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VIEWPOINT

Alpha-particle therapy for neuroendocrine tumors: A focused review

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Since Rudolf Heidenhain first identified neuroendocrine cells in 1870, our understanding of neuroendocrine tumors (NETs) has advanced significantly. The increasing incidence and prevalence of NETs, combined with complete tumor resection being the only curative option, has driven the search for effective treatments. Peptide receptor radionuclide therapy, which combines radioactive elements with octreotide derivatives, has emerged as a promising therapeutic approach. While β-particle emitters are currently used in clinical practice, targeted alpha-particle therapy (TAT) shows particular potential for NET treatment. This review examines the physical and radiobiological characteristics of α- and β-particles, evaluates preclinical and clinical evidence for TAT in somatostatin receptor–expressing NETs, and explores both challenges and future developments in α-particle therapy for NETs.

Introduction

In the early 1990s, peptide receptor radionuclide therapy (PRRT) was developed using ^{111}In-DTPA-octreotide (*Octreoscan*) due to its properties of releasing secondary β-radiation to cause targeted DNA tumor damage. They had reasonable response rates, but responses were not durable (1). β-emitting ^{90}Y was the first second-generation radionuclide used for PRRT with good symptomatic and objective response rates but a significantly increased risk of permanent kidney damage due to tubular damage and microangiopathy (2). Subsequently, the safer β-emitting ^{177}Lu was developed, and over the last decade, ^{177}Lu-DOTATATE (*Lutathera*) has become the most widely used PRRT and is licensed by both the *Food and Drug Administration* (FDA) and *European Marketing Authority* (EMA). However, despite the success of ^{177}Lu-DOTATATE, especially following the results of the NETTER-1 trial, patients invariably relapse in 2–3 years following PRRT. The recent NETTER-2 trial has also shown the efficacy of PRRT for high-grade well-differentiated tumors (3). Many strategies have been investigated to improve the effectiveness of PRRT, but targeted α-particle therapy (TAT) has gained the most attention over the past few years. We summarize and update the results of our recent review, to which we refer for a more in-depth analysis of earlier studies (4).

Physical and Radiobiological Properties of α- and β-particles

1. **α-particles**
   Alpha-particles comprise two protons and two neutrons. They are produced in the process known as α-decay. As shown in Figure 1, as they have high particle energy, high linear energy transfer (LET), and a short therapeutic range (c.100μ), they cause highly-selective double-strand breaks (DSBs) in the DNA of cancer cells, but without affecting surrounding normal cells (4). Alpha-particles have a higher relative biological effectiveness for the same absorbed radiation dose.
2. **β-particles**
   The β-particle, an energetic electron, is created by β-decay, a process in which, in an unstable nucleus, a neutron is converted to a proton with the release of an electron. They have comparatively low particle energy and a low LET but a high therapeutic range (c.1mm). Due to these properties, many more β-particles are required compared with α-particles for a similar absorbed dose. They are also more likely to cause single-strand breaks (SSBs) than DSB and more likely to affect the surrounding normal cells (4).

Figure 1 and Table 1 depict the major physical and radiobiological differences between α- and β-particles.

TAT and Neuroendocrine Tumors

^{223}Ra-chloride (*Xofigo*) was the first licensed α-emitting radiopharmaceutical used in the treatment of prostate cancer with bone metastases. Subsequently, several α-emitting radiopharmaceuticals, such as ^{225}Ac, ^{213}Bi, and ^{212}Pb, have been used clinically in the treatment of neuroendocrine tumors (NETs) (5).

1. **^{225}Ac**
   ^{229}Th serves as the main source of ^{225}Ac and its parent ^{225}Ra. ^{225}Ac has a half-life of 9.9 days and a 6-step process decay scheme to stable ^{209}Bi. During this process, a total of four α-particles (of 6–8 MeV energy each) and three β-particles are emitted. A half-life of 10 days and high overall α-emission energies of 27.5 MeV render ^{225}Ac a potentially appealing radionuclide for TAT (4).
2. **^{213}Bi**
   Being a daughter of ^{225}Ac, ^{213}Bi follows a similar decay scheme. It has a half-life of 45 min and produces one α-particle but no β-particles, with a mean energy of 8.3 MeV. It has not been used extensively due to its short half-life, which would necessitate on-site labeling (6, 7).
3. **^{212}Pb**
   ^{212}Pb produces an α-emitting daughter ^{212}Bi that produces a single α-particle with a mean energy of 7.8 MeV. ^{212}Pb is a daughter product from the decay of ^{228}Th: ^{212}Pb has a half-life of 10.6 h, which allows for ease of radiolabelling and administration (8).

Preclinical Animal Studies using TAT in SSR-expressing Tumors

All three radionuclides (^{213}Bi, ^{212}Pb, ^{225}Ac) discussed earlier have been studied in animals in preclinical trials. ^{213}Bi-DOTATOC and ^{213}Bi-DOTATATE have been investigated in a rat pancreatic carcinoma model and mice bearing somatostatin receptor (SSR)-expressing NETs, respectively (9, 10). In both studies, investigators found reduction and delay in tumor growth. They reported no significant renal or bone marrow toxicity (9, 10). Stallons and colleagues investigated ^{212}Pb-DOTAMTATE in a rat pancreatic cell line, where they found increased median survival compared with the control group. The survival was further improved by adding 5-fluorouracil. They observed reversible bone marrow toxicity at a dose of 740 kBq of ^{212}Pb-DOTAMTATE (11). ^{225}Ac-DOTATOC and ^{225}Ac-DOTATATE were investigated in mice (12, 13). ^{225}Ac had a mean energy 70 times higher compared with ^{177}Lu. ^{225}Ac-DOTATATE at a dose of $<$111 kBq was found to be safe and was associated with a significant delay in tumor growth compared with controls (12, 13).

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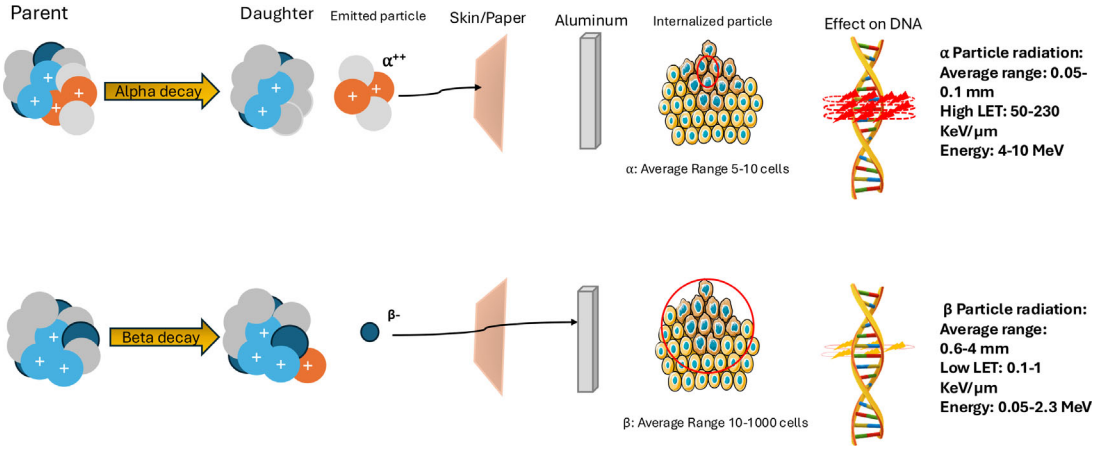

Figure 1. A schematic diagram of the physical and radiobiological properties of the radionuclide decay of α- and β-particles, subsequent potential DNA damage and differences in biodistribution of both particles.

Clinical Studies using TAT in NETs

^{213}Bi-SSA

The first-in-human TAT study was conducted in a group of 8 patients with progressive, ^{90}Y/^{177}Lu-DOTATOC treatment-refractory, NETs. ^{213}Bi-DOTATOC was administered via the intra-arterial route (usually the hepatic artery) in 7 out of 8 patients; 50% of the patients showed a response to TAT [1 had a complete response (CR), 3 had partial responses (PR)]. One patient with diffuse bone marrow metastases received one cycle of systemic TAT with no significant bone marrow toxicity. The toxicity studies showed a mean glomerular filtration rate (GFR) reduction of 30% at 2 years following TAT. One patient developed grade 2 thrombocytopenia following ^{213}Bi-DOTATOC; however, he had developed grade 4 thrombocytopenia following ^{90}Y-DOTATOC therapy previously. One patient developed myelodysplastic syndrome, followed by acute myeloid leukemia on follow-up (7).

^{212}Pb-SSA

In a phase I clinical trial published in the *Journal of Nuclear Medicine* in 2022 by Delpassand and colleagues, they assessed the effect of the α-emitter ^{212}Pb-DOTAMTATE (*AlphaMedix*) (NCT03466216) in PRRT-naïve patients. They reported an impressive 80% disease control rate (DCR) (70% PR and 10% CR) in the 10-patient cohort without significant acute hematological toxicity. A few patients developed transient reversible renal toxicity. One patient with previous co-morbidities developed stage 3 chronic kidney disease (14). Following this, the US-FDA has announced "Breakthrough Therapy Designation" for this drug in the treatment of PRRT-naïve adults with unresectable or metastatic, progressive SSR-expressing gastroenteropancreatic neuroendocrine tumors (GEP-NETs) (4).

^{225}Ac-SSA

Ballal and colleagues studied the efficacy and safety of ^{225}Ac-DOTATATE in patients who previously had received ^{177}Lu-DOTATATE but had stable or progressive disease following ^{177}Lu-DOTATATE therapy: 15 out of 24 (63%) patients had partial response and 9 patients (38%) had stable disease following TAT. No grade 3/4 hematological or renal toxicities were seen (15). The same group reported treating 9 patients with paragangliomas with ^{225}Ac-DOTATATE, seven of whom had had ^{177}Lu-DOTATATE

Table 1. Physical and radiobiological differences between α- and β-particles

	Alpha	Beta
Effects on DNA	Causes more double-strand breaks (DSBs), multiple damage sites. The damage is less likely to be reparable	Causes more single-strand breaks (SSBs). The damage is more likely to be reparable
Oxygenation	Effective in hypoxic tumors	Less effective in hypoxic tumors
Tumor crossfire	No	Yes
Bystander and abscopal Effect	Yes	Yes
Dose rates	Linear exponential reduction in tumor survival as absorbed dose increases	Low-dose rates: More SSBs with shouldering of the dose–response curve High-dose rates: Tumor reduction close to linear exponential
Main mechanism of damage	At low to moderate doses, it causes DSBs with less chances of repair by cellular mechanisms. At high doses, it causes widespread DNA damage leading to significant cellular damage and cell death with reduced repair capability. However, it could cause mutations with potential long-term effects.	At low to moderate doses, it causes SSBs and minor chemical modifications to DNA. At high doses, it causes DNA damage at the rate which may exceed the cell's repair capacity, leading to the accumulation of misrepaired or nonrepaired DNA.
DNA repair and biological consequences	Leads to more frequent, persistent or unrepaired DNA breaks, higher risk of chromosomal aberrations, apoptosis, and cell death	Fewer unrepaired breaks, more efficient and effective repair, but potential for mis-repair leading to mutations.

Tumor crossfire: The killing of malignant cells that are not directly bound by the antibody; **Bystander effect:** Radiation damage to an irradiated area induces a cellular signal which results in similar damage to unirradiated surroundings cells; **Abscopal effect:** Enhanced immune system response in remote untargeted lesions

previously. The DCR was 88%, with no grade 3/4 hematological, renal, or hepatic toxicity were encountered. Quality of life data showed significant improvement in symptoms and quality of life (16). Kratochwil and colleagues conducted a 5-year follow-up study in patients treated with ^{225}Ac-DOTATOC. A single dose above 40 MBq or a repeated dose greater than approximately 20 MBq/cycle of ^{225}Ac-DOTATOC was found to be toxic to bone marrow. Similar to their experience with β-emitting PRRT, an average eGFR-loss of 8.4 mL/min (9.9%) per year was seen (7). In 2023, Demirci and colleagues evaluated the safety, stability, and efficacy of ^{225}Ac-DOTATATE in 11 patients with grade 1 and 2 NETs. Most of them had previously been treated with ^{177}Lu-DOTATATE. They observed that the DCR was 89% with a median PFS of 12 months. One patient developed grade 2 renal toxicity and bone marrow toxicity, whereas no grade 3-4 toxicities were reported (17). In 2024, Yang and colleagues evaluated the efficacy and safety of ^{225}Ac-DOTATATE TAT in patients with NETs and high SSR expression. They observed a DCR of 80%, and no grade 3/4 hematological renal toxicities were observed (18).

Ongoing Clinical Trials

Currently, a small number of clinical trials are underway evaluating the effects of ^{212}Pb and ^{225}Ac in patients with SSR-2-expressing NETs. There is a commercial phase II study (NCT05153772) on ^{212}Pb-DOTAMTATE (*AlphaMedix*) to explore treating patients with SSR-2-expressing NETs refractory to standard therapies. Primary outcome measures are overall response rate and adverse events. This trial is expected to report later in early 2025 (4, 19). Another ^{212}Pb-SSA TAT has been investigated by *Perspective Therapeutics* (^{212}Pb-PSC-PEG2-TOC) (VMT-α-NET) and is undergoing early clinical trials. In this trial, investigators will establish a recommended phase II dose (RP2D) followed by a phase IIa dose-expansion cohort evaluating efficacy using the RP2D (19). *RayzeBio Inc*. is assessing the efficacy of ^{225}Ac-DOTATATE (RYZ101) in multicentre clinical trials [ACTION-1 clinical trial (NCT05477576)] after progression through ^{177}Lu-SSA in SSR-expressing GEP-NETs. In Part 1 of the trial (phase Ib), they concluded that 120 kBq/kg should be the recommended phase III dose. The study will proceed to Part 2 (phase III) with a comparison of RYZ101 at 120 kBq/kg with "standard of care" in patients with GEP-NETs with disease progression following prior ^{177}Lu-labeled SSAs (4, 19). An investigator-run phase I trial conducted by Fukushima Medical University in Japan is studying ^{211}At-meta-astatobenzylguanidine (MABG) in patients with malignant phaeochromocytoma or paraganglioma. MABG targets adrenergic tissue through the norepinephrine transporter; the dose escalation trial will determine safety, MTD (maximum tolerated dose), and RP2D (19).

Limitations, Challenges, and Future Directions

As these isotopes used for cancer treatment decay relatively rapidly, are heavily regulated, and are expensive to make, the use of TAT in a routine clinical practice is highly challenging. For example, the use of ^{213}Bi is limited, given its short half-life and need for onsite labeling. Additionally, its production, purification, chelation, shipping, and administration must be highly choreographed to be successful. Any disruption in the supply chain can leave a patient missing a dose. Despite these challenges, several companies worldwide are developing ^{212}Pb generators, which are also readily available through private and government sources. It may become the most widely used α-emitting radionuclide (8). However, regulatory hurdles such as regulatory compliance on production, transportation, disposal by nuclear regulatory agencies, radiation containment protocols, complex study designs, stricter pharmacovigilance, waste disposal, and environmental impact makes it challenging to develop and implement TAT (20). These hurdles could be overcome by diversification of production sources, international collaboration, early engagement with regulatory bodies, automated manufacturing systems, improving targeting agents, advanced dosimetry models, international standardization, and eco-friendly disposal methods (21).

While the studies discussed above have shown promising results, it should be considered that reporting of the response criteria across the different studies has varied. Another major concern is regarding hematological and renal toxicity associated with TAT. However, in a recent meta-analysis, the incidence of toxicities was uncommon, in the range of 2.1% to 3.4%. Despite this rarity, due to the lack of robust evidence on safety profiles, this will necessitate careful monitoring for such toxicities in patients receiving TAT therapy (22). Detailed previous treatment history with other radionuclide therapy, such as β-emitting therapy with ^{177}Lu, should also be considered before offering TAT to patients as it increases the risk of toxicity with TAT (23). Dosimetry (calculating the dose of radiation delivered to organs and tumors) is difficult by macrodosimetry with current alpha emitters. The majority of radionuclides, which emit α-particles, emit no or little gamma irradiation or positrons for imaging with SPECT or PET, and there is heterogeneous antigen expression among cancer cells (19). However, Singh and colleagues have calculated image-guided dosimetry and response assessment using ^{212}Pb-VMT-α-NET in a patient with a metastatic NET; the patient received a cumulative radiation dose of 3.9 Gy to the target lesions with the dose for all critical organs remained within acceptable limits (24). Newer microdosimetry techniques of TAT, as a function of the source-target configuration, cell geometry, other biological factors, and cell sensitivity, should help to overcome these hurdles (25).

Conclusions

TAT is an exciting and promising therapeutic modality for SSR-expressing NETs. TAT has potential advantages over β-emitting therapy due to the high energy and short path length of α-particles and overcoming radioresistant conditions, such as hypoxia. Although TAT-related long-term hematological toxicity data are not available, currently available toxicity data suggest low acute grade 3/4 hematological toxicities at defined administered activities. The kidney may prove to be a critical organ for TAT due to the high LET of TAT and associated renal tubular damage. However, in due course, other ways of improving on α-particle therapy, such as have been suggested and trialed for standard β-emitting PRRT, including the use of chemotherapy or PARP inhibitors, may render it even more effective. These are exciting times in the realm of theranostics, and interest in neuroendocrinology, now subsuming all neuroendocrine cells in the body and the pituitary, builds on the fundamental work of Sy Reichlin.

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The authors acknowledge our outstanding debt to Dr Seymour Reichlin for his inspiration and devotion to research in the field of neuroendocrinology. Dr Reichlin was one of the founders of the "new" science of neuroendocrinology. Born in 1924 to Russian immigrants to New York, he sadly lost his sister to an endocrine-secreting tumor of the pancreas, probably a VIPoma, an important albeit rare type of tumor regarding which our brief review is relevant. He started his medical training at Washington University and the University of Rochester, becoming fascinated by Selye's concept of stress. However, the seminal moment in his career was his attendance at a lecture by Geoffrey Harris, which stimulated him to move to London in 1952 and work with Harris to establish the neural-hypothalamic – control of the pituitary, initially in terms of thyroid function. In subsequent work back in New England, he showed that the hypothalamus contained growth hormone and prolactin-releasing factors, all eventually chemically identified by the Nobel Laureates Roger Guillemin and Andrew Schally. He must therefore be considered as the "father" of neuroendocrinology and one on whose superb foundations we now rely for medical practice.

Author Contributions

A.B.G. conceived the review topic. K.M.S. drafted the initial manuscript, tables, and images. S.N. and A.B.G. reviewed, edited, and supervised the work. No related work is under consideration elsewhere. All authors revised and approved the final version.

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