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Targeted α-Emitter Therapy of Neuroendocrine Tumors

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Neuroendocrine tumors (NET) are a heterogeneous group of neoplasms, arising from cells of the endocrine system, with various clinical behaviors. Although these neoplasms are considered rare, a significant increase in the incidence and detectability of NET has been noted in many epidemiological studies in recent years. Among the various therapeutic options, peptide receptor radionuclide therapy (PRRT), using somatostatine has been shown to be highly effective and a well-tolerated therapy, improving survival parameters. The current use of radionuclides for PRRT is β-emitters. Due to hypoxia cancer tissue could be resistant for β-emitters. Quite long penetration range had a significant impact on side effects. α-particles with higher energy and shorter penetration range in comparison to β-particles, have distinct advantages for use in targeted therapy. The clinical experience with somatostatine based targeted α therapy (TAT) in NET showed very promising results even in patienicts refractory to treatment with β-emitters. This article summarizes current developments in preclinical and clinical investigation on TAT in NET.

Introduction

Neuroendocrine neoplasia (NEN) is a heterogeneous group of neoplasms, arising from cells of the endocrine system, with various clinical behaviors. Although these neoplasms are considered rare, a significant increase in the incidence and detectability of NEN has been noted in many epidemiological studies in recent years.[1-4] Currently, the new pathologic classification of NEN is based on UICC/AJCC, divided NEN into well differentiated neuroendocrine tumors (NET) NET G1 (Ki-67 < 3%), G2 (Ki-67 3%-20%) and G3 (Ki-67 21%-55%), and poor differentiated neuroendocrine carcinoma (NEC) (Ki-67 > 20%).[5] It is a new, modified version of the previous one based on ENETS/WHO classification from 2010.

The 80s brought the discovery of somatostatin receptor overexpression on neuroendocrine tumor cells. This finding enables the use of radiolabeled somatostatine analogues in the receptor imaging and as next step somatostatin based radiopeptide therapy.

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Peptide Receptor Radionuclide Therapy (PRRT) - treatment with radiolabeled somatostatin analogues is currently, an accepted option of the therapy for patients with metastatic and/or unresectable well differentiated NET. This is one of the most successful examples of the theragnostic concept in nuclear medicine. This method has been evaluated for more than 25 years in dedicated centers. The main goal of PRRT is to deliver the high dose of radiation to the tumor cells and limit the dose to normal tissues.

History of PRRT

Initially, [^{111}In-diethylenetriaminepentaacetic acid (DTPA)^{0}]-octreotide was first used in some clinical trials, with a limited response - regression was observed only in 8% of patients. The limited results were associated with physical characteristics of ^{111}In which emits short range of Auger electrons.[6,7]

The next generation of the PRRT used a modified somatostatin analogue, and different chelator, DOTA instead of DTPA. DOTA chelator allowed to obtain more stable radiopharmaceuticals labelled with β-emitters.

Currently, β-emitting ^{90}Y and ^{177}Lu are used, each of them shows some potential advantages. ^{90}Y emits β-particles with high maximum energy ([E_{max}] 2.27 MeV) and a long maximum particle range (10 mm). ^{177}Lu has lower energy ([E_{max}]

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0.497 MeV) and a shorter particle range (maximum 2-4 mm). This isotope has additionally γ-emission, which is suitable for post-therapeutic imaging (133 keV [6.5%]; 208 keV [11%]). Therefore, potentially, ^{90}Y allows the deposition of high radiation doses in large metastases, ^{177}Lu allows the concentration of most doses in small metastases.

^{90}Y-DOTA0-Tyr3−octreotide (^{90}Y-DOTATOC) was the first radiopeptide with β-emission used in PRRT. Studies assessing the efficacy of ^{90}Y-DOTATOC, despite differences in the protocols used, showed a favorable response to treatment in 10%-34% of patients.[8-11]

The application of ^{90}Y-DOTATOC analogues resulted in nephrotoxicity in significant number of patients. The pretreatment infusion of lysine and arginine reduce a 40% of renal absorbed dose compared with the control investigation and stays standard part of treatment procedure.[12]

Another tracer with higher affinity to somatostatine receptor type 2 and 5, labeled with ^{90}Y was LANREOTIDE. ^{90}Y-DOTALAN treatment was evaluated in the MAURITIUS trial.[13] Unfortunately, due to structural changed, the affinity to receptors was lower than expected, resulted minor response in 14% of patients, and stabilization of the disease in 41% of patients. Additionally, DOTATOC showed higher tumor uptake than DOTALAN in most patients. The treatment with ^{90}Y-DOTALAN was discontinued.

The new somatostatin analogue [Tyr3] octreotate with the higher affinity for sst2 was recently introduced in targeted radiotherapy.

The initial report of using ^{177}Lu DOTATATE was published by Kwekkeboom et al in 2003 with complete and partial responses in 38% patients (WHO criteria).[14] The side effects of therapy with ^{177}Lu DOTATATE were minor and mostly transient, the most common finding was mild bone marrow suppression. Kidney function did not deteriorate in any patient.

In 2005, de Jong at el described the combined treatment as consisting of 50% ^{177}Lu-DOTATATE and 50% ^{90}Y-DOTATOC.This treatment schedule extended three times the survival time in rats. The main explanation was complementary physical characteristics of both isotopes which allow more homogenous irradiation of large and small metastases.[15,16] This finding was confirmed in human where simultaneous use of ^{90}Y/^{177}Lu-DOTATATE prolong OS in the group of patients treated with ^{90}Y-DOTATATE alone.[17] The better survival outcome with simultaneous use of ^{90}Y/^{177}Lu-DOTATATE was confirmed in long term follow-up and by other authors.[18-23] Example of therapeutic effect of simultaneous use of ^{90}Y/^{177}Lu-DOTATATE is presented in Figure 1.

After 25 years' experience of PRRT, first open, randomized, controlled, parallel- trial the NETTER-1 was published. In patients with advanced midgut NET PRRT with ^{177}Lu-DOTATATE significantly improved PFS compared to Octreotide LAR (Sandostatin LAR; Novartis; 60 mg) (PFS 40 months vs 8.4 months).[24] The obtain survival parameters in NETER-1 trial was comparable with reported nonrandomized trials data.

These results clearly showed that midgut NET patients treated by PRRT had a survival advantage compared to other forms of treatment including targeted therapy with mTOR or kinase inhibitor.[25,26]

Why α-Emitters?

PRRT with β-emitters has a good clinical effect, on the other hand, a fairly large penetration range has a significant impact on side effects. Additionally, due to hypoxia cancer tissue could be resistant for β-emitters treatment.

Radioisotopes emitting α-particles which have higher energy and shorter penetration range in comparison to β-particles have distinct advantages for use in targeted therapy.

α-particles with high linear energy transfer (LET $\approx$100 keV/μm) give the higher probability of double strand breaks compared with β-particles with low LET (probability of double strand break increase $\sim$20 times).[27] On the other hand the short range ($<$100 μm) of α-particles in human tissue resulted in minimizing damage to surrounding healthy tissue.

Cell death induced by α-radiation is predominantly due to DNA double strand breaks and induce apoptosis so it is largely independent of cell cycle phase and cell oxygenation status.[27,28]

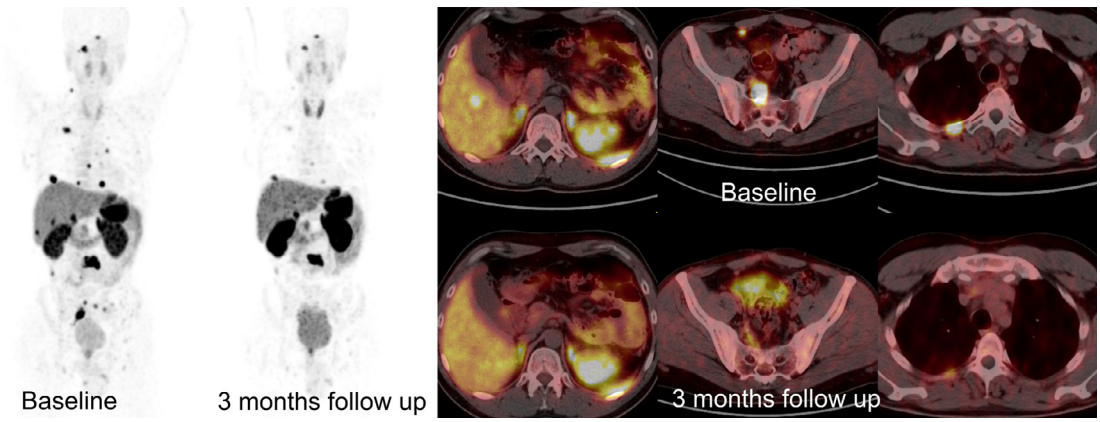

Figure 1 Example of tandem ^{90}Y/^{177}Lu-DOTATATE therapy effect. A 36-year-old man with non-functional rectal NET G2 and multiple liver, lymph nodes and peritoneal metastases, after primary surgical treatment and progression during long acting somatostatine analogues therapy. ^{68}Ga- DOTATATE PET/CT before treatment showing uptake in the metastatic lesions. At 3 months of follow up, ^{68}Ga- DOTATATE PET/CT showed partial treatment response.

Due to problems of availability and production, half-life, cost and the ability to chemically and stably incorporate them into a suitable vector, only a few of α-radionuclides are medically relevant and available for potential clinical use. These include ^{211}At, ^{212}Bi, ^{213}Bi, ^{225}Ac, ^{223}Ra, ^{212}Pb, ^{227}Th, and ^{149}Tb.[28]

Among them, the generator derived radionuclide pair ^{225}Ac and ^{213}Bi has emerged as particularly promising.

^{225}Ac is a pure α-emitter with a half-life of 10 days. The predominant decay path of ^{225}Ac yields net 4 α-particles with a large cumulative energy of 28 MeV and 2 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 α decay mainly ^{213}Po with energy 8.4 MeV α-particle, while only 7.3 % of decay energy is contributed by β-particle emission, including the decay of ^{209}Pb.

The new interesting α-emitter is ^{212}Pb which could be obtain 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 parental nuclide of ^{212}Bi ($T_{1/2}$ = 61 minutes).

Preclinical Studies

In the literature, there are a few studies about using α-emitters in NET.

One of first by Norenberg et al described treatment with ^{213}Bi-DOTATOC in rat pancreatic carcinoma.[29] It showed a significant reduction of tumor growth for low volume tumors below 0.75 mm^3 treated with 12.6 MBq and large tumors with volume 1720 mm^3 treated with 22.2 MBq. The high dose resulted in one case of acute mild nephrotoxicity, no chronic nephrotoxicity was seen. There were no observed acute or chronic hematological toxicities.

Other somatostatine analogs DOTATATE was investigated by Chan et al.[30,31]

^{213}Bi-DOTATATE was used in two models (H69 human small-cell lung carcinoma and CA20948 rat pancreatic tumor) and tumors with different sizes (50 and 200 mm^3).[30]

Therapeutic anti-tumors effects were observed in all animals treated with ^{213}Bi-DOTATATE with the delay of tumors growth in both, different size of tumors.

In large tumors, the inhibition of tumors growth was initiated around 30 days leading to a tumor growth delay time of 50 days in the model of CA20948 bearing animals, in H69 tumor bearing animals delay time was around 70 days.

In small tumors of CA20948 and H69 tumor-bearing animals, a delay of tumor growth was found for around 30 days after therapy. The higher anti-tumor effect and longer time to reach a tumor volume 2000 mm^3 in small tumors was observed.

All animals treated with ^{213}Bi-DOTATATE showed a higher survival rate in comparison to control animals.

The authors didn't observe significant changes in kidney function examine by ^{99m}Tc -DTPA uptake, in next step impact of amino-acid Lysine was investigated.

Infusion of Lysine reduced the renal absorbed dose by 50% 20 Gy was found as the LD50 value.[31]

Other authors compared therapy with α and β-emitters.

Nayak et al[32] in human pancreatic adenocarcinoma cells showed that ^{213}Bi-DOTATOC was 3.4 higher effective than ^{177}Lu-DOTATOC. Miederer et al[33] investigated other α-emitter ^{225}Ac in mouse tumor xenograft implants. Therapy with ^{225}Ac-DOTATOC resulted in the higher reduction of tumor mass in comparison to therapy with ^{177}Lu-DOTATOC or cold (unlabeled) DOTATOC (0.12 vs 0.52 vs 0.89 g, respectively). The highest tolerated dose was determined on level 20 kBq per mouse. The activities more than 30 kBq resulted in tubular necrosis.

Other authors investigated potential use for PRRT, DOTATOC or DOTAMTATE, the octreotate analogue labelled with other α-emitter - ^{212}Pb.

^{212}Pb-DOTATOC showed on cell model significantly inhibited tumor growth however, the therapeutic effect was accompanied by observable renal toxicity.[34]

Stallons et al investigated ^{212}Pb-DOTAMTATE alone or in combination with a chemotherapeutic agent 5-fluorouracil, on mice bearing AR42J rat pancreatic cells model. The 2.4-fold longer mean survival time was observed even with a single injection 10 μCi of ^{212}Pb-DOTAMTATE. The best efficacy was obtained by three treatment cycles of ^{212}Pb-DOTAMTATE in 2 weeks interval. 5-fluorouracil given as a chemo-sensitizing agent, in combination with three cycles of 10 μCi ^{212}Pb-DOTAMTATE improved further efficacy. These conditions led to 79% of the animals being tumor free at the end of the 31-week study.[35]

The Studies in Human

The first time complete response of targeted α therapy with somatostatin analogues ^{213}Bi-DOTATOC in patients refractory to β therapy was showed during SNMMI, it was awarded to image of the year 2012.[36]

Currently only one original paper according to possibility to use somatostatin analogues labelled with α-emitters (^{213}Bi -DOTATOC) is published.[37]

This first human experience with ^{213}Bi -DOTATOC described the treatment of seven patients with progressive advanced neuroendocrine tumors with liver metastases refractory to treatment with ^{90}Y-DOTATOC or ^{177}Lu-DOTATOC. The six patients were treated with an intra-arterial infusion of ^{213}Bi-DOTATOC to originate hepatic vessels. One patient with bone marrow involvement was treated with a systemic infusion of ^{213}Bi-DOTATOC. This study showed promising data with partial remission of metastases, and favorable side effects: chronic kidney toxicity was moderate and hematotoxicity was less pronounced than with preceding β therapies. It was interesting that a systemic treatment of neuroendocrine prostate cancer patients with bone metastases and bone marrow involvement, consisting of 3.3 GBq of ^{213}Bi-DOTATOC, didn't show acute hematological side effects. The patient was still alive after more than 12 months follow-up.

The authors continued this work and summary latest experience with 25 patients in review article.[38] Twenty-one patients received treatment interarterially into the main tumor-feeding vessel, while four patients received intravenous

injections, with cumulative activity 2.6 to 21 GBq of ^{213}Bi-DOTATOC. They conclude that targeted α therapy can offer a valuable additional treatment option to patients refractory to therapy with β-emitters.

At present, there are no other published clinical studies for TAT in NET.

Kratochwil et al presented dose escalation study data of single cycle and fractionation concepts for ^{225}Ac-DOTATOC in TAT on European Association of Nuclear Medicine (EANM) conference in 2015.[39] Treatment was performed in 34 patients (46 treatment cycles) with progressive NET. The maximum tolerated dose of a single cycle ^{225}Ac-DOTATOC was considered to be 40 MBq. They investigated tolerability of fractions - multiple fractions were tolerated with 25 MBq injected activity every 4 months or 18.5 MBq every 2 months up to cumulative activity of 75 MBq. It was no preference of a particular fractionation concept in the radiologic treatment response.

At European Neuroendocrine Tumor Society (ENETS) conference 2018 was presented treatment results of 10 patients with progressive metastatic neuroendocrine tumors, refractory to ^{177}Lu-DOTATATE therapy.[40] One to two cycles (average 1.2) of ^{213}Bi or ^{225}Ac -DOTATOC was done. Eight weeks post therapy PET/CT with ^{68}Ga-DOTANOC showed in 60% patients up to 40% reduction of target tumor volume. The side effects were mild, only grade 1 and 2 hematological toxicity was seen.

Example of therapeutic effect of ^{225}Ac-DOTATATE is presented in Figure 2.

The results of TAT in NET are very promising, especially gives the opportunity to treat patients refractory to β-emitters. The limited number of publication on the efficacy, toxicity, and long term tolerability need future evaluation in larger group of patients.

Current Clinical Trial with α-Emitters

Radiomedix is sponsoring clinical trial of ^{212}Pb-octreotate analog- (AlphaMedixTM) NCT03466216.[41] This is a phase 1 trial examining the dose tolerance of ^{212}Pb-AR-RMX in PRRT-naive patients. The first results were shown during 11th International Symposium on Targeted-Alpha-Therapy in May 2019 (TAT11).[42] In nine enrolled patients treatment was well-tolerated with single ascending or the first multi-ascending doses of ^{212}Pb-AR-RMX. Few mild adverse events were reported during the follow-up visits (nausea and mild hair loss in 2 of 9 patients; the abdominal pain and diarrhea in 3 of 9 patients, the fatigue in 2 of 9 patients).[42] There was no dose-limiting toxicity. This clinical trial is ongoing.

The Neuroendocrine Tumor Research Foundation in collaboration with the Education and Research Foundation for Nuclear Medicine and Imaging has open Nuclear Medicine Pilot Grant "Functionalized Silica Nanoparticles: Development of a Combined PET and TAT Theranostic Agent for Neuroendocrine Tumors".

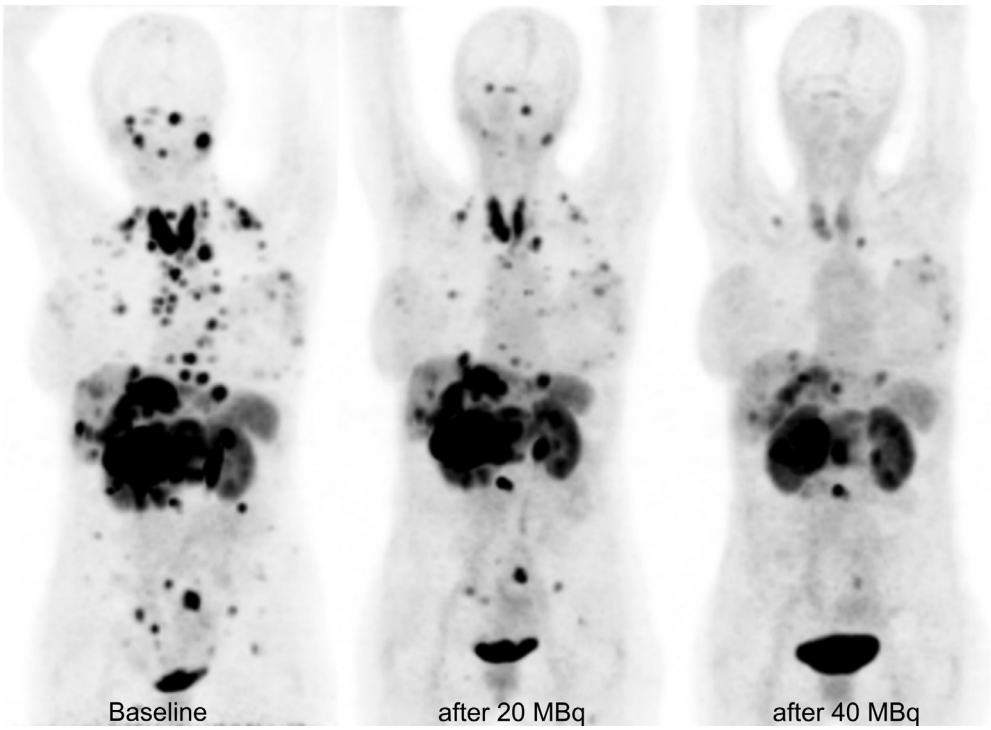

Figure 2 Example of ^{225}Ac-DOTATATE therapy effect (Courtesy to Clemens Kratochwil, Heidelberg). Patient with CUP NET G2 after multiple line treatment: long acting somatostatine analogue, PRRT: 3 cycle of ^{90}Y-DOTATOC with 4 GBq activity and 2 cycle of tandem therapy 2 GBq of ^{90}Y-DOTATOC and 4 GBq of ^{177}Lu-DOTATOC, 3 times TACE, 4 cycles of chemotherapy with FOLFOX scheme, mTOR inhibitor and radiotherapy for orbital metastases. ^{68}Ga-DOTATATE PET/CT before treatment showing uptake in the disseminated metastatic lesions. Patients was treated with ^{225}Ac-DOTATOC with dose escalation, first cycle of 20 MBq and next 40 MBq. The follow up ^{68}Ga- DOTATATE PET/CT showed partial treatment response.

In the University of Utah α-emitting radionuclide ^{225}Ac will be placed in a silica nanoparticle, to contain radioactive daughters produced during decay, consequently, reduce healthy cell exposure and increase cancer cell damage. Additionally, the same procedure will be done for β + emitter ^{89}Zr to treatment planning and monitoring. The nanoparticle system will be tested for stability in laboratory models.

The theragnostic agent (^{225}Ac/^{89}Zr-octreotate silica nanoparticles) is intended to be delivered using PRRT.[43]

Conclusions

The somatostatin receptor base targeted therapy is a perfect example of the theranostic concept in nuclear medicine. The α-emitters have potential advantages over β-emitting particles radioisotopes due to the high energy and short path length of particles causing mainly in double-stranded breaks in DNA. The clinical experience with TAT in NET showed very promising results even in patients refractory to treatment with β-particle. However, this data is very limited and need future investigation.

Declaration of Competing Interest

No conflict of interest.

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