still unclear, but interference with the megalin-mediated tubular reabsorption is suspected. A drawback of its use is the risk of allergic reactions. Although these reactions are rare, some can result in a life-threatening anaphylactic syndrome. Therefore, caution and awareness from doctors administering the compound is vital [57,58].

7.2.2. Albumin fragments

Albumin is a natural megalin-cubilin ligand. However, because of its large size, only a small fraction is filtered in the glomeruli. Therefore, smaller fragments of albumin might be more suitable for inhibiting tubular reabsorption of radiopeptides. In vitro and in vivo studies in rats with different albumin-derived peptides demonstrated efficient reduction of radiopeptide renal uptake and suggested albumin-derived peptides to be promising candidates to ameliorate kidney protection in PRRT. However, as the physical and chemical characteristics of the fragments might differ from these of intact albumin, toxicity studies must be performed to ensure a safe administration in patients [59,60].

7.2.3. Renal brush border strategy

In a study by Arano et al., the renal brush border strategy is described as a potential alternative solution to the problem of high and persistent radioactivity levels in the kidney after PRRT [61]. This research focuses on the design of a cleavable linkage in the radiopeptide, that generates a radio metabolite by enzymes on the renal brush border membrane, which subsequently has a high elimination rate from the renal cells into the urine. However, it is important for the linkage to remain stable in plasma to avoid a decrease of radioactivity levels in the tumour. Reduced renal radioactivity levels have already been shown with
gallium-67-labelled low molecular weight antibodies in mice, but subsequent studies are needed to further refine the strategy and assess its clinical applicability.

7.3. Reducing the harmful effects of radiation to the kidneys

7.3.1. Dose fractionation

In EBRT, the linear-quadratic (LQ) model has been best validated to predict the biological response after irradiation. It takes into account not only the total dose, but also the characteristics of the treatment schedule such as fractionation. The main parameters of the LQ model, α and β, represent the intrinsic radio sensitivity of the irradiated cells. Tissues with low α/β values (kidneys) are more sensitive to absorbed dose rate changes compared to tissues with high α/β values (tumours) [62]. From EBRT it is known that dose fractionation results in better therapy tolerance, enabling the administration of higher total doses. During the dose delivery and in the interval between the fractions, the kidneys (and other healthy organs) have the capacity to repair from sub lethal radiation damage [3]. In the current treatment regime with $^{[177}\text{Lu}]$Lu-DOTA-TATE, the cumulative dose of 29.6 GBq is fractionated into 4 treatment cycles of 7.4 GBq each. A dose fractionation study with $^{[177}\text{Lu}]$Lu-DOTA-TATE in rats showed significant beneficial effects on kidney function. Injection of a single high dose of 355 MBq $^{[177}\text{Lu}]$Lu-DOTA-TATE resulted in severe renal damage, indicated by proteinuria, elevated serum creatinine and histological damage. Two weekly doses of 278 MBq resulted in significantly lower renal damage scores. Three doses of 185 MBq with intervals of a day, a week or a month showed decreasing serum creatinine levels in accordance with increasing fractionation intervals. Furthermore, the anti-tumour efficacy of fractionated PRRT showed to be comparable to that of the unfractonated dose [33]. However, NETs represent a heterogeneous group of malignancies, including both aggressive and indolent tumours. In slow-growing NETs, which are most probably represented by lower α/β-values, the protection by fractionation might not necessarily be much higher in kidneys compared to tumours. In addition, the lower dose rate for PRRT, compared to EBRT, might as well diminish the beneficial effects of fractionation.

7.3.2. α1-Microglobulin (A1M)

Coadministration of renal protective agents can potentially improve clinical PRRT. For example, α1-microglobulin (A1M), a human physiological radical scavenger and antioxidan, has shown to protect bystander tissue against irradiation damage. Ionizing radiation causes a chronic state of oxidative stress with continuous production of reactive oxygen species. A1M is a small plasma protein (26 kDA) able to bind and neutralize free radicals and to reduce oxidants and oxidative lesions. This way it can protect normal tissue from cell death. Kristiansson et al. demonstrated that A1M effectively inhibits short- and long-term radiation-induced renal damage in mice treated with $^{[177}\text{Lu}]$Lu-DOTA-TATE [63]. However, for A1M to be used as a renal radio protector during PRRT, its radio protective effect should only occur in the kidneys and not in the tumour (and metastases) to avoid a reduction in tumour control. This was confirmed by Andersson et al. who examined the influence of A1M on the in vivo biokinetics of $^{[177}\text{Lu}]$Lu-DOTA-TATE in NET-bearing mice, with a focus on tumour tissue [64]. No significant difference was found in the biodistribution of $^{[177}\text{Lu}]$Lu-DOTA-TATE and therapeutic efficacy (measured by reduction in tumour volume) between the $^{[177}\text{Lu}]$Lu-DOTA-TATE group and the coadministration group. It could be concluded that A1M does not negatively impact the therapeutic response in tumour tissue subjected to $^{[177}\text{Lu}]$Lu-DOTA-TATE treatment and may therefore be a promising kidney protector in conjunction with PRRT. The mechanism behind these findings still needs further investigation. A possible explanation, is that A1M is specifically localized in the kidneys and not (or to a much lesser extent) in the tumours. Whether the same effects will occur in humans, remains to be investigated. Further protective potential of A1M on liver, spleen, bone marrow etc. in $^{[177}\text{Lu}]$Lu-DOTA-TATE therapy might as well be explored in future studies.

7.3.3. Amifostine

Similarly, the radio protective drug amifostine can be used to reduce oxidative stress induced by ionizing radiation in healthy tissues. An alkaline phosphatase converts this prodrug into an active radio scavenger whereafter it is taken up into the cells. The concentration of the active metabolite has shown to be 100 times higher in kidneys compared to tumours, leading to a selective protection of kidneys and not tumours. Amifostine has shown its success in EBRT and chemotherapy and has therefore been approved as a radio protectant for clinical use. A rat study with $^{[177}\text{Lu}]$Lu-DOTA-TATE showed amifostine to be equally effective as lysine in the prevention of nephrotoxicity [65]. Another study showed coadministration of amifostine resulted in a decrease in renal uptake of $^{[177}\text{Lu}]$Lu-DOTA-TATE without affecting tumour uptake [66]. However, what the eventual effects on effectiveness of $^{[177}\text{Lu}]$Lu-DOTA-TATE treatment are, requires further investigation. In addition to its radio protective effect, amifostine (and its metabolite) might as well compete with radiopeptides in the megalin-mediated renal absorption. These findings suggest the application of amifostine during PRRT to reduce radiation absorbed dose to the kidneys and hereby prevent late development of renal fibrosis.

7.3.4. Blockers of the renin-angiotensin-aldosterone system (RAAS)

The renin–angiotensin–aldosterone system (RAAS) is a hormone system that regulates blood volume and systemic vascular resistance. It is composed of three major compounds: renin, angiotensin II, and aldosterone. These act to elevate blood volume and arterial tone in response to i.a. decreased renal blood pressure. The RAAS is frequently manipulated in the management of heart failure, hypertension, diabetes mellitus, etc. [67]. From EBRT, it is known that blocking the RAAS causes a reduction in radiation induced nephritis and fibrosis. Different studies showed the RAAS to be an important mediator of the inflammatory response in irradiated kidneys [68,69]. Therefore, RAAS inhibiting drugs have been investigated for their nephroprotective characteristics in PRRT. These drugs can be classified according to their mechanism of action and include angiotensin-converting-enzyme (ACE) inhibitors (e.g. captopril, enalapril), angiotensin II receptor blockers (sartans) and aldosterone receptor blockers (e.g. spironolactone). A recent study showed enalapril to be effective for nephroprotection during $^{[177}\text{Lu}]$Lu-DOTA-TATE therapy [70]. Both recovery of renal function and reduction of histological damage was observed in mice treated with enalapril for three months after PRRT with $^{[177}\text{Lu}]$Lu-DOTA-TATE. Surprisingly, another study showed coadministration of captopril to exacerbate the decline in renal function in mice after injection with actinium-225 labelled antibodies [71]. Additionally, more severe and extensive histopathologic kidney damage was observed in the captopril-treated mice compared to the placebo control group. In the same study, however, spironolactone significantly prevented the development of histopathologic and functional changes, while angiotensin receptor-1 blockade offered moderate kidney protection. These studies show a clear difference in the efficacy of mitigating radiation-injury by different RAAS antagonists. A possible explanation for the discrepancy in the protective effect of the ACE inhibitors (enalapril versus captopril) could be the different characteristics of the radionuclides (lutetium-177 versus actinium-225) used in both studies, resulting in varying sites and extentiveness of renal damage. Also the binding of bismuth-213, the daughter nuclide of actinium-225, to the cortex and the proximal renal tubules, may lead to enhanced renal toxicity [72]. This implicates that additional investigations are needed to clarify the (un)beneficial effects of RAAS inhibitors on various radiation induced renal injuries.

7.3.5. Metformine

A recent mouse study investigated the antidiabetic drug metformine for its nephroprotective effect in PRRT [73]. Both intravenous and oral administration of metformine with indium–111-labelled SSA reduced
renal accumulation of the radiopeptide to the same level as confiusion with lysine. These reductions were accompanied by higher uptake in tumours. Moreover, histologic scores of mice pre-treated with metformine showed a reduction in radiation-induced necrotic damage to kidney glomerular and tubular cells. Evaluation of kidney function demonstrated a reduction of serum creatinine levels to baseline in the metformine coadministration group. Further research is needed to investigate if the same effects occur with lutetium-177 labelled SSA and to clarify the mechanisms behind these observations. Again, metformine may interact with the megalin system to block reabsorption and retention of the radiounclides in the proximal tubular cells. However, the drug may be involved in several other pathways as well. From its first-line use in the treatment of type 2 diabetes, metformine is known to alter multiple enzyme activities resulting in reduced blood glucose levels and improved cell sensitivity to insulin. Furthermore, metformine has also demonstrated antioxidant and cancer-preventive effects. Exposing cancer cells to metformine, slows down cellular proliferation and can induce cell death upon glucose deprivation [74]. Whether or not this decreased cell proliferation is beneficial, as it might as well result in decreased radiation sensitivity of the tumour, requires further investigation.

8. Discussion

Despite the success of PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\), the majority of patients still cannot be cured and relapses occur on average 2–3 years after starting treatment [75]. Therefore, investigators are actively exploring strategies to improve the treatment efficacy. One major point of uncertainty, is whether the fixed activity regime, of 4 cycles of 7.4 GBq, leaves room for activity escalation as a means to optimize therapy. The kidneys, together with the bone marrow, have shown to play an important role in defining a patient’s tolerability to PRRT. We can assume that, with the current fixed regime and the applied protective strategies, the kidneys are not dose-limiting in the majority of patients. It seems that in most cases, the kidneys can manage even more than 4 treatment cycles, without developing any pronounced toxicity [76]. In patients with suboptimal renal functions, who are currently excluded from PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\), clearance of the radiopeptides is less efficient. This causes longer circulation times and subsequently longer and/or higher systemic radiation exposure. Therefore, the dose-limiting role of the bone marrow might be of greater importance, as it seems that increasing the injected activity per cycle and/or the number of cycles is associated with increased hematologic toxicities [44].

Personalized dosimetry could provide better insights into these uncertainties. It could help in determining the absorbed dose limits for critical organs (such as the kidneys and bone marrow) and the desirable absorbed doses to the tumours. It would allow adjustment of the injected activities accordingly, reducing both relapse rates (caused by under-treatment) and potential toxicities (caused by over-treatment). Therefore, the establishment of an accurate, standardizable and accessible dosimetric method is essential. Different studies have already been performed, aiming to simplify dosimetry by reducing the numbers of scans, while maintaining a good estimation of the absorbed doses in the treatment cycle [77,78]. This might lead to the implementation of a sufficiently simple, yet reliable dosimetric method that can be adopted on a wider scale, to estimate the actual absorbed doses and relate these to observed therapeutic effects or radiation toxicity events.

In addition, there are currently no molecular biomarkers that can predict PRRT toxicity [9]. Because potential kidney toxicity after administration of PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) usually occurs late, an early biomarker would be of particular interest to enable early detection and anticipation of nephrotoxicity. Different biomarkers of radiation damage in kidney tissue have already been proposed, but further studies are needed to evaluate their clinical usefulness [31,79]. To facilitate the search of biomarkers indicative of radiation-induced kidney injury, a detailed understanding of the kidney tissue responses after exposure to PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) is needed.

The abovementioned studies show that multiple mediators play a role in the renal radiation effects of radiolabelled SSA. For most of the observed nephroprotective strategies, the exact underlying mechanisms are not yet fully elucidated. Therefore, a better understanding of the (cytotoxic) responses of PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) is needed as well. By increasing our knowledge on the biological mechanisms contributing to the (side) effects of PRRT, we can optimize existing and develop new nephroprotective strategies to reach the ultimate goal of keeping the kidney exposure as low as reasonably achievable. Meanwhile, amino acid infusions have shown their value by decreasing the renal uptake of the radiopeptides via the megalin receptor system. Nonetheless, a significant absorbed dose to the kidneys remains, leaving room for further improvement of renoprotection during PRRT. This might be accomplished by combining multiple agents or strategies. Examination of the optimal timing and routes of administration is needed, to ensure an additive effect instead of a competition. Important is to beware that the radio protective effects of the applied strategies should only occur in the kidneys and not in the tumour lesions to avoid a reduction in efficacy. In the future this might allow the administration of higher \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) treatment activities and/or an increased number of treatment fractions to achieve a more potent tumour killing. In addition, patients with renal risk factors, who would normally be excluded from PRRT, might then become eligible.

One major limitation of most PRRT nephroprotective studies, is their varying treatment protocols (e.g. different radioligands, activities, follow-up methods, etc.), making it very difficult to compare obtained results. Moreover, limited evidence is provided by single small studies. Therefore, standardized studies using larger trial set-ups, such as NETTER-1, are required. In addition, because the majority of studies have been performed in vitro or in mice/rat models, the question whether these finding can be extrapolated to humans can be raised. Next to validation studies of different strategies and agents in protecting the kidneys from radiation damage, general safety studies should be performed in parallel to evaluate their tolerability in the human body. It is important for the nephroprotective benefit to outweigh possible concomitant risks and side effects.

9. Conclusion

PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) has shown to be a promising treatment option for patients with GEP-NETs. However, many questions remain regarding the establishment of an optimal treatment protocol. The ideal balance between efficient tumour killing, while sparing healthy tissues has not yet been reached. Taking up this challenge, requires joined forces from both radiobiologists, investigating PRRT biological radiation responses, and dosimetrists, estimating target absorbed dose to the tumour together with dose limits to critical organs. From this review, we can conclude that with the current fixed treatment regime (4 × 7.4 GBq) and a LysArg co-infusion, nephrotoxicity with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) for the treatment of GEP-NETs is low. Nonetheless, the kidneys have shown to play an important role in defining a patient’s tolerability to PRRT, due to the retention of radionuclides in the renal interstitium, generating a risk for the development of radiation nephropathy and due to the longer circulation time of \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) in patients with suboptimal renal functions, leading to increased hematologic toxicities. Therefore, we believe that improving existing or developing new radio protective strategies, which further reduce radiation doses to critical organs (such as kidneys and bone marrow), can be of value in further enlarging the therapeutic window for PRRT with \([{177}\text{Lu}]{\text{DOTA}}^{-}\text{TATE}\) and increase its eligibility.

Funding

This work was supported by a joint doctoral grant of SCK CEN and Erasmus MC.
Declaring of competing interest

The authors declare that they have no competing interests.

Acknowledgments

All images were created using BioRender.com.

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