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REVIEW

Alpha therapies: where and when is the future in neuroendocrine tumours?

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Abstract

Neuroendocrine tumors (NETs) represent a diverse group of neoplasms arising from neuroendocrine cells, treatable with various modalities including targeted radionuclide therapy. Traditional treatments such as surgery, somatostatin analogues, chemotherapy, target therapies and peptide receptor radionuclide therapy (PRRT) with beta-emitting isotopes like ^{177}Lu-DOTATATE have shown good clinical efficacy. However, ^{177}Lu-DOTATATE may be less effective in refractory or progressive cases, necessitating the transition to alpha-emitting therapies. The emergence of alpha therapies, leveraging the potent cytotoxicity of alpha-emitting isotopes, signifies a notable advancement in the therapeutic landscape for NETs. This review aims to provide an overview of the most significant developments and evidence for the use of targeted alpha therapies in neuroendocrine tumors. Alpha particles, with their high linear energy transfer (LET) and short range, offer distinct advantages over beta particles. Their potent cytotoxicity can cause double-strand DNA breaks, leading to higher tumor cell kill rates. Several alpha-emitting isotopes, including Actinium-225, Bismuth-213, and Lead-212, are currently being investigated for their therapeutic potential in NETs. These isotopes deliver lethal radiation doses to tumor cells while minimizing collateral damage to healthy tissues, even more targeted in hepatic disease when intraarterial administration is feasible. Despite challenges related to Ac-225 production, availability, costs, dosimetry, standardization, and sufficient long-term follow-up data, the clinical success in treating resistant and aggressive forms of NETs underscores the need for increased investment and research to optimize production and distribution processes. Developing reliable supply chains and comprehending the potential long-term effects of alpha emitters are essential steps. The time for Targeted Alpha Therapies is undeniably here and now, with continued advancements holding the potential to revolutionize the treatment of neuroendocrine tumors, providing hope and improved outcomes for patients globally.

Keywords TAT · NET · Ac-225 · Pb-212 · Targeted radionuclide therapies · Theranostics

Introduction

Neuroendocrine tumours (NETs) represent a heterogeneous group of neoplasms arising from neuroendocrine cells distributed throughout the body [1]. Traditional treatment modalities, including surgery, somatostatin analogues, chemotherapy, target therapies and peptide receptor radionuclide therapy (PRRT) with beta-emitting isotopes like ^{177}Lu-DOTATATE, have shown efficacy but often fall short in cases of refractory or progressive disease [2]. The promising emergence of alpha therapies, which harness the potent cytotoxicity of alpha-emitting isotopes, marks a significant advancement in the therapeutic landscape for NETs [3–5].

Results from both the NETTER 1 and 2 trials have been pivotal in establishing the efficacy of ^{177}Lu-DOTATATE. Both trials demonstrated that ^{177}Lu-DOTATATE is effective

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in prolonging progression-free survival compared to standard treatments like high-dose octreotide LAR in patients with midgut and GEP-NETs. ^{177}Lu-DOTATATE also showed higher objective response rates, indicating better tumor response. Overall survival data showed a positive trend favouring ^{177}Lu-DOTATATE but did not reach statistical significance at the time of initial analysis. PRRT was generally well-tolerated, with manageable adverse effects.

In summary, these trials have provided sufficient evidence to recommend ^{177}Lu-DOTATATE as an effective alternative treatment option for patients with advanced neuroendocrine tumours, that offers improved outcomes compared to traditional therapies in terms of both progression-free survival and tumor response rates. These trials have also laid the groundwork for exploring alpha-emitting isotopes [6–9].

The transition from beta-emitting ^{177}Lu-based therapies to alpha-emitting ^{225}Ac therapies represents a natural evolution driven by the need for more effective treatment options.

Alpha particles, characterized by their high linear energy transfer (LET) and short range, offer distinct advantages over beta particles. Their potent cytotoxicity can cause double-strand DNA breaks, leading to higher tumour cell kill rates. Moreover, the abscopal effect observed with alpha therapies suggests a potential to induce systemic anti-tumor immune responses, enhancing their therapeutic impact beyond the primary treatment site. These advantages over beta particles have the potential to overcome resistance and to improve patient outcomes [10].

Timelines for FDA approvals and wider clinical application of targeted alpha therapies in NETs are likely to follow the same trends set by the use of ^{177}Lu-PSMA therapies in prostate cancer in how it is paving the way for similar advancements with ^{225}Ac-PSMA, focusing on mechanisms of resistance and overall survival [11].

Several alpha-emitting isotopes are being investigated for their therapeutic potential in NETs, including Actinium-225, Bi-213 and Pb-212. These isotopes are chosen for their ability to deliver lethal doses of radiation to tumor cells while minimizing collateral damage to surrounding healthy tissues. The selection of specific alpha emitters is guided by factors such as half-life, energy emission, and radiochemical stability [12].

Resistance to conventional therapies, including PRRT with ^{177}Lu-DOTATATE, occurs in a significant subset of NET patients, necessitating the exploration of alternative treatment strategies [2]. Alpha therapies are particularly promising in this context, offering a new line of defence against resistant and recurrent NETs. The frequency of resistance highlights the urgent need for novel treatments that can provide durable responses and improve patient outcomes.

Alpha therapies represents a frontier in the treatment of neuroendocrine tumours, with the potential to transform the clinical management of this challenging disease. As ongoing research and clinical trials continue to elucidate the benefits and optimal application of alpha emitters, their future in neuroendocrine tumor therapy looks promising and poised for significant advancements.

The aim of this review is to provide an overview of the most important developments and evidence for the use of targeted alpha therapies in neuroendocrine tumours.

^{213}Bi-DOTATOC

The first-in human study by Kratochwil et al. on ^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy focused on evaluating its effectiveness in patients with neuroendocrine tumours that were resistant to beta radiation therapy (^{90}Y/^{177}Lu-DOTATOC). Eight patients with progressive neuroendocrine liver metastases received ^{213}Bi-DOTATOC treatment. Toxicity levels were monitored using CTCAE criteria, and imaging assessments were performed with MRI and PET/CT scans. The results showed that the therapy led to specific tumor binding and enduring responses, with lower acute hematotoxicity compared to beta therapies and only moderate chronic kidney toxicity. Overall, ^{213}Bi-DOTATOC demonstrated potential in inducing remission in beta-resistant tumours while maintaining manageable toxicity levels [13].

The biodistribution of ^{213}Bi-DOTATOC was assessable with gamma emission scans imaged at 1 h post injection, (using the 440 keV emission) and demonstrated specific tumor binding similar to ^{68}Ga-DOTATOC PET scans. Pharmacokinetically, the time-activity curves in blood resembled those of diagnostic somatostatin analogues, with a significant portion of the radiopharmaceutical following renal excretion. The treatment regimen involved intra-arterial infusion for liver metastases and systemic infusion for bone marrow carcinosis. Therapy was administered in cycles, with increasing activities to evaluate toxicity and efficacy and post-treatment images validated the expected binding at tumor sites [13].

The clinical course of the patients revealed varied profiles of neuroendocrine tumours, mainly with liver metastases. Most patients showed significant responses to ^{213}Bi-DOTATOC, including partial and complete remissions. Responses were sustained for several months to years, although one patient developed myelodysplastic syndrome (MDS) that progressed to acute myeloid leukaemia (AML) [13].

Regarding toxicity, the acute hematologic toxicity was low, and kidney toxicity was moderate. There were no severe endocrine changes except for one case of therapy-associated Graves' disease. Chronic toxicity included a decline in Glomerular filtration rate (GFR) and tubular excretion rate (TER), but there were no cases of severe kidney failure requiring dialysis. Some patients experienced chronic anaemia, which was linked to sub-optimal kidney function rather than bone marrow issues [13].

This study demonstrated that ^{213}Bi-DOTATOC can effectively overcome beta resistance in neuroendocrine tumours with manageable acute and chronic toxicities and suggests the potential for broader application in therapeutic nuclear medicine, provided that production challenges can be addressed.

^{225}Ac-DOTATATE

The use of SSTR antagonists labelled to Ac-225 has now been investigated in the settings of neuroendocrine tumours that have become resistant to treatment with ^{177}Lu-DOTATATE, or those that have exceeded the maximum dose [14, 15]. Studies have also included its use in the treatment of paragangliomas in the head and neck [16], with reports on rare involvement of the thymus [17] and suggestions of targeted alpha therapies that precede those with beta emitters, based on exceptional responses reported in case studies [18].

What follows, is a short summary of some of the pertinent studies that illustrate the afore mentioned.

In a first-in human study pioneered by the Bad Berka group, the feasibility of intra-arterial ^{225}Ac-DOTATOC (at a dose of around 8 MBq) was evaluated in 10 patients with metastatic NETs who had progressed despite treatment with ^{90}Y– and/or ^{177}Lu–DOTATOC. Patients tolerated this form of therapy well and the researchers demonstrated its potential as a possible effective alternative in treating advanced NETs resistant to β-PRRT [19].

Kratochwil et al. [20]. conducted a retrospective cohort study to evaluate the use of ^{225}Ac-DOTATOC as an experimental salvage therapy for patients with aggressive, late-stage, or β-PRRT-resistant neuroendocrine tumours. This study aimed to determine the most effective treatment regimen and maximum cumulative dose while monitoring long-term hematologic and renal toxicity. The study included 39 patients with a mean age of 58 years, all of whom exhibited significant somatostatin receptor expression as determined by ^{68}Ga-DOTATOC PET/CT imaging. Most patients had exhausted other treatment options and had been pre-treated with either β- or α-PRRT [20].

Their findings indicated that hematologic toxicity was dose-dependent, with lower toxicity (Grade 0–2) observed at doses below 44 MBq. Higher doses (45 MBq and above) were associated with increased grade 3 and 4 adverse events. Additionally, repeated administrations resulted in additive toxicity, necessitating dose adjustments and optimal interval settings between cycles to mitigate adverse effects. Renal toxicity was evaluated over a median follow-up of 57 months, revealing chronic kidney disease (CKD) as the most significant late effect. Pre-existing CKD risk factors were present in the majority of patients, and those previously treated with β-PRRT showed lower kidney tolerance. While ^{225}Ac-DOTATOC caused less severe eGFR loss compared to ^{177}Lu-DOTATATE, the varying patient susceptibility due to prior treatments highlighted the complexity of assessing renal toxicities across different PRRT modalities [20].

In a prospective study by Ballal et al. [21], the researchers evaluated the safety and efficacy of ^{225}Ac-DOTATATE in 32 patients with either stable or progressive disease following treatment with ^{177}Lu-DOTATATE for metastatic GEP-NETs. They included fourteen patients who reached the maximum limit of targeted radionuclide therapy with ^{177}Lu-DOTATATE and eighteen patients that were refractory to this form of therapy. The researchers administered a dose of 100 kBq/kg at 8-week intervals up to a cumulative dose of 55 500 kBq (1.5 mCi). Their results demonstrated a morphological response (assessed in 24/32 patients), according to RECIST 1.1, that revealed partial remission in 15 and stable disease in nine in the median follow-up of 8 months, and a significant post-treatment decrease in the plasma chromogranin level. Although no patient achieved complete morphological response of the disease, partial response was demonstrated in 62.5% (15/24) patients, with stable disease in 37.5% of patients and a disease control rate of 100%. The most frequently reported side effects were nausea and loss of appetite and was related to the amino acid infusion. A statistically significant drop in platelet counts were detected post-treatment, but no Grade III/IV, neutropenia, thrombocytopenia, or lymphopenia was noted. Renal parameters did not reveal any significant difference in the s-urea, -creatinine or GFR levels pre- and post ^{225}Ac-DOTATATE therapy. Despite the limitations of the lack of a control group, short follow-up time and relatively small numbers, the authors demonstrated the feasibility of targeted alpha therapy with ^{225}Ac-DOTATATE as an alternative treatment option in patients who become refractory to ^{177}Lu-DOTATATE therapy or those that have reached the maximum prescribed cycles of PRRT [21].

In another insightful study by Ballal et al. [22]., the long-term outcomes of patients with metastatic gastroentero-pancreatic neuroendocrine tumours (GEP-NETs) treated with ^{225}Ac-DOTATATE targeted alpha-therapy (TAT) and capecitabine were examined. The study involved 91 patients, comprising 54 men and 37 women with a mean age of 54.3 years. These patients were all diagnosed with advanced-stage GEP-NETs expressing somatostatin receptors. To better understand the efficacy of this treatment, patients were divided into three groups: those who were refractory to prior ^{177}Lu-DOTATATE therapy, those who had stable disease post PRRT with ^{177}Lu-DOTATATE, and those who were PRRT-naive. In total, 453 treatment cycles were administered, with each patient receiving a median of four cycles, and the median follow-up duration was 24 months [22].

The researchers found that the median overall survival (OS) was not yet reached, which is promising, with a 24-month OS probability standing at 70.8%. Similarly, the median progression-free survival (PFS) was also not reached, with a 24-month PFS probability of 67.5%. However, certain prognostic factors such as the presence of bone metastases and ^{225}Ac-DOTATATE refractory disease were associated with poorer OS outcomes. These findings indicate that while the therapy is broadly effective, particular subgroups of patients may experience less favourable results [22].

The authors reported that 2.5% of patients achieved a complete response, 48% showed a partial response, 29% had stable disease, with disease progression noted in 20.2%. Interestingly, patients who were naive to ^{177}Lu-DOTATATE tended to fare better compared to those who were refractory to the treatment. This highlights the potential benefits of ^{225}Ac-DOTATATE TAT, especially for those who have not been previously treated with ^{177}Lu-DOTATATE [22].

Targeted alpha therapy was generally well-tolerated among patients, with minimal treatment-related toxicities reported. There were no significant renal or liver toxicities observed, which is encouraging for the safety profile of this treatment. Common side effects included fatigue, loss of appetite, nausea, and abdominal pain, but these were mostly transient and manageable. The study underscores the promise of ^{225}Ac-DOTATATE TAT in improving survival and controlling disease progression in GEP-NET patients, even those refractory to previous treatments. The favourable safety profile further suggests its potential as a salvage therapy for advanced GEP-NETs. However, the study also emphasizes the need for further large-scale, randomized trials to confirm these findings and optimize treatment protocols [22].

Demirci and colleagues [23] subsequently shared their initial results obtained from a retrospective study that included eleven patients (10 refractory to ^{177}Lu-DOTATATE) with metastatic NETs from different primary sites (bronchial, pancreatic, non- pancreatic gastroenteropancreatic NETs, paraganglioma, and unknown primary site) that were treated with ^{225}Ac-DOTATATE. Their aim was to evaluate the safety, stability and efficacy of alpha-targeted therapy with ^{225}Ac-DOTATATE in patients with grade 1/2 metastatic neuroendocrine tumours (NETs). Treatment efficacy was assessed based on ^{68}Ga-DOTATATE PET/CT images and the RECIST 1.1 criteria. They calculated both the in vivo and in vitro stability of ^{225}Ac- DOTATATE, and the safety profile was evaluated according to the Common Terminology Criteria for Adverse Events version 5 (CTCAE-v5.0) at three months post-therapy intervals. The researchers found that ^{225}Ac-DOTATATE remained stable for at least 5 h in vitro and 3 h in vivo, based on urine and blood samples. A single patient had Grade 2 renal- and hematotoxicity, with no grade 3–4 toxicities demonstrated. In this study, none of the patients complained of xerostomia, and SUVmax values before and after treatment remained essentially unchanged [23].

Post-treatment imaging with ^{68}Ga-DOTATATE PET/CT demonstrated progressive disease in a single patient, stable disease in four, and a partial response in another four. The disease control rate was reported at 89%, with a median progression-free survival estimated at one year (based on Kaplan-Meier analysis). Based on these preliminary results, these authors also suggested that ^{225}Ac-DOTATATE is safe, stable and effective in treating advanced and ^{177}Lu-DOTATATE-refractory NETs. Obvious limitations include the small patient numbers and retrospective analysis [23]. (See Fig. 1 for a patient example of disease control for a duration of a year following progression with ^{177}Lu-DOTATATE PRRT treated with ^{225}Ac-DOTATATE at Inkosi Albert Luthuli Central Hospital in Durban, South Africa).

A pilot study on the use of ^{225}Ac-DOTATATE in nine patients with metastatic paragangliomas [16] reported on its safety and efficacy with the concomitant radiosensitizer, capecitabine, at 8-weekly intervals up to a cumulative activity of around 74 MBq. Primary endpoints included treatment response evaluation and disease control rate (DCR) using the RECIST 1.1 criteria.

The authors reported remarkable clinical responses together with morphological partial responses noted in 50%, stable disease in 37.5%, disease progression in 12.5% and a DCR of 87.5%. An impressive 25% of patients discontinued their anti-hypertensive treatment, whilst 37.5% could reduce such treatment. Patients also reported significant improvements in the QLQ-H&N35 symptom scores regarding almost every aspect pertaining to quality of life.

No grade III/IV hematological, renal, and hepatological toxicities were noted and ^{225}Ac-DOTATATE therapy was suggested as a safe and effective option in the treatment of advanced-stage PGLs, also in those patients resistant to PRRT with ^{177}Lu-DOTATATE [16].

In an interesting image published in the Clinical Nuclear Medicine journal in 2021[17], Zhang and colleagues report on findings in a 63-year-old woman with a non-functioning neuroendocrine tumor (NET) of the thymus. This patients received 8 cycles of PRRT with ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and ^{177}Lu-DOTATOC over a period of 11 years with a cumulative administered activity of 46.9

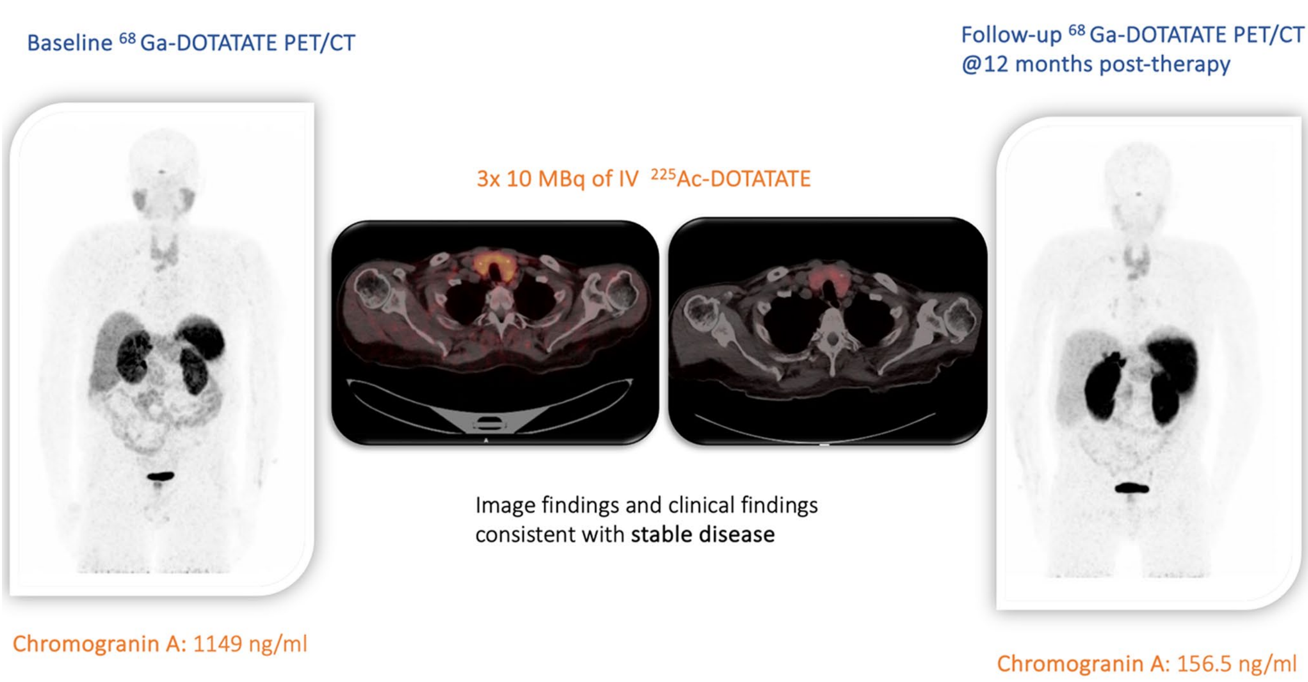

Fig. 1 61-yr old male with low-grade NET of the common bile duct treated with 3 doses of 10 MBq ^{225}Ac-DOTATATE IV which resulted in stable disease for 12 months. (May change the figure)

GBq, before she ultimately became resistant to PRRT. Her ^{68}Ga-DOTATOC PET/CT images demonstrated extensive, SSTR-positive pleural metastases, with massive carcinosis and extensive involvement of the entire thickened pleura on the left side, with new significant lymph node, pleural- and pericardial metastatic involvement. She was treated with 19 MBq of ^{225}Ac-DOTATOC and demonstrated an excellent treatment response both clinically and morphologically [17].

In a more recent interesting image published by the same journal, Satapathy [18] and colleagues share an exceptional response in a 46-year-old man with an inoperable grade 2 NET primary in the rectum and widespread skeletal metastases. He was treated with 6 cycles of 100 kBq/kg of ^{225}Ac-DOTATATE administered at intervals of 8 weeks, to which he responded symptomatically within 3 weeks of the first cycle with marked reduction in back pain and analgesic use after 3 weeks of the first cycle and complete symptom resolution by 6 weeks. There was a significant decline (89.6%) in Chromogranin A level and ^{68}Ga-DOTANOC PET/CECT demonstrated a partial morphological as well as molecular response with no grade 3/4 toxicity observed. This case demonstrated the possibility of the use of ^{225}Ac-DOTATATE as a novel, first-line treatment modality that offers safe and effective therapy for metastatic NETs with high skeletal disease burden [18].

^{212}Pb-DOTAM-TATE

The radionuclide pair of Pb-203 and Pb-212, which are elementally identical, has attracted considerable interest in the development of image-guided targeted alpha-particle therapy for cancer [24]. Recent studies indicate that ^{212}Pb-labeled peptide-based radiopharmaceuticals targeting somatostatin receptor subtype 2 (SSTR2) might offer enhanced efficacy compared to beta-particle-based therapies for treating neuroendocrine tumours (NETs). Pb-212 based radiopharmaceuticals offer a promising alternative to Ac-225 as an in vivo generator of alpha particles, and its relatively short half-life of 10.6 h is well suited to smaller peptides [25, 26].

In vivo evaluations demonstrate that ^{212}Pb-DOTAM-TATE and the newly developed radioligands demonstrate promising biodistribution and tumor uptake, with variations in the effectiveness and uptake across different tissues and organs. The inclusion of specific linkers and chelators plays a crucial role in the performance of these radioligands, impacting their stability, tumor targeting, and overall therapeutic potential. Targeted alpha therapy using Pb-212 labelled SSTR2 radioligands could be a promising alternative to current beta-particle-based therapies, offering enhanced effectiveness for treating neuroendocrine tumours [27].

A dose-escalation study by Delpassand et al. [28] included 20 PRRT-naïve patients to identify the maximum tolerated dose and to evaluate the initial therapeutic effects. This phase 1 clinical trial demonstrated that ^{212}Pb-DOTAMTATE was well-tolerated, with manageable side effects such as nausea, fatigue, and alopecia, and no severe adverse events were directly linked to the treatment. An objective radiologic response was observed in 80% of the subjects treated at the recommended phase 2 dose of 2.50 MBq/kg per cycle, showing promising preliminary efficacy. The study suggests that ^{212}Pb-DOTAMTATE could potentially offer significant advantages over existing PRRT options, such as ^{177}Lu-DOTATATE, particularly due to the higher cytotoxic potential of α-particles and their shorter path length, which may result in more effective tumor cell damage and fewer side effects. Further research and larger trials are needed to confirm these findings and establish ^{212}Pb-DOTAMTATE as a viable treatment for metastatic or inoperable SSTR-expressing NETs [28].

Following the afore-mentioned dose-finding study, Jonathan Strossberg [29] and his group conducted a phase 2 study (ALPHAMEDIX 02) to evaluate the safety and efficacy of TAT with ^{212}Pb-DOTAMTATE in patients with metastatic or unresectable GEP-NETs. Study participants were divided into two cohorts: PRRT-naive and PRRT-refractory subjects with SSTR positive GEP-NETs. The primary endpoints included overall response rate (ORR) and incidence of adverse events (AEs). Initial results from cohort 1 show an ORR of 47.2%, with promising duration of response (DOR) outcomes. Safety data indicate manageable toxicities comparable to ^{177}Lu-DOTATATE [29].

Singh and colleagues [30] shared their first-in-human post-therapy image-guided dosimetry estimates following administration of a single cycle of ^{212}Pb VMT-α-peptide to a 41-year-old symptomatic woman with an advanced grade 2 NET. PET/CT imaging demonstrated ^{68}Ga-DOTANOC–avid disease and the patient was subsequently treated with 130 MBq of ^{212}Pb- labelled VMT-α-NET. The therapy was well tolerated with no adverse effects reported. Whole-body planar and SPECT/CT image of ^{212}Pb VMT-α-NET were acquired at 18 h posttherapy, which was congruent to the findings on ^{68}Ga-DOTANOC PET/CT. A follow-PET 2 months post-treatment demonstrated a partial treatment response together with clinical improvement. The authors reported that SPECT/CT imaging with ^{212}Pb VMT-α-NET demonstrates immediate tumor accumulation, high tumor retention, and rapid renal excretion, and that their findings indicate its potential effectiveness [30].

In a study consisting of 11 participants, Delpassand and colleagues [31] evaluated the safety and efficacy of ^{212}Pb-DOTAMTATE in subjects with recurrent NETs who already underwent PRRT with ^{177}Lu/Y-90. Patients received up to four 2-monthly cycles of ^{212}Pb-DOTAMTATE at 67.6 µCi/kg/ cycle. Response to treatment was measured per RECIST 1.1 criteria and by ^{68}Ga/^{64}Cu-DOTATATE PET/CT, the latter demonstrating any treatment response in 70% of study participants. Although a substantial number of adverse effects were reported (145), 42% was considered unrelated or unlikely to be related to treatment, and only 3% was of Grade3/4 severity. The most frequently reported side effects were alopecia, nausea, fatigue and anaemia. This was the first clinical trial to evaluate the use of ^{212}Pb-targeted alpha-emitter therapy in subjects with NETs who progressed following prior PRRT. The authors concluded that "^{212}Pb-DOTAMTATE in the recurrent setting is highly effective with manageable toxicity and warrants further investigation." [31].

Although the evidence presented here is still very preliminary, it appears that targeted therapy with ^{212}Pb-DOTAMTATE is feasible, safe and potentially effective in patients with metastatic, unresectable and recurrent NETs.

Other possibilities

Various other exciting and interesting future possibilities exist, which includes the use of Astatine-211[32], the theranostic pairs of Copper-64/67[33] and Terbium-155/161[34] (although therapy here is based on auger emitters and therefore does not strictly fit the scope of this review). The SSTR antagonists are also receiving significant attention and LM3, labelled with ^{161}Tb, is currently being studied in combination with ^{177}Lu-DOTATOC. Compelling evidence is mounting on the use of Terbium radiometals regarding radiolabelling, stability, and QC aspects, with promising pre-clinical results and early clinical results emerging in the Tb-161-PSMA space [35].

A newly developed SSTR agonist PET agent, ^{64}Cu-SAR-TATE (^{64}Cu-MeCOSar-Tyr3-octreotate), has been pre-clinically evaluated. It utilizes an amine cage ligand known as sarcophagine (SAR), which offers more stable binding with copper than DOTA complexes and potentially prolongs radiotracer retention in tissues. ^{64}Cu-SAR-TATE's role in patient selection and dosimetry prediction has been explored, and it shows promise when paired with the theranostic agent Cu-67 PRRT. The diagnostic/theranostic pairing of Cu-64 and Cu-67 is currently under investigation. Potential benefits include ^{64}Cu-DOTATATE's high affinity for somatostatin receptors, that enables effective imaging of neuroendocrine tumours. It offers a longer half-life compared to other isotopes, allowing for delayed imaging and improved tumor localization. Drawbacks include the limited availability and higher cost of Cu-64 compared to other PET tracers and the potential for higher radiation dose to patients due to the longer half-life [36].

In a prospective clinical trial in Australia [37], 10 neuroendocrine tumor patients with SSTR-positive imaging on Ga-68 DOTA-TATE PET/CT underwent serial ^{64}Cu-SAR-TATE PET/CT imaging at 30 min, 1 h, 4 h, and 24 h post-injection. The images were analysed and compared, revealing significant radiotracer uptake in lesions at all time points. There was progressive hepatic clearance and tracer accumulation in disease sites, resulting in substantially higher lesion-to-liver contrast at 24-hour images. Similar lesion detection rates were observed with both tracers in all patients, but the newer agent showed a higher detection rate in hepatic lesions due to the progressive lesion-to-liver contrast. This improved ratio may enhance sensitivity for detecting hepatic disease. ^{64}Cu-SAR-TATE PET/CT has also demonstrated good diagnostic performance in neuroblastoma patients and can serve as the diagnostic component of therapy alongside Cu-67 SARTATE [37].

Recent/ ongoing clinical trials

In a recent review of current trials on TAT, Albert Jang and colleagues explore the three most prevalently studied conjugated/chelated alpha emitters: Actinium-225, Lead-212, and Astatine-211. Their review focused on contemporary clinical trials to appreciate the full scope of ongoing research [38]. Amongst the various pathologies that are currently under investigation for possible treatment with targeted alpha therapies, at least one phase III trial on neuroendocrine cancers has begun recruiting participants. Combination trials are also emerging as alpha emitters are integrated with other therapies to find solutions for advanced cancers.

Radiomedix, Inc. and Orano Med LLC are collaborating to evaluate ^{212}Pb-DOTAMTATE (AlphaMedixTM) in patients with unresectable, metastatic neuroendocrine tumours (NETs) that express somatostatin receptor type 2 (SSTR2). The phase I trial (NCT03466216) enrolled 33 patients with SSTR2-positive NETs naïve to peptide–receptor radionuclide therapy (PRRT). According to the treatment regimen that was determined by Delpassand and colleagues [28], patients received increasing doses with a recommended phase II dose (RP2D) consisting of four cycles of 2.50 MBq/kg per cycle (67.6 µCi/kg per cycle) of ^{212}Pb-DOTAMTATE. This regimen was well tolerated by 10 patients, eight of whom showed an objective radiographic response, including one complete response. There were no serious treatment-related adverse events. The phase II trial (NCT05153772) is currently evaluating this dose in 34 patients, with primary outcomes focused on the objective response rate as measured by RECIST 1.1 and adverse events. The estimated completion date for this study was December 2023 [38].

RayzeBio, Inc. is investigating RYZ101, which delivers Ac-225 to NETs expressing SSTR2. The phase Ib/III clinical trial ACTION-1 (NCT05477576) is enrolling 218 patients with SSTR-positive gastroenteropancreatic (GEP) NETs that have progressed following PRRT with ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC. In the phase Ib portion, the recommended phase III dose will be determined as patients receive up to four infusions of RYZ101 every eight weeks. In the phase III portion, RYZ101 will be compared with the standard of care (either everolimus, sunitinib, or a somatostatin analogue such as octreotide 60 mg monthly or lanreotide 120 mg every other week), with progression-free survival (PFS) based on RECIST 1.1 as the primary endpoint. The phase Ib results, presented at the 2023 ASCO Annual Meeting, showed that RYZ101 was well tolerated at 120 kBq/kg (3.2 µCi/kg), which was established as the recommended phase III dose. The phase III part of the trial began in May 2023 and RYZ101 is also being evaluated in combination with carboplatin, etoposide, and atezolizumab in a phase Ib trial (NCT05595460) This trial consists of 31 patients with extensive-stage small-cell lung cancer expressing SSTR and focuses on safety and tolerability. The estimated primary completion date of this trial was estimated for April 2024 [38].

Perspective Therapeutics investigated the use of VMT-α-NET, as a new SSTR2 targeting agent. In a phase I study (NCT05111509), the imaging agent ^{203}Pb-VMT-α-NET was used for somatostatin receptor imaging in 20 patients with NETs and with estimated primary completion date of June 2023. Additionally, a phase I/IIa TAT trial (NCT05636618) with ^{212}Pb-VMT-α-NET in patients with SSTR2-positive tumours was expected to commence. This trial will begin with a dose-escalation phase to determine the recommended phase II dose (RP2D), followed by a phase IIa dose-expansion cohort to evaluate efficacy using the established RP2D [38].

Fukushima Medical University in Japan is conducting research on ^{211}At-meta-astatobenzylguanidine (MABG) for patients with malignant pheochromocytoma or paraganglioma. Preclinical studies have shown that ^{211}At-MIBG has significant anti-tumor effects in a pheochromocytoma mouse model. MABG targets adrenergic tissue via the norepinephrine transporter. The ongoing dose-escalation trial aims to determine the safety, maximum tolerated dose (MTD), and recommended phase II dose (RP2D) for this promising treatment [32].

Conclusion

Targeted Alpha Therapies (TAT) have shown significant promise in treating neuroendocrine tumors (NETs), particularly with the use of ^{225}Ac-DOTATATE and emerging evidence supporting ^{212}Pb-DOTAMTATE. The introduction of ^{212}Pb-DOTAMTATE expands the arsenal of TATs, offering new pathways for targeted therapy. As research progresses, these therapies are expected to provide more effective and personalized treatment options for NET patients.

^{225}Ac-DOTATATE has demonstrated good efficacy in treating resistant NETs, paragangliomas, and other rare types of neuroendocrine tumors, establishing its role in challenging clinical scenarios. TAT has shown relative success in managing metastatic head and neck paraganglioma, metastatic thymus NET, hypoxic tumors, and cases resistant to beta emitters.

Despite the promising initial results with targeted alpha therapies, several challenges remain. The widespread adoption of ^{225}Ac-DOTATATE is hindered by production, availability, and costs. Additional hurdles include dosimetry assessments, standardization, and obtaining sufficient long-term follow-up data. There is a need for better understanding of the relationship between the administered dose and the dose absorbed by the tumor, as well as the interplay between alpha particles and the immune system (abscopal effect). Progress in these areas is essential to realize the full clinical potential of targeted alpha therapies.

The clinical success in treating resistant and aggressive forms of NETs highlights the need for increased investment and research to optimize production and distribution processes. This includes developing reliable supply chains, gaining a better understanding of the relationship between administered and absorbed doses in both tissues and tumors to predict outcomes, and fully comprehending the potential long-term adverse effects of alpha emitters.

The time for Targeted Alpha Therapies is undeniably here and now. Continued advancements in this field have the potential to revolutionize the therapeutic landscape for neuroendocrine tumors, providing hope and improved outcomes for patients worldwide.

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Declarations

Competing interests The authors declare no competing interests.

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