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REVIEW ARTICLE

Yttrium-labelled peptides for therapy of NET

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Abstract Peptide receptor radionuclide therapy (PRRT) consists in the systemic administration of a synthetic peptide, labelled with a suitable beta-emitting radionuclide, able to irradiate tumours and their metastases via the internalization through a specific receptor, overexpressed on the cell membrane. After 15 years of experience, we can state that PRRT with ^{90}Y-labelled peptides is generally well tolerated. Acute side effects are usually mild, some of which are related to the co-administration of amino acids, such as nausea. Others are related to the radiopeptide, such as fatigue or the exacerbation of an endocrine syndrome, which rarely occurs in functioning tumours. Chronic and permanent effects on target organs, particularly the kidneys and the bone marrow, are generally mild if the necessary precautions are taken. Currently, the potential risk to kidney and red marrow limits the amount of radioactivity that may be administered. However, when tumour masses are irradiated with adequate doses, volume reduction may be observed. ^{90}Y-octreotide has been the most widely used radiopeptide in the first 8–10 years of experience. Unfortunately, all of the published results derive from different and inhomogeneous phase I/II studies. Hence, a direct comparison is virtually impossible to date. Nevertheless, even with these limitations, objective responses are registered in 10–34% of patients. The optimal timing of ^{90}Y-DOTATOC in the management of somatostatin receptor (SSTR)-positive tumours and the way in which it should be integrated with other treatments have yet to be defined, and prospective phase II/III trials comparing the efficacy and toxicity of different schemes of ^{90}Y-DOTATOC administration are still warranted.

Keywords ^{90}Y-DOTATOC · Peptide receptor radionuclide therapy · PRRT · Neuroendocrine tumours

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Introduction

In the past 15 years a new approach to neuroendocrine tumours (NETs) based on specific receptor targeting with radiolabelled somatostatin analogues was introduced into clinical practice in many European centres (Switzerland, The Netherlands, Italy, Germany, Poland, etc.). Peptide receptor radionuclide therapy (PRRT) consists in the systemic administration of a synthetic peptide, labelled with a suitable beta-emitting radionuclide. These compounds are able to irradiate tumours and their metastases via the internalization through a specific receptor, overexpressed on the cell membrane. Somatostatin analogues represent to date the prototype and the most successful paradigm of radiopeptide therapy, due to the fortunate discovery of a successful class of synthetic peptides, such as octreotide and its variants, and to the inhibiting properties of somatostatin and its analogues, which induce few and limited side effects.

After initial experiences with ^{111}In-pentetreotide, exploiting the high-energy, short-range Auger and conversion emissions

of ^{111}In, which led to unsatisfactory clinical results, the two most widely used radiopharmaceuticals are ^{90}Y-DOTA-Tyr^3-octreotide (or ^{90}Y-DOTATOC or ^{90}Y-octreotide) [1] and, more recently, ^{177}Lu-DOTA-Tyr^3-octreotate (or ^{177}Lu-DOTATATE or ^{177}Lu-octreotate) [2–4].

High-energy beta emitters, such as ^{90}Y, seemed, in fact, more adequate than Auger emitters to irradiate tumour lesions. The higher energy (maximum 2.2 MeV) and penetration range (R_{95} 5.7 mm) of β particles from ^{90}Y are advantageous, with a direct killing of somatostatin receptor (SSTR)-positive cells and a crossfire effect which hits nearby receptor-negative tumour cells. A modified octreotide, named Tyr^3-octreotide, with receptor affinity similar to that of the original octreotide, was developed. The DOTA (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid) chelated form can be easily labelled with radiometals, such as ^{90}Y. The newly formed molecule, at the University of Basel, was [^{90}Y-DOTA]^0-Tyr^3-octreotide or ^{90}Y-DOTATOC or ^{90}Y-octreotide [5, 6]. More recently, a new analogue, named octreotate (chemically a Tyr^3,Thr^8-substituted octreotide) was synthesized. The new compound has a six- to ninefold higher affinity for the SSTR subtype 2, the one most frequently overexpressed by NETs. Its DOTA chelated form, [DOTA]^0-Tyr^3-octreotate or DOTATATE, can be labelled with ^{90}Y or with the beta-gamma emitter ^{177}Lu [7]. Other clinical experiences have been gained with ^{90}Y-lanreotide, a different SSTR agonist [8].

Studies performed in the past 15 years demonstrated that PRRT with either ^{90}Y- or ^{177}Lu-labelled peptides can deliver consistent radiation doses to lesions, adequate to achieve significant tumour responses.

Tolerability

Clinical dosimetry

Dosimetry of normal organs and tumours is a preliminary step for patient selection and therapy planning, given the huge differences amongst patients as to the radiopeptide uptake in normal organs and tumour tissues. This is possibly related to varying SSTR densities on tumour cells as well as to factors such as tumour volume, interstitial pressure and viability.

In PRRT with ^{90}Y-labelled peptides, dosimetry cannot be easily reconstructed from the bremsstrahlung images, due to the lack of a gamma emission allowing a quantitative analysis. Therefore, two alternative approaches have been developed as surrogates for the original radiopeptide, namely therapy simulation with the ^{111}In-labelled peptide, biochemically similar to the original one, and simulation with the ^{86}Y-labelled peptide, biochemically identical to the therapeutic counterpart [9, 10].

Although [^{90}Y-DOTA^0,Tyr^3]octreotide (or lanreotide or octreotate) and its imageable counterpart [^{111}In-DOTA^0, Tyr^3]octreotide (or lanreotide or octreotate) are not the same molecule, the latter has been used for dosimetric simulation, based on the hypothesis that the similar physical and biological half-lives yield comparable in vivo pharmacokinetics and biodistribution, especially concerning the renal uptake, which depends mainly on aspecific phenomena. A drawback of this method is that the small structural modification due to the metal replacement can possibly affect the SSTR binding affinity [11].

The first results according to this method [9] pointed out a fast blood clearance [<1% injected activity (IA) in blood 10 h post-injection (p.i.)] and a rapid urine elimination (52± 12% IA 4 h p.i. and >70% 24 h p.i.), therefore determining a short-term total body irradiation deriving from [^{90}Y-DOTA^0, Tyr^3]octreotide. The in vivo stability of the radiopeptide, assessed both in urine and in plasma, appeared to be high, and no degradation product was found in blood. According to biodistribution, the organs receiving the highest predicted absorbed doses, in a first series of 18 patients, include the spleen (7.6±6.3 mGy/MBq), the kidneys (3.3±2.2 mGy/MBq) and the tumour (1.4-31 mGy/MBq, mean 10). Enlarging the study series to 30 patients, studied before therapy, namely without renal protection, a slightly higher value of kidney dose (3.9±1.9 mGy/MBq) was observed [12].

A thorough dosimetric study using the same chemical radiocompound, namely [DOTA^0,Tyr^3]octreotide labelled with the positron emitter ^{86}Y, was carried out in 24 patients [13]. Positron emission tomography (PET) with [^{86}Y-DOTA^0,Tyr^3]octreotide offers substantial advantages in spatial resolution and quantification; nevertheless, the short half-life of the radionuclide does not allow the later phases of the biokinetics to be studied other than with extrapolation estimates. Although the literature lacks an actual comparison study between the two simulation approaches, the pharmacokinetic parameters were similar (~5% IA in plasma 5 h p.i. and <1% after 24 h), as well as the kidney dose (4.4± 1.0 mGy/MBq, in four patients), to the ones calculated with [^{111}In-DOTA^0,Tyr^3]octreotide (3.9±1.9 Gy/GBq). The mean estimated tumour dose for ^{90}Y was highly variable (1.5–177.1 Gy delivered by the maximum activities administered).

Recently, a new potentiality of ^{90}Y imaging has emerged, pointing out the possibility of omitting simulations by ^{111}In or ^{86}Y imaging [14, 15].

Safety

After 15 years of experience, we can state that, from the safety point of view, PRRT with ^{90}Y-labelled peptides is generally well tolerated. Acute side effects are usually mild: some of them are related to the co-administration of amino acids, such as nausea (or more rarely vomiting). Others are

related to the radiopeptide, such as fatigue (commonly), or the exacerbation of an endocrine syndrome, which rarely occurs in functioning tumours. Chronic and permanent effects on target organs, particularly the kidneys and the bone marrow, are generally mild if the necessary precautions are taken [16].

Dosimetric studies indicated that it is possible to deliver elevated absorbed doses to the tumour, while limiting the dose to organs, such as kidneys and bone marrow, to tolerance limits.

While haematological toxicity mainly occurs immediately after PRRT and is usually mild and transient, permanent and severe bone marrow toxicity is a rare event after PRRT, since the resulting bone marrow absorbed doses is usually well below the threshold of toxicity [17]. In contrast, delayed renal toxicity that may occur if the dose threshold is exceeded is permanent.

Results from the two Milan phase I studies, considering escalating activities from 1.11 to 2.59 GBq per cycle without amino acid protection and from 2.96 to 5.55 GBq per cycle with amino acid co-infusion, pointed out a maximum tolerated activity of 5.18 GBq, based mainly on acute haematological toxicity. The maximum cumulative activity, resulting from dosimetric estimates, was based mainly on the dosimetric burden to the kidneys and ranged between 10 and 15 GBq [18, 19].

Kidneys

Due to their marked radiosensitivity, the kidneys represent the critical organs after administration of ^{90}Y-DOTA-peptides at the doses that are normally reached with PRRT. Renal irradiation arises from the proximal tubular reabsorption of the radiopeptide and the resulting retention in the interstitium. According to external radiotherapy studies, the renal tolerance dose is conventionally considered to be in the range of 23–27 Gy [20].

Different absorbed dose limits are expected to apply to radionuclide therapy as compared to radiotherapy, due to the intrinsically different dose rate delivered by the two radiation modalities. Recently, radiobiology concepts applied to nuclear medicine therapy indicated that bioeffective doses (BED) are more accurate in predicting toxicity and 40 Gy of BED was indicated as a more likely threshold for renal toxicity [21, 22].

Recent studies demonstrated a longer residence time of DOTATATE in the kidneys [23]. Hence, even higher renal absorbed doses can be predicted after ^{90}Y-DOTATATE [16].

The strategy of co-infusing positively charged amino acids, such as lysine or arginine, competitively inhibiting the radiopeptide reabsorption, leads to a 9–53% reduction of the renal doses [24, 25]. Doses are further reduced up to 39% by prolonging infusion over 10 h and up to 65% by prolonging it over 2 days after radiopeptide administration, thus covering more extensively the elimination phase through the kidneys [12].

Despite renal protection, a loss of renal function of variable degree (generally mild) may appear months after the end of PRRT. Cases of severe, end-stage renal damage are rare nowadays. They mainly occurred at the beginning of PRRT experience, when very high activities were administered, especially in patients who had received >7.4 GBq/m^2, and when renal protection was not in use [26].

However, independently of the development of clinically evident renal damage, renal function is "consumed" to some extent after PRRT, and a decline in creatinine clearance occurs with time. This loss is more pronounced for ^{90}Y-octreotide (median 7.3% per year) than for ^{177}Lu-octreotate (median 3.8% per year), at least with the therapeutic schemes analysed [27].

Nephrotoxicity is accelerated by other risk factors besides cumulative activity. Studies demonstrated that a higher and more persistent decline in creatinine clearance and the subsequent development of renal toxicity occurred in those patients with risk factors for delayed renal toxicity, particularly long-standing and poorly controlled diabetes and hypertension. In a long-term evaluation of renal toxicity after PRRT in a group of 28 patients undergoing PRRT with dosimetric analysis, 23 of whom were treated with ^{90}Y-DOTATOC, toxicity on creatinine, according to National Cancer Institute (NCI) criteria, occurred in 9 patients (7 grade 1, 1 grade 2, 1 grade 3). Creatinine clearance loss at 1 year was >5% in 12 cases and >10% in 8. A low, 28 Gy BED threshold was observed in patients with risk factors (mainly hypertension and diabetes), while it was 40 Gy in patients without risk factors [28].

In a retrospective series of 1,109 patients treated with ^{90}Y-DOTATOC at the University of Basel, 103 subjects (9.2%) experienced grade 4 to 5 permanent renal toxicity [29]. Multivariable regression revealed that the initial kidney uptake was predictive for severe renal toxicity, although the role of the high administered activities per cycle (3.7 GBq/m^2 body surface, namely activities of about 6.4 GBq per cycle in a standard male patient) in such a rather high frequency cannot be ruled out.

Clinical experience and dosimetric studies clearly indicate that the renal absorbed dose estimated by conventional dosimetry does not accurately correlate with the renal toxicity observed in patients treated with [^{90}Y-DOTA^0,Tyr^3] octreotide. Additional parameters, such as patient-specific kidney volume and distribution of the radionuclide, appeared to give a better correlation with the clinical effects [22]. Assessment of individual kidney volume by CT scan yields a wide variability, when compared to the standardized phantom. New techniques accounting for the difference in radioactivity placement in the kidneys, by a CT-based volumetric analysis, appear more realistic [30].

Unfortunately, data from ex vivo autoradiography in humans regarding the activity distribution of radiolabelled somatostatin analogues are contradictory and not conclusive [31], since radioactivity distribution of ^{111}In-pentetreotide was reported as inhomogeneously distributed, about 70% in the cortex and 30% in the medulla, while ^{90}Y/^{111}In-DOTATOC was found to be homogeneously distributed in the cortical and medullary structures, without significant gradient [32]. A possible explanation for these differences relies on the effect of amino acid protectors, used for therapy, which interfere with the natural localization of peptides.

Kidney radiation toxicity is typically evident several months after irradiation, due to the slow repair characteristics of renal cells.

PRRT is a form of continuous radiation delivery with a decreasing dose rate over time. The irradiation produces both lethal and sublethal damage, which can be repaired during the irradiation itself, but the differential between creating new damage and the repair depends on the specific dose rate at any particular time and on the repair capability of the tissue. Low dose rates, as in PRRT, will spare normal tissues more than the tumour and this may allow benefits as in fractionation in external radiotherapy [33].

The linear quadratic model mathematically interprets this differential sparing and the BED concept is used to quantify the biological effects induced by different patterns of radiation delivery. This model has been recently revised for radionuclide therapy and has been applied in particular to PRRT with the intent of increasing the dose-response correlation [21]. Focussing on kidney concerns, the BED has proven to be a reliable predictor of renal toxicity, helpful in the implementation of individual treatment planning [22]. In PRRT the BED has been shown to correlate with renal injury. However, BED is a relatively young concept applied to nuclear medicine and still has to be fully validated with a wider series of data.

The main radiobiological parameter required in such assessment is the tissue α/β ratio, which gives an indication of the sensitivity of a tumour or normal tissue cell to the effect of dose rate (and/or fractionation), and is generally higher for tumours (5–25 Gy) than for late-responding normal tissues (2–5 Gy), such as the kidneys.

Bone marrow

From a haematological point of view, PRRT is generally well tolerated. Severe, WHO grade 3 or 4, toxicity does not occur in more than 13% of cases after ^{90}Y-octreotide. Nevertheless, sporadic cases of myelodysplastic syndrome (MDS) or even overt acute myeloid leukaemia (AML) have been reported [3].

Previous dose-finding phase I studies demonstrated that maximum cumulative administrable activity per cycle of ^{90}Y-octreotide, with renal protection, is 5.18 GBq [19]. Dosimetric studies showed the advantage of hyperfractionation in lowering the renal and bone marrow dose [17, 28].

Although predicted absorbed doses are much lower than the conventional threshold for toxicity, the other target organ raising concerns about acute and permanent toxicity is the bone marrow, particularly in repeated administrations [2, 3, 12]. The fast pharmacokinetics of radiopeptides, as well as the lack of an evident red marrow uptake in scintigraphic images, indicate a low marrow irradiation. Nonetheless, many effects observed after PRRT were not expected to occur at the low marrow doses estimated. In order to check for additional causes of bone marrow irradiation, the expression of SSTR on stem cells was postulated. A comparison of the radioactivity concentration in blood and bone marrow aspirates in patients treated with ^{177}Lu-DOTATATE was performed and linked to the change in platelet counts. The results showed an identical activity concentration in bone marrow and blood and that the radiopharmaceutical does not bind significantly to bone marrow precursor stem cells. No correlation emerged between marrow doses and change in platelet count and the study confirmed the appropriateness of the models used [34].

Recently, the study of the possible uptake of ^{111}In-octreotide and ^{86}Y-DOTATOC in bone or bone marrow on single photon emission computed tomography (SPECT) and PET images, respectively, showed, in some patients, some faint (~1%) uptake in the spine, absent in long bones and vertebrae, evident the next day, indicating that the uptake mechanism is not receptor related [35]. The study of the in vitro behaviour of ^{111}In-octreotide and ^{86}Y-DOTATOC, on the other hand, showed a transchelation of ^{111}In and ^{86}Y to the free transferrin, which could explain the delayed red marrow uptake and, therefore, the toxicity.

A further source of red marrow irradiation is the possible coexistence of unconjugated radionuclides, such as free ^{90}Y, that have bone tropism. This can occur due to incomplete labelling, impurities or in vivo deconjugation, as has been reported in relation to several radionuclide therapies.

Others

Finally, the possibility of exacerbation of endocrine syndromes, such as carcinoid, hypoglycaemic, or Zollinger-Ellison syndrome, must be taken into account, although quite rare. This appears to be related to the massive cell lysis and hormonal stimulation occurring after PRRT, which must be prevented and treated accordingly [36, 37].

Efficacy

Tumour irradiation

The major task for PRRT is to deliver the maximal detrimental dose to the tumour while limiting the irradiation of normal organs as much as possible. Currently, the potential risk of kidney and red marrow limits the amount of radioactivity that may be administered. However, when tumour masses are irradiated with adequate doses, volume reduction may be observed [38]. Tumour remission is positively correlated with a high uptake on [^{111}In-DTPA^{0}]octreotide scintigraphy [4].

Nevertheless, tumour dose does not depend directly only on the administered activity and the uptake versus time, namely on the amount of energy released, but also on the tumour mass. Roughly, smaller masses have higher chances of reduction, owing to a higher absorbed dose in the tumour.

Another factor influencing tumour irradiation, and therefore the response, is the choice of the radionuclide. Each of the β emitters currently used for therapy, ^{177}Lu and ^{90}Y, shows potential advantages. In particular, ^{90}Y particles are highly energetic and penetrating, leading to better crossfire through the tumour, which is particularly valuable in larger tumours and when heterogeneous receptor and/or activity distribution exists. The shorter half-life of ^{90}Y allows a higher dose rate. ^{177}Lu, on the other hand, has lower energy and smaller particle range, allowing a better absorption in smaller tumours [39]. Figure 1 illustrates an example of response to ^{90}Y-DOTATOC in a patient affected by massive liver and abdominal lymph node metastases from a neuroendocrine carcinoma of unknown primary.

Mathematical models showed that ^{177}Lu is better in small tumours, with an optimal diameter of 2 mm, whilst ^{90}Y is better in larger ones, with an optimal diameter of 34 mm. ^{90}Y seems therefore less suitable for PRRT of small tumours, because very small masses will not be able to absorb all the β energy released in the tumour cells. ^{177}Lu, instead, appears less suitable for larger tumours, due to the lack of uniformity of activity distribution over the tumour mass. Finally, differences in dose rate must be taken into account: the longer physical half-life of ^{177}Lu means a longer period needed to deliver the same dose as ^{90}Y. This may allow more time for tumour repopulation [40]. A combination therapy with ^{90}Y and ^{177}Lu, either simultaneously or in distinct settings, has been therefore suggested to overcome the difficulties of the real clinical situation of different-sized lesions. Nevertheless, clinical experiences are still limited.

Studies comparing the doses recorded at any cycle of PRRT showed that tumour uptake gradually reduced in subsequent cycles, most likely due to saturation or down-regulation of the receptors. The contribution to the tumour absorbed dose diminished progressively (~35% of the cumulative dose being released at the first cycle, whereas ~15% at the fourth cycle), with the first two cycles having major impact [41]. These findings are in agreement with the clinical outcomes shown by van Essen et al., who observed lower antitumour effects from additional treatment after regular cycles in patients with short time to progression [42].

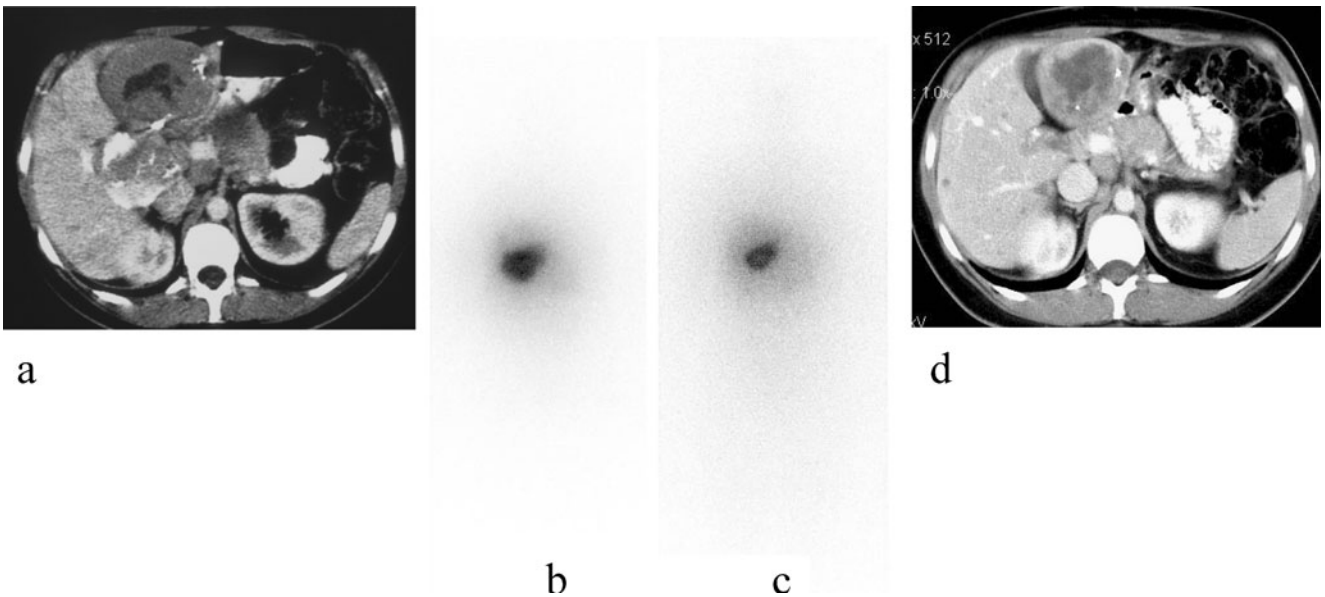

Fig. 1 PRRT with ^{90}Y-DOTATOC in a patient affected by massive liver and retroperitoneal lymph node metastases from a neuroendocrine carcinoma of unknown primary (**a** basal CT scan, **b** bremsstrahlung scan after first cycle). The post-therapy CT scan (**d**) shows an objective response, already visible at the bremsstrahlung scan after the last cycle of ^{90}Y-DOTATOC (**c** note that the normal liver is now recognizable as a faint shadow around the bigger liver lesion)

Tumour response

In almost 15 years PRRT with ^{90}Y-octreotide proved to be efficient, with tumour responses, symptom relief and improvement in quality of life, biomarker reduction and, ultimately, an impact on survival.

^{90}Y-octreotide has been the most widely used radiopeptide in the first 8–10 years of experience. Alas, all of the published results derive from different phase I/II studies, inhomogeneous as to inclusion criteria and treatment schemes. Hence, a direct comparison is virtually impossible to date. Nevertheless, even with these limitations, objective responses have been registered in 10–34% of patients [3, 12, 18, 29, 43, 44].

Presently, the therapy administration protocols rely mostly on empirical criteria. Many of them schedule the injection of standard activities, as derived from escalation studies and clinical experience or for historical reasons, with huge differences among protocols as to activities, fixed or related to body weight or surface, number of cycles and time intervals between cycles.

Protocols combining ^{177}Lu- and ^{90}Y-labelled peptides have been recently contemplated, in order to benefit from the different physical properties of the radionuclides, although ^{177}Lu and ^{90}Y activities have been designed empirically and not based on dosimetric values [40, 45].

The first studies with ^{90}Y-octreotide were carried out in relatively advanced phases of disease, while further trials demonstrated a higher efficacy of PRRT in earlier phases of disease. This is supported by numerous reasons, primarily radiobiological, related to the volume of tumour masses, and biological factors, since more advanced tumours express less SSTR and, on the other hand, bear many genetic mutations, such as p53, which make them less prone to respond to any treatment. Previous studies have indicated that the tumour load, especially in the liver, and the performance status would influence the outcome of PRRT. Therefore, early treatment rather than a "wait and see" approach could be advantageous. In addition, the type of disease has to be taken into account, as e.g. pancreatic NETs tend to show higher tumour reductions.

In a study carried out at Basel University, 39 patients with NETs, mostly of gastroenteropancreatic (GEP) origin, were treated with 4 cycles of ^{90}Y-octreotide, with a cumulative activity of 7.4 GBq. Objective responses, according to WHO criteria, were described in 23%, with a complete remission in 2 patients, partial in 7 and disease stabilization in 27. Pancreatic NETs (13 patients) showed a better objective response (38% partial+complete) than the other classes did. A significant amelioration of related symptoms occurred in the majority of patients [43].

In another multicentre phase I study, carried out at Rotterdam, Louvain and Tampa Universities, 60 patients affected by GEP NETs were treated with 4 cycles of 0.9, 1.8, 2.8, 3.7, 4.6 and 5.5 GBq/m^2 administered 6–9 weeks apart. In an initial evaluation of the results published in 2002 in 32 evaluable patients, objective responses, according to Southwest Oncology Group (SWOG) criteria, consisted in about 9% of partial responses and 9% of minor responses [46]. In a later analysis of the same population published in 2006 on 58 assessable patients who were treated with cumulative activities of 1.7–32.8 GBq, a 57% clinical benefit, including stabilization and minor responses, was observed, according to SWOG criteria. A true objective response was described in 5% of the patients. The most relevant finding of the study was the observed overall survival, with a median value of about 37 months and a median progression-free survival of about 29 months. These results compared well with the 12-month overall survival of the historical group treated with ^{111}In-pentetreotide. The median progression-free survival was 29 months [44].

The results of two phase I/II studies and a retrospective evaluation in 141 patients were published by the Milan group in 2004. Patients were affected mainly by NETs and were treated with a cumulative activity of 7.4–26.4 GBq of ^{90}Y-octreotide, divided into 2–16 cycles, administered 4–6 weeks apart. The objective response rate was 26%, including partial and complete responses, according to SWOG criteria. Disease stabilization was observed in 55% of the patients and disease progression in 18%. The mean duration of response ranged between 2 and 59 months (median 18). The majority of the patients who responded had GEP NETs. The study showed that, by dividing the objective response according to the basal status, stable patients at baseline had better outcome (partial and complete responses in 32%) than did progressive ones (partial and complete responses in 24%) [12].

Recently, a multicentre study aimed at studying the role of ^{90}Y-octreotide in 90 patients with symptomatic, metastatic "carcinoids", namely NETs originating from the small intestines, was published. This study showed that PRRT with ^{90}Y-octreotide was able to induce stabilization or tumour response, according to SWOG criteria, in 74% of patients as well as a durable amelioration of all the symptoms related to the tumour mass and the hypersecretion of bioactive amines. Interestingly, the symptomatic response had an impact on survival, since progression-free survival was significantly longer in those who had durable diarrhoea improvement [47].

More recently, the Basel group published the results of their open-label phase II trial in 1,109 patients treated with ^{90}Y-octreotide, divided into multiple cycles of 3.7 GBq/m^2 each. Objective morphological responses, according to RECIST criteria, were observed in 378 (34.1%), biochemical response in 172 (15.5%) and symptomatic response in 329 (29.7%). Longer survival was correlated with tumour and symptomatic response. The best predictor of survival was the tumour uptake at baseline [29].

A number of phase II studies, mostly retrospective, oriented at defining the objective response in specific classes of diseases, were published in the past few years.

As regards meningiomas, a dedicated study of PRRT with ^{90}Y-octreotide in a series of 29 patients, 14 with benign, 9 with atypical and 6 with malignant forms, was published in 2009 by the Milan group. Patients received cumulative activities of 5–15 GBq divided into 2–6 cycles. According to SWOG criteria, disease stabilization occurred in 19 of 29 patients (66%), while progression was observed in the other 10 (34%). Better results occurred in patients with low-grade meningiomas, with a median progression-free survival of 61 months, compared to atypical and malignant forms, with a median progression-free survival of 13 months. These data point out the need for treating patients with an adjuvant approach, shortly after surgery, particularly in high-grade meningiomas, where lesions tend to be large and multiple [48].

^{90}Y-DOTATOC (7.5–19.2 GBq in 2–8 cycles) has been administered in 21 patients affected by metastatic medullary thyroid carcinoma with positive OctreoScan, progressing after conventional treatments. Two patients (10%) obtained a complete response, as evaluated by CT, MRI and/or ultrasound, while a stabilization of disease was observed in 12 patients (57%); 7 patients (33%) did not respond to therapy. The duration of the response ranged between 3 and 40 months. Using biochemical parameters (calcitonin and carcinoembryonic antigen), a complete response was observed in one patient (5%), while a partial response was noted in five patients (24%) and stabilization in three patients (14%). Twelve patients had progression (57%). Complete responses were observed in patients with lower tumour burden and calcitonin values at the time of the enrolment. This retrospective analysis is consistent with the literature, regarding a low response rate in medullary thyroid cancers treated with ^{90}Y-DOTATOC. Nevertheless, patients with smaller tumours and higher uptake of the radiopeptide tended to respond better [49].

An interesting perspective of PRRT in lymphoproliferative disorders is possible due to the presence of SSTR in B lymphocytes, but today no data are available regarding their use as targets for therapy. Sporadic observations have been reported in the literature, such as the case report of successful PRRT with ^{90}Y-DOTATOC in B-cell chronic lymphocytic leukaemia in a patient affected by Binet stage A chronic lymphocytic leukaemia and advanced neuroendocrine Merkel cell carcinoma. The presence of SSTR both in normal and neoplastic B cells, and the selective drop of B lymphocytes normally observed after ^{90}Y-DOTATOC, constitutes the basis for setting up PRRT specifically in B-cell lymphoma and leukaemia [50, 51].

As to the survival after ^{90}Y-DOTATOC, a phase I/II study of 58 patients with GEP NETs treated with 1.7–32.8 GBq reports a clinical benefit (including stabilization and minor response) in 57% (with true objective response in 20%), a median overall survival of 36.7 months (vs 12 months in the historical group treated with ^{111}In-octreotide) and a median progression-free survival of 29 months. Characteristically, patients stable at baseline had a better overall survival than had patients progressive at baseline, and the extent of disease at baseline was a predictive factor for survival [44].

Finally, PRRT has also been administered in children and young adults with SSTR-positive tumours. A prospective phase I study involved 17 subjects (2–24 years old) affected by neuroblastomas, multiple endocrine neoplasia type 2B, gliomas and NETs. Patients were treated with ^{90}Y-octreotide with activities ranging from 1.1 to 1.85 GBq/m^2 per cycle for a total of 3 cycles, administered 6 weeks apart. According to Pediatric Oncology Group criteria, partial responses were observed in 12% and minor responses in 29%. Improved quality of life during the treatment was a major advantage of the therapy. Therefore, PRRT proved to be efficient and tolerated also in young patients [52].

Experiences have also been gained with ^{90}Y-DOTATATE. A group of 60 patients with histologically proven GEP NETs were treated with 4.1–16.2 GBq per patient (mean 3.7 GBq per therapy) in 1–3 cycles. Six months after PRRT completion, partial response was registered in 13 patients (23%), while the remaining patients showed stable disease (77%). Median progression-free survival was 17 months, while the median overall survival was 22 months. Haematological toxicity WHO grade 3 and 4 was noted during therapy in 10% of patients and persisted in 5%. After 24 months of follow-up, renal toxicity grade 2 was seen in seven patients, and the authors pointed out the need for careful renal monitoring [53].

Considerations and perspectives

^{90}Y vs ^{177}Lu

PRRT with ^{90}Y-octreotide was demonstrated to be efficient and relatively safe up to the known thresholds of absorbed and bioeffective dose. The toxicity profile is acceptable from a renal and haematological point of view, if necessary protective measures are taken, such as amino acid protection and activity fractionation.

PRRT proved to induce a significant improvement of the quality of life and of all the symptoms related to the disease in the majority of patients treated.

A major open issue remains the definition of the optimal radiopeptide and, even before that, which of the two investigated radionuclides is optimal. Even in the absence of randomized trials, some considerations can be made. The analysis of the residence times for DOTATATE and DOTATOC, calculated by means of the ^{177}Lu-labelled peptides, showed that

residence times for DOTATATE are significantly longer in kidney and tumour (ratios DOTATATE:DOTATOC=1.4 and 2.1, respectively), allowing higher tumour doses but also higher renal doses [23]. Therefore, considering the higher tumour dose, ^{177}Lu appears more beneficial when labelling DOTATATE, while, in view of the higher renal dose, ^{90}Y appears more convenient to label DOTATOC. From dosimetric projections, we can infer that, for peptides such as DOTATATE, switching the radiolabel from ^{177}Lu to ^{90}Y can increase the doses by a factor of 2–4 to the tumour, depending on the tumour size, but also to normal organs, kidneys in particular. Therefore, the benefit-risk balance remains to be established for each patient [17].

In conclusion, from a dosimetric point of view ^{177}Lu-DOTATATE appears handier than ^{90}Y-DOTATOC, as regards safety, considering that the commonly administered activities are not equivalent to the renal dose. Anyhow, ^{90}Y-DOTATOC is more powerful than ^{177}Lu-DOTATATE, as regards the tumour dose. The choice of the radiopeptide depends on the particular clinical scenario of the patient. Bigger lesions may benefit from ^{90}Y-DOTATOC while smaller ones from ^{177}Lu-DOTATATE. Especially when using ^{90}Y-DOTATOC, particular attention has to be paid to risk factors for renal toxicity, which should suggest caution (lower doses, hyperfractionation) or switching to ^{177}Lu-DOTATATE. However, in order to establish which treatment scheme and which radiolabelled somatostatin analogue or combination is optimal, a clinical randomized study comparing the two treatments is needed.

Final considerations

Since PRRT is a relatively young therapy, much is still to be understood and explored, and researchers are trying to give an answer to the present limitations and unresolved issues. PRRT, in fact, was born at the beginning of the 1990s as the next logical step to hormonal peptide biotherapies in endocrine tumours. From the beginning, the favourable results prompted an enthusiastic use in clinical trials, although sometimes conclusions on the efficacy, particularly in comparison with other therapies, were drawn from studies not oncologically designed for that purpose. In this respect, results, mainly with ^{90}Y-DOTATOC, have been inferred from many phase I/II studies, carried out by various groups, but rather poor in patient number and inhomogeneous as to patient selection, inclusion criteria and treatment schemes [4]. Therefore, an inter-study comparison is virtually impossible. Clinical phase II and III trials have been skipped, and today the use of PRRT has become quite customary, following eagerly the many brilliant results obtained in patients. Still there is lack of data, but an oncologically correct sequence of clinical trials seems now out of season.

Only prospective phase I studies have been carried out so far, and data regarding the efficacy of ^{90}Y-DOTATOC, in terms of objective response and impact on survival parameters, are still not conclusive. In fact, they have not been obtained with the same methodology and need to be confirmed by more extensive studies specifically addressing this issue. The optimal timing of ^{90}Y-DOTATOC in the management of SSTR-positive tumours and the way in which it should be integrated with other treatment have yet to be defined, and prospective phase II/III trials comparing the efficacy and toxicity of different schemes of ^{90}Y-DOTATOC administration are still warranted. One important point to be clarified is the dose fractionation, i.e. whether the same maximum injectable cumulative activity yields different results in terms of efficacy and toxicity when it is divided into a series of low-activity cycles given at short intervals or into a few high-activity cycles spread over a longer period.

Today the accomplishment of such studies in nuclear medicine, and the consequent knowledge on large numbers of patients, appears rather difficult to obtain, for many reasons, logistical, economical and political. Hopefully, incoming phase III registration clinical studies will help clarify at least some of these open issues.

Almost all of the studies carried out to date focussed merely on antitumour activity and, unfortunately, due the small numbers and relatively short follow-up, still cannot demonstrate formal oncological significance of the impact of PRRT on the most important aim in oncology, namely the overall survival, or at least its surrogate endpoint, time to progression.

A further consideration can be made on the need to identify the patients who are going to respond to PRRT and their specific biological parameters, such as Ki-67 proliferation index, besides the known basal OctreoScan uptake and disease extension.

Apart from radiobiological speculations regarding the better irradiation of the smallest disease as possible, the exact place of PRRT in the therapeutic algorithm of NETs is still unknown.

In addition, the possible renal and bone marrow toxicity is still not fully understood and remains something that worries clinicians, particularly the referring oncologists. Radiation burden to tumour and normal organs, in fact, is difficult to establish with satisfactory accuracy. Nevertheless, treating patients with an excessively conservative approach, not considering the individual dosimetry, may limit in turn the efficacy of treatment.

Safety is the dark side of the moon in radionuclide therapy with radiopeptides, and individual dosimetry of normal organs and tumour is a preliminary step for patient selection and therapy planning, necessary because there are huge differences amongst patients as to the radiopeptide uptake in normal organs and tumour tissues.

In this regard, the comprehension of the radiobiological features inherent in radiopeptide therapy could allow a patient-tailored treatment, as to the tumour irradiation and the tolerability of normal organs. Therefore, researchers must fill this gap to define the characteristics and the role of PRRT in the management of NETs, and, most important, to acquire the necessary authorizations from regulatory organizations for the commercialization and broad diffusion of these radiopharmaceuticals.

Conflicts of interest LB and GP declare one-occasion consultancy with Advanced Accelerator Applications during the preliminary phase of product development of ^{177}Lu-DOTATATE in Italy. All other authors declare that they have no conflicts of interest.

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