PEER REVIEWED

Emerging Treatment, Peptide Receptor Radionuclide Therapy, Provides New Treatment Option for Gastroenteropancreatic Neuroendocrine Tumours

With nuclear medicine therapeutics expected to represent 60% of the projected $26 billion global nuclear medicine market by 2030,[1] new alternative treatments are now beginning to emerge for conditions including gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Of these nuclear medicine innovations, Peptide Receptor Radionuclide Therapy (PRRT) is an option that combines the advantages of two of the most successful approaches to cancer treatment: external beam radiation and tumour targeted therapy. By using targeting molecules to selectively deliver radioactive payloads inside tumour cells, PRRT has the potential to provide efficacy and safety in the treatment of GEP-NETs. But why have GEP-NETs previously been so difficult to treat and what benefit does PRRT bring to patients?

What are GEP-NETs and How Challenging are they to Diagnose?

Neuroendocrine tumours are a group of tumours originating in the neuroendocrine cells of numerous organs. The term neuroendocrine refers to the dual features of these cells, which are a cross between nerve cells and hormone-producing endocrine cells. GEP-NETs are subdivided into two primary categories: tumours of the gastrointestinal tract and those in the pancreas. GEP-NETs are also a rare disease. According to the European Society for Medical Oncology (ESMO), the incidence of GEP-NETs is estimated to be 5.25 per 100,000 per year.[2] In the UK specifically, the estimated incidence of gastrointestinal NETs is approximately 2.65 per 100,000 per year, while the estimated incidence of pancreatic NETs in the UK is less than 0.2 per 100,000 per year.[3] Nevertheless, the prevalence of NETs is relatively high, as they are often slow-growing malignancies and generally associated with prolonged survival, if properly managed.[4]

NETs are generally slow-growing, and in many cases do not secrete hormones. As a result, they can remain clinically silent in the early years of the disease process, often delaying diagnosis in many patients.[5] Other patients do experience symptoms, which may include abdominal pain, diarrhoea, fatigue and flushing, among others; however, these symptoms can vary widely between individual patients and are often mistaken for other conditions.[6] Misdiagnoses can include irritable bowel syndrome, rosacea, ulcer, allergies, Crohn's disease, anxiety and menopause.[7]

GEP-NET Treatment Options

Treatment options for patients with GEP-NETs vary from person to person, depending on the origin of their tumour, as well as the stage, grade, tumour burden, patient health history, and other factors. Following diagnosis of GEP-NETs, surgery is often the first-line therapy for treating early-stage NETs. However, many patients with NETs are diagnosed once metastases have already occurred, limiting the curative ability of surgical approaches.

Other treatments currently available for GEP-NETs include somatostatin analogues (SSAs) such as octreotide LAR and lanreotide autogel, which are recommended as first-line systemic therapy in midgut NETs to control tumour growth.[8]

There are further targeted treatments available for these patients, such as everolimus and sunitinib, which are approved for pancreatic NETs based on the results of two placebo-controlled trials in progressive pancreatic NETs. These are considered first-line therapies, when SSAs are not a viable option.[8] Everolimus is also considered an option for patients with progressive gastrointestinal NETs.[8]

Systemic chemotherapy is another option indicated in progressive pancreatic NETs and can be used in both Grade 1 and Grade 2 tumours. However, this treatment is only recommended in patients with higher tumour burden or in patients with significant tumour progression within 6–12 months.[8]

External beam radiation, which is commonly used in other cancers, is not typically considered for patients with advanced GEP-NETs, due to the diffuse nature of the disease.

What does Peptide Receptor Radionuclide Therapy Provide as a Treatment for GEP-NETs?

Peptide Receptor Radionuclide Therapy (PRRT) is a form of targeted treatment using a small molecule which carries a radioactive component. Administered intravenously, the targeting molecule binds to a specific receptor expressed by the tumour cells, and is then internalised into the target cell. The radioactive component of PRRT (called the radionuclide) emits energy radiation that can destroy tumour cells. Because this radionuclide is attached to the molecule which binds to receptors on tumour lesions, the radiation can be specifically targeted to tumour cells in order to destroy them. PRRT is administered concomitantly with an amino acid solution to protect against renal uptake of the radionuclide as it is cleared from the body.

Lutetium 177 (Lu 177) is a commonly-used radionuclide for PRRT, selected for its medium-energy beta emissions and relatively short tissue penetration of 2 mm, which results in direct impact to tumours with minimal ancillary damage to surrounding normal tissues. Lu 177 also has a relatively long half-life of approximately 6.73 days compared to some other radionuclides used in targeted therapy.[9]

PRRT was originally developed in the early 1990s by clinicians at Erasmus Medical Center in Rotterdam, Netherlands, to treat advanced neuroendocrine tumours (NETs). A

small number of hospitals in Europe started using PRRT in the late 1990s and early 2000s (University Hospital in Basel, Switzerland; the European Institute of Oncology in Milan, Italy; Zentralklinik Bad Berka in Bad Berka, Germany; Uppsala University in Uppsala, Sweden; and Medical University of Innsbruck in Innsbruck, Austria) and there are many additional centres using it today.

In the late 1990s and early 2000s, "early adopters" of PRRT were successfully using another isotope called yttrium 90 (Y 90) coupled to various somatostatin analogs used to treat patients with NETs. In 1998, Y 90-labeled dotatoc was used in the treatment of 10 patients with different somatostatin receptor–positive tumours. In 2001, the results of a Phase II study of Y 90-labeled dotatoc in 41 patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) and bronchial neuroendocrine tumours demonstrated an overall response rate of 24% and a significant reduction in carcinoid syndrome in 83% of the patients.[10]

In 1998, a group called Specific Peptides for Imaging and Radio Isotope Therapy (S.P.I.R.I.T.) was established to develop marketable radiopharmaceuticals using targeting peptides and peptide-like molecules to deliver diagnostic or therapeutic medical doses to specific sites within the body. One of the peptides originating from this network was lutetium (177Lu) oxodotreotide. The first clinical studies with lutetium (177Lu) oxodotreotide started in 2000.[10] In 2003, a study of lutetium (177Lu) oxodotreotide therapy in 35 patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) demonstrated complete remission in one patient (3%), partial remission in 12 patients (35%), stable disease in 14 patients (41%), and progressive disease in seven patients (21%), including three patients who died during the treatment period.[10]

In 2010, Advanced Accelerator Applications, S.A. stepped in and developed Good Manufacturing Process-compliant manufacturing of lutetium (177Lu) oxodotreotide, negotiated a regulatory pathway with the US Food and Drug Administration and the European Medicines Agency, and started a pivotal multinational Phase III study (NETTER-1) at 41 global sites in 2012.[10]

By 2015, the NETTER-1 study had met its primary endpoint of assessing progression-free survival, demonstrating that treatment with lutetium (177Lu) oxodotreotide and standard of care (octreotide LAR injection) significantly improved progression-free survival compared with a high dose of octreotide acetate injection in patients with advanced midgut NETs. In January 2017, the results of this Phase III trial of lutetium (177Lu) oxodotreotide in patients with midgut NETs were published in the *New England Journal of Medicine*.[10]

Subsequent NETTER-1 Quality of Life (QoL) analysis also provided evidence of benefit in key domains that are pertinent to midgut NETs, including global health and diarrhoea.[11,12]

Lutetium (177Lu) oxodotreotide PRRT was approved by the European Commission in September 2017, based on data from the NETTER-1 study and data from an open-label trial conducted by Erasmus Medical Center in Rotterdam, Netherlands in patients with somatostatin receptor positive tumours. This is the very first registered peptide receptor radionuclide therapy to be brought to the European NET patient community.

What is Next for PRRT?

As clinical experience with PRRT for NETs has grown over the past decades, researchers have studied similar approaches for other malignancies. One such example is the development of radio-labelled ligands for prostate-specific membrane antigen (PSMA), a protein known to be over-expressed in prostate cancer. Since some of these newer compounds are not necessarily using a peptide base, such as in PRRT, this approach is increasingly being referred to as radioligand therapy, or RLT.[10] Regardless of the nomenclature used, PRRT has established a new treatment paradigm in oncology.

* As of January 2018, Advanced Accelerator Applications, S.A. is a Novartis company.

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Product News

Sartorius Stedim Biotech launches new ambr® 250 high throughput bioreactor system for perfusion culture

- **Unique, single-use perfusion system offers a fast-track to intensified**
- **cell culture process development**

It has been specially designed for rapid cell culture perfusion process development to optimize production of therapeutic antibodies.

The ambr 250ht perfusion system has been developed in collaboration with major biopharma companies. It combines 12 or 24 single-use perfusion mini bioreactors (100-250 mL working volume) with associated single-use perfusion components, all controlled by one automated workstation. The combination of this multi-parallel processing capacity and fully single-use perfusion vessel enables scientists to perform more perfusion culture experiments in a fraction of the time and cost of using traditional perfusion-enabled bench top bioreactors. This new innovation supports a range of hollow fiber perfusion applications, enabling Design of Experiments (DoE) studies for high cell density process development in a Quality by Design (QbD) approach.

The ambr 250ht perfusion system has been specially designed for rapid cell culture perfusion process development to optimize production of therapeutic antibodies.

Central to the system is the novel perfusion bioreactor assembly, which is based on the established and award-winning ambr® 250 bioreactor design. Intensified cell culture processing is enabled via new components such as high efficiency spargers, perfusion pump chambers and an industry standard hollow fibre for cell retention filter. The geometrical similarity of the mini perfusion bioreactor design to BIOSTAT STR® pilot and manufacturing scale bioreactors, enables rapid scale-up of optimized perfusion processes, and shorter development timelines.

The ambr 250ht perfusion system is simple to set up and use, due to the fully assembled and irradiated perfusion bioreactors which include all the essential components. This includes single-use sensors to continuously monitor pressure at the culture fluid inlet and permeate outlet, enabling online monitoring of transmembrane pressure, as well as standard parameters such as pH and DO.

Dr Barney Zoro, ambr Product Manager at Sartorius Stedim Biotech, explains: "By introducing our new ambr 250ht perfusion system, we are offering our customers an important enabling technology for early-stage development of intensified cell culture processes. Transitioning from fed-batch to perfusion culture offers the potential to reduce capital intensive risk by using 1-2000L single-use bioreactors instead of 10,000L production volumes in stainless steel. ambr 250ht perfusion is a predictive process development tool that could lower the cost of goods of antibody production, as well as significantly shortening development timelines."

ambr® systems are designed and manufactured by Sartorius Stedim Biotech/TAP (Royston UK), specialized for automated cell culture and fermentation systems for life science research, development and production. The ambr® systems are widely used for cell line development and process optimization at pharmaceutical, biotechnology and academic laboratories. They are proven to provide a reliable model and consistent scalability to a range of upstream processes.

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