Evidence Base for the Use of PRRT

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Abstract

The development of peptide receptor radionuclide therapy (PRRT) in disseminated neuroendocrine tumors (NETs) has been a long and protracted process. The idea was born within nuclear medicine academia but its translation to clinical practice has been marked by misunderstanding of the rigors of the processes used in drug registration. There were several false starts and some of the required basic science did not occur until after first in man studies.

The standard process of preclinical, phase 1, 2 and 3 clinical trials were sometimes blurred and the required data including the assurances that patients were studied on protocol was missing from subsequent publications. Despite this there was a growing conviction and increasing evidence that the use of PRRT had a positive benefit in both survival and symptom relief in about 80% of treated patients.

After a decade and a half of false starts and incomplete data a formal randomized controlled trial was conducted comparing PRRT with high dose somatostatin which clearly proved that PRRT was both safe, effective and the treatment of choice in hormone refractory NETs.

One of the major innovations in the world of theragnostics in the past decade has been the licensing of peptide receptor radionuclide therapy (PRRT) for the treatment of neuroendocrine tumors (NETs). However, the path to this development has not been smooth and has shown in many ways how not to develop a new idea from laboratory to bedside. There is a saying in the English language that “the path to hell is littered by good intentions.” This is pretty much the story of PRRT. The first patients were treated by a form of PRRT in the mid-1990s when much of academic medicine was idea led and it was possible to pursue any idea with the minimum of evidence and sometimes this worked and sometimes not. Twenty years later we live in an era of evidence based medicine. In 2020 research is normally conducted by teams not individuals and required patients to be studied on formal and registered clinical trials. This then is a story of how it almost all went wrong and it could have led to PRRT not becoming the success it is now.

Clinical Trials

The essence of any new development in medicine is that it must be backed by evidence. This evidence must be collected in a systematic and objective way. Only evidence built on such a foundation will become acceptable to the world's major licensing authorities such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Data must be collected systematically and be collated by an independent organization especially in the latter stages of any research setting. These organizations are known as Clinical Research Organizations (CROs) and can be either commercial or academic. However, engaging a CRO is not a cheap option and as many nuclear medicine departments have difficulty obtaining

Table 1. Research Phases for Clinical Trials of Therapeutic Radiopharmaceuticals

Stage of Research	Aim of Stage	Number of Subjects
Stage 0	A preclinical stage showing proof of concept, some pharmacodynamic and pharmacokinetic data. Some idea of expected toxicity and for radiopharmaceuticals dosimetry	Variable depending on expected toxicity for diagnostic agents normally 10-40 mice. For therapeutics may also include larger animals including primates
Phase 1	Dose ranging toxicity trial, this will include using graduated doses of the new agent until significant grade 3,4 toxicity found. For radiopharmaceuticals radiation activity and dose may be more important than pharmaceutical dose. Each stage of treatment level normally includes 3 patients. Dosimetric, pharmacodynamic and pharmacokinetic data as well as effect on various organ function collected. Efficacy data can be collected but is not the aim of this stage. Normally a single site study	Between 9 and 20 patients all with an advanced state of the target disease
Phase 2	Using the radioactivity and dosimetry data. A single dose and radioactivity level is set and a group of patients studied to determine the expected efficacy of the treatment. This should be collected across more than 1 site and CRO involvement is needed	Up to 100 patients with the target disease at the stage of disease it is proposed the treatment is aimed at
Phase 3 trails	A full randomised controlled trial is set up comparing the new treatment with the best treatment presently available. The number of patients is determined by the results of phase 2. It will be multi-site and involve a CRO. The control arm should be the most effective current treatment or if not available the best supportive care available	Depends on the expected efficacy but can be about 100-200 for a diagnostic agent and between 300 and 1000 for most new therapy agents. All patients will have the stage of their disease that is proposed for the final licenced product. The treatment arm can have twice the number of subjects than the control arm

research grants they are not able to employ a CRO. If their research has not been performed in this way it cannot be published in the highest cited journals so they are unsuccessful in obtaining high level grants and so a viscous cycle is set up such that the prospect of high level research becomes reduced. Such was the case for PRRT.

Classically in the development of any new radiopharmaceutical, such as PRRT, there are four stages of research (Table 1)

Preclinical Trials

The development of different compounds for use in PRRT was centered on two European cities, Basle and Rotterdam and complicated by patent rules. The first product developed for use in humans was an octopeptide version of natural somatostatin-octreotide which was developed in the 1960s. This product was initially used for the treatment of acromegaly but was soon found to control the symptoms of the carcinoid syndrome via the somatostatin-2 sub type receptor.

This was labeled with a diagnostic radionuclide Iodine-123 in Basle and Indium-111 in Rotterdam. Without much formal laboratory work the product was then used to image neuroendocrine tumors including pancreatic and nonsecreting NETs. . Within a few years over 1000 patients with a variety of NETs and some other tumors had been imaged. This lead, as was possible at that time, to the licensing of the product for diagnostic purposes. In the mid-1990s the Rotterdam group used high activity Indium-111 octreotide to treat some patients with carcinoid relying on the Auger electron produced by indium to have a therapeutic effect. A few other groups also worked with this agent but with limited success. It was clear that either massive activities of indium-111 would need to be given which would be very expensive and because of the high yield of gamma particles need excessive radiation protection which was impractical. The problem was indium was attached to the peptide chain via a diethylenetriamine penta-acetic acid (DTPA) linker which could chelate indium but not beta emitting metals such as Yttrium. The answer came from the Basle group who used a different chelator 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA) which could allow yttrium to be attached to the peptide chain. The next innovation of the Basle group was to then alter the peptide chain itself to improve affinity for the somatostatin receptor subtype 2 receptor (SSR2). This resulted in a chemical DOTATATE as the prime candidate. It was at this point that some significant preclinical work was finally done primarily by the Rotterdam group which looked at mice models of SSR2 and various compounds including natural somatostatin, Indium-111 octreotide, Yttrium-90 octreotide, Yttrium-90 DOTATATE, Yttrium-90 lanreotide (another commercial SSR2 analogue) and Lutetium-177 DOTATATE.

The highest affinity was with Yttrium-90 DOTATATE with an IC_{50} of 1.6 nmol followed by Yttrium-90 octreotide at 11 nmol and Lutetium-177 at 15 nmol. This compares to the IC_{50} of 2.7 nmol for natural somatostatin.

The reason Lutetium-177 was included in the list was because in the confused development of PRRT the preclinical work came after the product had been trailed in patients. In the early clinical experience the transfer of isotope from Indium-111 to Ytrrium-90 had indeed resulted in a significant improvement in symptoms and some evidence of tumor regression but at the cost of increased toxicity especially to the kidneys. Some work had shown the Yttrium-90 PRRT actually bound to the renal tubules leading to irreversible radiation nephritis in some patients.

Though this could be blocked by the use of intravenous loading with arginine and lysine, the concentration of amino acids needed was about 30 g over 6 hours enough to cause severe vomiting. It was hoped that the lower penetrating energy of the beta emitted from Lutetium-177 would cause less kidney damage. The Rotterdam group was about to show in a group of Lewis mice with a CA 90428 NET cell line that the DOTATATE or tyrosine DOTATATE combination provided the optimal tumor to kidney ratio whilst maintaining effective tumor kill.

The stage was now set to drive forward with clinical trials or would have been if some of those trials had not already happened

Early Phase trials

The first uses of PRRT were small trails based on Auger therapy with Indium-111 octreotide from the Rotterdam group

and Yttrium-90 DOTA octreotide from the Basel and Milan groups. ' These were empirical trials with the amount of peptide determined with what was available within standard vials and the radioactivity limited as much by cost and availability as by any scientific principle. Other factors with the Indium-111 octreotide was the radiation protection issues to staff and family due to the high yield of gamma emitters. With both the Yttrium-90 and Indium-111 in various countries there was also limits on how much could be held within a certain hospital and disposed of normally as urinary or fecal activity into the local sewage system. Neither product really had a formal phase 1 trial based on increasing steps of radioactivity given as seen with Iodine-131 CHT25 in Hodgkin's lymphoma or a dosimetry based approach as seen in Iodine-131 tositomomab in non-Hodgkin's lymphoma. '

In both these approaches either the activity or the dose is increased till grade 3 or 4 toxicity is reached and then the activity or dosage level below this is the one that is used in phase 2 trial and this is called to maximum tolerated dose.

These grades of toxicity can be measured in any parameter and include clinical symptoms as well as parameters in blood testing. They have been defined by the World Health Organisation (WHO) (Table 2).

Table 2. General Principles of WHO Toxicity

WHO Toxicity Grade	Clinical or Laboratory Criteria
Garde 1	Minor symptoms not requiring any intervention or monitoring or minor change in laboratory criteria (normally about 10%)
Grade 2	More significant symptoms that the patient has but does not require treatment, a more significant change in laboratory counts (>10%) but treatment not needed
Garde 3	Symptoms requiring treatment or changes in blood test results requiring treatment. The test dug is no longer given or can be introduced at a lower dose once the patient has recovered
Grade 4	Severe symptoms or changes in laboratory tests requiring hospitalisation or death of the patient

With most radiopharmaceutical treatments it is possible using data on dosimetry to determine the most likely site of toxicity as dosimetry should be performed though this can be difficult with pure beta emitters such as Yttrium-90 as only bremsstrahlung imaging can be performed. However, it became clear that though there was some expected hematological toxicity the most significant toxicity was to the kidneys which in early trails lead to some patients requiring dialysis within a year of treatment.

Calculations were made showing that because of the binding of the Yttrium-90 octreotide to the kidneys and the long path length of the emitted beta the 3000Rad (30Gy) radiation limit for radiation nephritis could be reached with a little as 100mCi (3.7GBq) Yttrium-90. [,] This could be blocked by the use of high levels or arginine and lysine extending the maximum activity that could be given to a total of 540mCi (20GBq) of Yttrium-90. At this point the target organ became the bone marrow with dose limiting toxicity affecting in particular the platelets. This appeared more common in those with pretreatment with cytotoxic drugs. To search for a less toxicity but maintain efficacy in PRRT Lutetium-177 was proposed with an activity of 200 mCi (7.4B Gq) per cycle, again this was not set by a formal phase 1 trial but by a dosimetric calculation that 4 cycles of 200 mCi (7.4 GBq) Lutetium-177 DOTATATE with lysine and arginine given for each cycle would keep the renal radiation dose to less than 3000 Rad (30 Gy) as determined by both the group in Rotterdam and Bad Berka. [,,]

Phase 2 Trials

A phase 2 trial should identify the efficacy of a treatment. Most importantly it should be run to an agreed protocol in particular there should be an agreed inclusion criteria. For trials of an oncology drug this should include evidence for progression which for secreting NETs such as carcinoid can include biochemical progression. Patients should have been offered the best effective treatment which at the time would be long acting somatostatin analogs for mid gut NETs and chemotherapy with and without long-acting somatostatin analogs for pancreatic NETs. It is unclear from many of phase 2 studies whether these requirements had been adhered to. It took nearly a decade to unmuddle the resulting data sets resulting in a significant delay in the licensing of PRRT.

There is a single prospective phase 2 trial sponsored by Novartis using yttrium-90 octreotide. This trial was not published for about 7 years after it was completed. The results were not encouraging as it was thought many patients were studied with very advanced disease in whom no treatment was likely to work. Results were that in the 90 patients treated with the carcinoid syndrome 74% had some symptom relief but median overall survival was only 18 months reflecting the advanced state of disease in those patients entered into the trial.

A tangential approach was to label another long acting analog of somatostatin, lanreotide with Ytrrium-90. A multicountry multicenter trial however, did not produce a good clinical outcome partly as significant bone marrow toxicity was found with cumulative activities of 108-145 mCi (4-5 GBq) Y-90 lanreotide. There were than a series of phase 2 trials using Yttrium-90 DOTATATE in Bad Berka, London and Warsaw.

In the London and Warsaw the principles of a phase 2 trial were closely followed, it is not stated that all the patients in Bad Berka had progressive disease in the 6 months prior to commencement of treatment. However, there was more detailed dosimetry in the Bad Berka trail showing that cumulative activities of 432-541 mCi (16-20 GBq) would result in the maximum tolerated radiation dose to the kidney of 3000 Rad (30 Gy), in fact they tried not to

exceed a kidney dose of 2300 Rad (23 Gy). Using this approach they were able to tailor the activity given to maximize the antitumor effect of the PRRT. Overall from the main toxicity seen in this group because of the use of amino-acid protection was about 4% grade 3-4 hematological toxicity.

In parallel the Rotterdam group was working on the use of Lutetium-177 DOTATATE and published a hybrid phase 1-2 trail in which 151 patients received cumulative activities of between 595 and 811 mCi (22 and 30 GBq) Lutetium-177 DOTATATE.

They only had follow-up data on 125 patients. This is of significant concern as in the eyes of a regulator a patient without follow-up is a dead patient giving Lutetium-177 DOTATATE a mortality rate of 17%. This would be most unexpected and probably just reflects poor data keeping. In addition there is no real information concerning tumor progression before therapy but despite this about 28% of patients achieved partial or complete response which had not been seen with any previous treatment in this patient group. A total of 54% of patients achieved disease stability (they had a strange nononcological category called minimal response which was really disease stability). In a follow-up paper of 310 patients the same group however, produced the most interesting result in that they showed very long progression free and overall survival in patients with both tumor shrinkage and disease stability on CT, with 75% of patients being alive 48 months.

The only poor prognosis group was those with radiological progressive disease with a median overall survival of around 10 months. Therefore this showed us that radiological response except for progressive disease cannot be used as a surrogate for survival. In a subgroup of 36 patients a formal assessment of symptomology was made with 21 of these patients (78%) showing significant symptom relief. It was also noted whilst this was less than seen with Yttrium-90 DOTATATE this was achieved with minimal toxicity with only 1% of patients showing grade 3-4 bone marrow toxicity.

Towards a Phase 3 Study

The results of phase 2 studies though flawed did point the way to Lutetium-177 DOTATATE being a successful treatment for NETs but then development ground to a halt. Centers that could make the product and could find funding were able to continue to treat, primarily the Rotterdam and Bad Berka groups however, treatment was generally not available to a large number of patients in particular in North America. Government and Insurance funders are largely data led in the decisions they make concerning funding and for them the gold standard test is the randomized control trial. As such a trial did not exist for PRRT. A group from Busan, South Korea looked at all the available evidence concerning Lutetium-177 DOTATATE therapy in NETs and initially found 6 series which would qualify as a well-run prospective phase 2 study with 473 patients from Italy, Switzerland and the Netherlands.

Using Forest plots they determined that the overall response rate in tumor size reduction was 29% and if disease stability was counted as successful in patients with prior progressive disease the overall rate of success was 82%.

Phase 3 Trial

After the PRRT story had continued for 2 decades the definitive answer came in 2016 with the publication of a phase 3 randomized controlled trial of Lutetium-177 DOTATATE vs

high-dose somatostatin the NETTER-1 trial. To run such a trial cost of tens of millions of US Dollars, this will mean commercial organizations will have to be involved and also when the final product is marketed this invested money will need to be recovered. The NETTER-1 trial only included patients who had disease progression on the maximum clinically used dose of slow release Octreotide (Somatostatin LAR) which was 30 mg per month.

As PRRT has only ever been shown to be the effective long term treatment for mid gut NETs (the group studied in NETTER-1) the FDA decided that the "control" arm should be treated with Somatostatin LAR 60 mg per month. This was not entirely logical but it did feel as though something was being done for those patients not receiving PRRT. Originally the trial was powered at 140 patients for progression free survival but this was increased to 240 patients so the study could be powered for overall survival. It was a multicenter, multinational study spread across the globe. Patients with renal, hepatic or bone marrow failure were excluded. To keep to the theragnostic principle the patients needed uptake of Indium-111 octreotide or Gallium-68 DOTATATE greater than normal liver to be included. Up to 4 cycles of 200mCi (7.4 GBq) Lutetium-177 were administered 8 weeks apart under amino acid cover (for consistency only 2 amino acid products were allowed). At present only an interim analysis has been published and it is expected to take 5 years after the last patient was randomized before 50% of the patients receiving PRRT has died which is not predicted to occur until 2020 at the earliest. The results of this interim analysis of 229 patients equally randomized to PRRT or 60 mg somatostatin LAR monthly was as expected from phase 2 data. The results showed a 79% reduction in death in those patients taking PRRT. The 20 months progression free survival was 65% in the PRRT group as against just 11% in the control group. By 20 months half the control group had died compared with 30% of the PRRT group. This response was seen in all patient groups independent of age, tumor grade, site of disease or secretory status. There was an overall 2% of patients in the PRRT group who suffered significant bone marrow toxicity. Subsequent studies have shown the best predictor of poor prognosis in patients receiving PRRT is positivity on Fluorine-18 FDG scanning.

Future Phase 3 Trials

There is a need for future trails to look at those aspects of PRRT not covered by the NETTER-1 trial. The first of these is NETTER-2. This trial will involve 222 patients with grade 2 and 3 NETs of gastro-intestinal origin and will compare the progression free survival when 4 cycles of 7.4 GBq Lu-177 DOTATATE is given compared with 60 mg of octreotide LAR 4 weekly as the first line of treatment when patients with such tumors are initially diagnosed.

This is an interesting concept as it would be expected the efficacy of Lu-177 DOTATATE to be less in these grade tumors than grade 1 tumors treated in NETTER-2. This study is due for completion in 2026.

A second major trial uses a form of PRRT which differs in that it uses 4 cycles of 7.4 GBq Lu-177 DOTA-octreotide (also known as edotreotide) which will be compared in a randomized controlled trial against 10 mg of evriolimus given daily. In this study known as COMPETE 330 patients will be randomized and it is powered to look at both progressive free survival and overall survival. The patients being studied may have gastro-intestinal or pancreatic NETs. Recruitment is expected to be completed by 2024.

Conclusion

A journey of 20 years for PRRT came to its end on the publication of NETTER-1. From this point on it became standard for care in mid gut NETs and to a lesser extent fore gut NETs. However, though the journey has been long it has left many unanswered questions. How much activity should be given and how often. Should patients with a good partial response be given intermittent “maintenance” PRRT. Is a second course of PRRT in relapsed patients as successful as the first treatment cycle. Instead of using standard activities should a dosimetric approach be used. Also there is a group on nongut NETs such as lung carcinoids, malignant pheochromocytomas and paragangliomas in which we need to prove PRRT can work as well and at present is subject of a phase 2 trail.

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