Targeted alpha-particle therapy in neuroendocrine neoplasms: A systematic review

ABSTRACT

Neuroendocrine neoplasms (NENs) are a very diverse group of tumors with a worldwide rise in incidence. Systemic therapy remains the mainstay treatment for unresectable and/or metastatic NENs. $^{177}$Lu-DOTATATE, a radiopharmaceutical which emits beta particles, has emerged as a promising therapy for metastatic gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). However, limited treatment options are available particularly after the failure of $^{177}$Lu-DOTATATE therapy. This review aims to identify and summarize the available evidence for, and potential adverse events of, targeted alpha-particle therapy (TAT) in the treatment of metastatic NENs, specifically GEP-NENs. The MEDLINE, EMBASE, SCOPUS, and Cochrane Library databases were searched. Two articles which met the inclusion criteria were identified and included in the review. Putative radiopharmaceuticals that can be considered for metastatic NEN treatment include $^{225}$Ac-DOTATATE and $^{213}$Bi-DOTATOC. There was evidence of partial response using both radiopharmaceutical agents without significant hematological, renal, or hepatotoxicity. Future studies should consider longer term, randomized controlled trials investigating the role of TAT, in particular, $^{225}$Ac-DOTATATE, in the treatment of metastatic NENs.

Keywords: $^{213}$Bismuth, $^{225}$Actinium, endocrine, neuroendocrine neoplasms, oncology, radionuclide therapy, radionuclide therapy, targeted alpha therapy

INTRODUCTION

Neuroendocrine neoplasms (NENs) are an uncommon heterogeneous group of neoplasms originating from endocrine cells that secrete biogenic amines and polypeptide hormones. Data from Europe and the USA from 1994 to 2003 demonstrate a rise in incidence, in part due to improved awareness and detection, and is approximately 2/100,000 per year.\textsuperscript{[1]} A retrospective, population-based study using nationally representative data from the Surveillance, Epidemiology, and End Results program in the USA from 1973 to 2012 revealed that the age-adjusted annual incidence of neuroendocrine tumors (NETs) increased from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012, a 6.4-fold increase.\textsuperscript{[2]} Within Australia, based on the data from the Australian Institute of Health and Welfare, there were 10,108 patients diagnosed with NEN in the 5-year period of 2012–2016. In 2016, the age-standardized incidence rate was 15 cases per 100,000 persons, which has shown an increase from 1982, wherein the age-standardized incidence rate was 8.9 cases per 100,000 persons.\textsuperscript{[3]}

The clinical behavior of NENs is variable; they may be hormonally active or endocrinologically nonfunctioning and range from low-grade, slow-growing tumors to highly malignant and aggressive tumors. The current WHO/ENETs Pathologic Classification divides NENs into well-differentiated...
neuroendocrine tumors (WDNETs) G1 (Ki-67 <3%), G2 (Ki-67 3%–20%), and G3 (Ki-67 >20%), which is in turn divided into WDNET (G3 WDNET) and poorly-differentiated neuroendocrine carcinoma (G3 PDNEC). Ki-67 is a nuclear protein which is associated with cellular proliferation.[4,5]

The most frequent primary sites are the gastrointestinal (GI) tract, including the pancreas (62%–67%) and the lung (22%–27%).[6] NENs of the gastroenteropancreatic (GEP) origin (GEP-NENs) characteristically present at the age of 50–60 years and are challenging to diagnose. GEP-NENs are subdivided into two categories: NENs of the luminal GI tract and pancreatic NENs. Up to 90% of NENs of the GEP origin Express somatostatin receptors (SSRs) on its cell membrane. This forms the basis of first-line therapy with somatostatin analog (SSA) therapy such as octreotide or lanreotide, with the CLARINET and PROMID studies, respectively, demonstrating significantly improved progression-free survival (PFS) and longer time to tumor progression with SSA compared to placebo.[7,8] On further tumor progression, despite SSA therapy and ensuring eligibility criteria are met, patients are considered for SSA-based radionuclide therapy, also known as peptide receptor radionuclide therapy (PRRT).[9]

PRRT is an accepted option of therapy for patients with advanced, progressive NENs. PRRT is a form of systemic radiotherapy that delivers the radionuclides directly into tumor cells, with subsequent DNA damage and cell death through the emission of particulate radiation. The first PRRT was carried out in Rotterdam with 111In-DTPA-octreotide (OctreoScan®) in 2002 which demonstrated only modest disease response, wherein several patients had significant clinical improvement in classic carcinoid symptoms.[10] The development of radionuclides led to the next generation of beta-emitting radionuclides, specifically 90Y (with maximum energy of beta particles of 2.28 MeV) conjugated to DOTA peptides (DOTATATE and DOTATOC), which showed further promising results.[11] However, transient hematologic toxicities and severe permanent nephrotoxicity were experienced in a small cohort of this patient group, in turn limiting its use.[12] In recent years, the use of 177Lu has largely replaced 90Y as the radionuclide of choice in part due to the reduction of complications such as nephrotoxicity, as a result of lower maximum energies of emitted beta particles (<0.5 MeV).[13]

177Lu-DOTATATE has emerged as the preferred agent as supported by the NETTER-1 trial. The NETTER-1 trial (NCT01578239) is a randomized, multicenter, open-label, active-controlled trial in 229 patients with progressive, well-differentiated, locally advanced/inoperable, or metastatic SSR-positive mid-gut NENs. Treatment with 177Lu-DOTATATE compared with high-dose octreotide LAR resulted in an increase in PFS (65.2% at month 20 in the 177Lu-DOTATATE group vs. 10.8% in the control group) and a significantly higher response rate (18% in the 177Lu-DOTATATE group vs. 3% in the control group (P < 0.001) among patients with advanced mid-gut NETs at the data cutoff date for the primary analysis (approximately 34 months from the date of commencement of the trial).[14] 177Lu-DOTATATE has since been approved by the FDA in January 2018 for use in GEP-NEN.[15]

Targeted alpha-particle therapy (TAT) has emerged as an alternative treatment option to beta emitters in PRRT. The use of alpha emitters for cancer therapy has two advantages over beta emitter PRRT. The short range of alpha particles of only a few cell diameters (<0.1 mm) allows for selective ablation of the target cancer cells, while sparing the surrounding healthy tissue. In addition, the higher linear energy transfer (LET), when compared to conventional beta emitters, results in the formation of complex DNA double-strand and DNA cluster breaks, which ultimately lead to cell death.[16]

Despite this, the evidence of TAT in the treatment of GEP-NET is sparse. The aim of this systematic review is to evaluate the current evidence for TAT in the treatment of GEP-NET/NENs and to identify current and potential alpha emitters that can be used in future TAT trials.

MATERIALS AND METHODS

Search strategy
We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. A literature search of MEDLINE, EMBASE, SCOPUS, and Cochrane Library database from 1985 to September 2020 resulted in 2073 potentially relevant articles using the following search string: (“peptide receptor radionuclide therapy” OR “radiosotope therapy” OR “radionuclide therapy” OR “radiolabeled therapy” OR “alpha-emitter” OR “212Pb” OR “213Bi OR “PRRT” “targeted alpha particle therapy” or “targeted alpha therapy” or “225Ac” or “225-Ac”) AND (neuroendocrine OR carcinoma OR paraganglioma OR pheochromocytoma OR neuroblastoma OR somatostatin).

In addition, corresponding search terms were used to search free text, and manual reference checks (i.e., pearlring) of included articles of previously published reviews were performed to compliment the electronic searches.

Inclusion and exclusion criteria
All peer-reviewed original articles were examined for the use of TAT in the treatment of GEP-NENs. Only articles in the
English language were included. Articles were included if they had reported all of the following: (i) NET or GEP-NET, (ii) the use of TAT, and (iii) an outcome.

Studies were excluded in non-NET or non-NET patients, studies involving $^{177}$Lu, $^{99m}$Tc, $^{18}$F, Y-90, and $^{68}$Ga, those without reported outcomes, animal/in vitro studies, case reviews, and comments/letters to the editor.

Selection of articles
A flowchart of the selection of eligible articles is shown in Figure 1. Two authors (T.K. and G.C.) independently reviewed all titles and abstracts for inclusion. Disagreement was resolved by discussion and reference to the full text of the paper. If consensus could not be reached, a third author (E.B.) made a final decision.

Data extraction
All methods for exclusion criteria, data extraction, and quality assessment were specified in advance. However, due to the evaluated number of participants and variation in reporting and data collection of overall survival (OS), freedom from local progression (FFLP), progression free survival (PFS) and median survival time (MST), a systematic analysis was not possible due to the lack of consistency. Data were, however, extracted and tabulated to provide a clear integrative overview of the results to date for TAT for NENs. Data extracted included pretreatment with either chemotherapy or PRRT and outcome measures such as RECIST 1.1 staging and chromogranin A levels. The review protocol was not registered with any organization.

RESULTS
Search results
Of the 2334 articles identified, 258 were duplicates. One article, an ongoing trial on the use of TAT in GEP-NET, was included following review of current literature. Of the remaining 2076 articles, a further 2065 were excluded based on the inclusion/exclusion criteria, leaving 11 articles; of

Figure 1: Summary of citations included in review
which 2 studies were original articles describing the use of targeted alpha therapy in neuroendocrine tumours more specifically GEP-NENs. One case report and one ongoing phase 1 prospective trial which did not meet our inclusion criteria are discussed separately in the “Discussion” section.

**Study characteristics**

Only two articles were included in the study. These studies were published in 2014 and 2019, were prospective, and retrospective in design. No randomized controlled trials were identified. The study lengths varied from 2 to 34 months. The median/mean age of the patients in the prospective study was 52 years (range 43–61); The age of the patients in the retrospective study was not clearly described; however, the study cohort is assumed to be in an adult population based on the epidemiology of this disease. All patients had metastatic NET of which more than 70% are related to GEP-NET. All patients had also received standard first/second-line systemic therapy (including SSA and chemotherapy) as well as treatment with PRRT using $^{177}$Lu-DOTATATE. These patients were either stable or refractory to the standard therapy. The studies used two different types of TAT, namely $^{213}$Bismuth ($^{213}$Bi)-DOTATOC and $^{225}$Ac-DOATATE-DOTATATE. The administration of therapy varied between the studies with $^{213}$Bi-DOTATOC infused intra-arterially through the common hepatic artery (1 patient of the study had $^{213}$Bi-DOTATOC infused intravenously), while $^{225}$Ac-DOTATATE was administered intravenously. The baseline treatment characteristics of the individual articles are described in Table 1.

**Efficacy and safety of $^{225}$Actinium-DOTATATE**

The therapeutic outcome of the study was objective tumor response by RECIST 1.1 criteria and biochemical response [Table 2]. Treatment-related adverse events during $^{225}$Ac-DOTATATE therapy were assessed according to the CTCAE V5 criteria and reported in two categories: Adverse events-related laboratory parameters and other clinical adverse events. The median follow-up duration was 8 months (2–13 months) from the start of $^{225}$Ac-DOTATATE therapy.

Thirty-two patients were recruited for the study; however, only 24 patients underwent interim analysis which was conducted 8 weeks after the second cycle of $^{225}$Ac-DOTATATE therapy. The remaining 8 patients were awaiting rescanning. 62.5% (15/24) of patients revealed partial response and the remaining 37.5% of patients showed stabilization of disease (minimal response 6/24, stable disease [SD] 3/24) based on the RECIST 1.1 criteria. Biochemical response showed a significant decrease in CgA levels post-$^{225}$Ac-DOTATATE.

Median CgA level of 326.4 ng/mL (interquartile range [IQR] 125–1055 ng/mL) was measured before therapy. At the end of the follow-up, it was 126 ng/mL (IQR 51.6–574.4) ($p < 0.0001$).

With regard to adverse effects-related laboratory parameters, no significant difference in hemoglobin levels was seen ($p = 0.5138$) although a statistically significant decrease in the platelet counts was noted ($p = 0.0380$). No significant biochemical complications such as grade III/IV hematological, renal, or hepatotoxicity were documented. The most common clinical adverse events reported was abdominal distension (100%), followed by vomiting 29/32 (90.6%), headache 25/32 (78%), and diarrhea 24/32 (75%) The most severe clinical adverse effect was grade III/IV gastritis 7/32 (22%), and the incidence of peptic ulcer disease however was not reported.

**Efficacy and safety of $^{213}$Bismuth-DOTATOC**

In this retrospective case series, eight patients were studied and followed up. The therapeutic outcome of the study was tumor response by RECIST 1.1 criteria. A specific time point for the analysis of the treatment outcome (i.e., following x number of cycles after treatment) was not described. Biochemical response was not assessed. Treatment-related adverse events during $^{213}$Bi-DOTATOC were described. The median follow-up duration was 22.5 months (6–34 months) from the start of $^{213}$Bi-DOTATOC therapy.

25% (2/8) of the patients showed partial response, 37.5% (3/8) patients showed SD, while 12.5% (1/8) showed complete response. 25% (2/8) of the patients did not have a RECIST 1.1 score provided. With regard to adverse effects, 37.5% (3/8) patients developed chronic anemia while 12.5% (1/8) developed myelodysplastic syndrome/acute myeloid leukemia (AML). 12.5% (1/8) developed Graves’ disease as thyroid cells can also express somatostatin receptors, and as such, this is considered a treatment-related adverse event. 12.5% (1/8) had an elevated creatinine value between 1 and 1.5 times the upper limit of normal 2 years after therapy. No clinically significant nephrotoxicity was described in the rest of the cohort [Table 2].

**DISCUSSION**

NENs are very heterogeneous tumors which are challenging to manage given varying behavior as well as the propensity of some NENs to produce hormones. While some patients have indolent disease, many progress despite systemic treatment and patients may die from progressive disease. There are limited treatment options, particularly after the failure of $^{177}$Lu-DOTATATE (PRRT) therapy. Therefore, there is an urgent need for further-line, well-tolerated therapies for metastatic NEN.
Alpha emitters have two distinct advantages over conventional beta emitter therapy. First, the short range of alpha radiation in the human tissue (of only a few cells or 40–100 μm) allows for more selective killing of targeted cancer cells while preserving surrounding healthy tissue. Second, the high LET of alpha radiation results in dense ionization along the particle track as compared to sparsely ionizing beta particles. This allows for more effective cell killing via increased production of DNA double-strand and DNA cluster breaks.\(^{20}\) As such, TAT therapy can target cells which are otherwise resistant to treatment with conventional beta and gamma particles or chemotherapeutic drugs.

Alpha particle therapy in the treatment of various cancers such as prostate, NENs, breast, colon, myeloma, and ovarian cancer has been investigated.\(^{20,21}\) However, the safety and efficacy of TAT in the treatment of NENs have not been clearly established in clinical studies. This is due to the lack of a well-designed prospective randomized controlled trial and lack of well-designed safety profile trials. This is the first systematic review performed to date to understand and identify the clinical evidence of targeted alpha therapy in the treatment of NENs. Our systematic review has identified two clinical studies, both of which are retrospective and prospective case series, which meet our inclusion criteria for review. Unfortunately, due to the limited number of studies identified and the significant heterogeneity of the intervention and outcome measurement, a meta-analysis cannot be performed. Through this systematic review, we also identified one case report and one ongoing phase 1 prospective trial which did not meet our inclusion criteria but are worth discussing in this section.

**Putative targeted alpha particle therapy agents in the treatment of neuroendocrine tumors and its outcomes**

\(^{225}\)Ac-DOTATATE, \(^{211}\)Bi-DOTATOC, and \(^{212}\)Pb-octreotate have been investigated for the treatment of NETs.\(^{19,22-26}\) These agents have been predominantly used in patients who have had conventional therapy and are found to be refractory or stable on these treatments. Based on our current review, intravenous/systemic use of \(^{225}\)Ac-DOTATATE shows the most promise as a putative TAT agent. The study by Ballal et al. is a well-designed prospective case series with a well-defined patient cohort, a systematic treatment algorithm, and a standardized measurement of outcome, with regard to the timing of the radiological acquisition and assessment of biochemical response with CgA. The study showed that 67.5% of its patients achieved partial remission following two cycles of \(^{225}\)Ac-DOTATATE of 100 kBq/kg without any patients experiencing progressive disease. Clinically significant adverse effects such as myelodysplasia, nephrotoxicity, and hepatotoxicity were not documented during the initial/early follow-up period. A similar response to \(^{225}\)Ac-DOTATATE
Ga DOTATATE PET/CT revealed almost a complete response

Further long-term studies are required to further assess the therapeutic efficacy and safety profile of $^{212}$Pb-octreotate.

Adverse events related to targeted alpha particle therapy
Severe clinical adverse events such as hepatotoxicity, nephrotoxicity, and myelodysplasia have not been found to be the dominant adverse events experienced by patients who underwent TAT according to the reviewed studies. Kratochwil et al. reported a single case of myelodysplastic syndrome which progressed to AML 24 months following the last treatment of intra-arterial $^{213}$Bi-DOTATOC (a total of 5 cycles which is equivalent to 16.0 GBq); however, the occurrence of myelodysplasia may have been confounded by prior intra-arterial PRRT with beta emitters ($^{90}$Y and $^{177}$Lu). Other reported adverse events across the studies include loss of appetite, nausea, vomiting, gastritis, and chronic anemia.

CONCLUSION
Currently, there is limited published data on the safety and efficacy of TAT in the treatment of NENs. However, TAT remains a promising treatment option for metastatic and treatment-resistant NEN. $^{225}$Ac-DOTATATE has been shown to be effective in the treatment of metastatic NEN with minimal clinically significant adverse events. Further long-term randomized controlled trials are needed to assess the treatment outcome, adverse events, and placement of TAT in the overall treatment algorithm for NENs.

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Conflicts of interest
There are no conflicts of interest.

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