EMERGING SCIENCE FOR PRRT FOR TREATMENT OF NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms arising from cells of the endocrine system with various clinical behaviors. NET cells are characterized by an overexpression of somatostatin receptors. Some somatostatin analogues and targeted therapies have been developed for NETs but with minimal response rates. Peptide receptor radionuclide therapy (PRRT) is a novel approach to treatment of unresectable or metastatic NETs and has changed the landscape of treatment for NETs. It is a form of targeted therapy in which a radiolabeled somatostatin analogue delivers radiation specifically to tumor cells expressing the somatostatin receptor. PRRT using somatostatin has been shown to be highly effective and a well-tolerated therapy, improving survival. Radionuclides currently used for PRRT are mainly β-emitters such as ^{90}Y and ^{177}Lu.

^{90}Y emits β-particles with high maximum energy ([Emax] 2.27 MeV) and a long maximum particle range (10 mm). ^{177}Lu has lower energy ([Emax] 0.497 MeV) and a shorter particle range (maximum 2-4 mm). ^{177}Lu also has γ-emission, which is suitable for post-therapeutic imaging (133 keV [6.5%]; 208 keV [11%]) using gamma camera. Therefore, potentially, ^{90}Y allows the deposition of high radiation doses in large metastases, while ^{177}Lu is suitable for micro metastases. Combined therapy with the two isotopes is also possible as shown by Kunikowska et al. in 2017 by using simultaneous ^{90}Y/^{177}Lu-DOTATATE.

PRRT with β-emitters has a good clinical effect, but the long penetration range causes more adverse side effects. Linear energy transfer (LET, measurement of ionizing density responsible for molecular damage of a particle per length) for β-particles decay along the path lengths is low (0.2 KeV/μm). This means a higher dose of β-emitters is required to damage DNA and disrupt the growth of NETs. α-particles on the other hand have high LET (100 keV/ mm), and increase damage in NETs (probability of DNA double strand break increases ~20 times). In addition, α-particles have higher energy and shorter penetration range in comparison to β-particles, thus, lower dose of α-emitting radionuclides are required for effective therapy. The short range (<100 μm) of α-particles in human tissue improves the chance to damage a cell's nucleus, and minimizes damage to surrounding healthy tissue.

The promising α-emitters for human therapy include: ^{211}At, ^{212}Bi, ^{213}Bi, ^{225}Ac, ^{223}Ra, ^{212}Pb, ^{227}Th, and ^{149}Tb (Kim et al., 2012). Among them, research has focused mostly on ^{213}Bi, ^{225}Ac and ^{212}Pb due to their cost, availability and production/chemistry capabilities.

^{225}Ac is a pure α-emitter with a half-life of 10 days. The predominant decay path of ^{225}Ac yields α-particles with a large cumulative energy of 28 MeV and β-disintegrations of 1.6 and 0.6 MeV maximum energy. The short-lived daughter nuclide ^{213}Bi is a mixed α/ β-emitter with a half-life of 46 minutes. The majority of the total particle energy emitted per disintegration of ^{213}Bi originates from a decay mainly from 213Po with an energy of 8.4 MeV (alpha-particle). Only 7.3% of decay energy is contributed by beta-particle emission, including the decay of 209Pb.

The first reported use of somatostatin analogues labelled with an α-emitter (^{213}Bi-DOTATOC) appeared in 2014 (Kratochwil et al.). The first in human experience with ^{213}Bi-DOTATOC to treat NETs with metastases, refractory to treatment with β-therapy, showed promise with partial remission of metastases and favorable side effects (Morgenstern et al., 2018).

The newest clinically interesting α-emitter is ^{212}Pb which can be obtained from the ^{224}Ra/^{212}Pb generator. ^{212}Pb decays by β-particle emission to ^{212}Bi, which decays by mixed α-/β-particle emissions to ^{208}Tl, ^{212}Po, and finally to stable ^{208}Pb. ^{212}Pb is the immediate parent nuclide of ^{212}Bi (T1/2= 61 minutes). Clinical trials are now underway in adult subjects with NETs using α-emitting ^{212}Pb, chelated with somatostatin (^{212}Pb-DOTAMTATE by AlphaMedix™) Substitution of high-LET, α-emitting ^{212}Pb for lower LET β-emitting ^{177}Lu or ^{90}Y is expected to produce more NET cell death and less collateral damage to surrounding healthy tissues.

Conducting clinical trials with PPRT requires specialized skills to manage radiation safety, product distributions, imaging and calibration for radiation dosimetry. Managing these details across the multiple sites needed to acquire data in sufficient patient populations to reach statistical endpoints, demands attention from an industrial core laboratory with experience and the right expertise from in-house physics, imaging and operational personnel. Medpace Imaging Core Laboratory offers these capabilities within a framework that is large enough to manage a global PPRT clinical trial yet small enough to focus attention the unique and complex details of managing radiopharmaceutical trials.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical, and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

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