Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Editorial

Can the peptide receptor radionuclide therapy [^{177}Lu]Lu-DOTA-TATE provide a net benefit for NET patients?

Keywords:
Cost
Cost-effectiveness
Neuroendocrine tumours
[^{177}Lu]Lu-DOTA-TATE
Quality of life
PFS
OS
PRRT
GEP-NETs

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms, with origins in the diffuse neuroendocrine system [1]. The gastro-entero-pancreatic (GEP) system is a key primary site of these tumours, and GEP-NETs represent the second most prevalent type of digestive cancer [2]. In 2017, Dasari et al. reported data from the Surveillance, Epidemiology, and End Results program in the US, showing an increasing annual age-adjusted incidence rate from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012 [3]. Improvements in methods of detection and diagnosis are thought to play a role in this trend, however, there appears to be a genuine increase, although the reasons remain unclear. Prognosis and symptomology of GEP-NETs reflect the heterogeneous nature of the neoplasms [4,5]. For example, small intestine GEP-NETs generally have malignant potential but tend to progress indolently. Pancreatic NETs also have high malignant potential when >2 cm in size and following metastasis progress more rapidly than intestinal NETs. Gastric NETs such as type I gastric carcinoid are associated with atrophic gastritis and hypergastrinaemia but rarely metastasise and, if they do, are more indolent than type 3 gastric carcinoids, which are sporadic, not associated with atrophic gastritis or hypergastrinaemia and have a more aggressive metastatic course. Oesophageal NENs are rare, but when diagnosed are usually of high grade and have high malignancy potential. Rectal NETs <1 cm rarely metastasise, whereas those >2 cm carry a much greater risk of metastasis. As well as tumour size, ethnicity plays an important role with rectal NETs more common in Afro-Caribbean and Asian ethnic groups [6]. Most GEP-NETs are not associated with a hormonal syndrome and are thus considered 'non-functional', however, 10–20% of intestinal NETs are associated with carcinoid syndrome, especially diarrhoea and flushing. Pancreatic GEP-NETs are typically hormonally silent i.e. 'non-functional', but a minority can produce symptomatic hormones, such as insulin, gastrin, glucagon or vasoactive intestinal polypeptide, which can lead to debilitating clinical 'functional' symptoms, e.g. insulinoma syndrome with hypoglycaemia causing sweating and loss of consciousness; gastrinoma Zollinger Ellison syndrome with recurrent peptic ulceration and diarrhoea; glucagonoma syndrome with rash, prothrombotic tendency and diabetes mellitus; VIPoma syndrome with profuse watery diarrhoea) [7].

Treatment of GEP-NETs is challenging due to their prominent heterogeneity [5]. In recent years, however, a number of new systemic treatments for tumour and symptom control have become available that have been shown to delay progression and reduce symptoms related to hormone secretion [5]. Wherever possible, surgical resection is preferred as it

represents the only curative treatment option currently available in early diagnosed diseases [4,5,8,9]. However, owing to the often advanced, metastatic nature of GEP-NETs at the time of diagnosis, systemic therapies have a very important role to play. Treatment guidelines recommend somatostatin analogues such as long-acting formulations of octreotide and lanreotide targeting the somatostatin receptors, which are commonly overexpressed in NETs. Somatostatin analogues are the first-line therapy options in functioning tumours for hormonal syndrome control and anti-tumour control in both non-functioning and functioning, progressive grade 1–2 NETs [7,8,10–13]. Subsequent therapy may include the multi-targeted receptor tyrosine kinase inhibitor sunitinib particularly for pancreatic NETs, and mammalian target of rapamycin inhibitor everolimus for G1 and G2 GEP-NETs, as well as bronchial NETs [14–16]. Chemotherapy is reserved for high-grade neuroendocrine cancer (NEC) and progressive or large volume well-differentiated NETs with particular efficacy in pancreatic NETs provided by streptozocin or temozolomide regimens [17]. There is a smaller amount of data to support consideration of interferon-alpha and the monoclonal antibody bevacizumab. In addition, peptide receptor radionuclide therapy (PRRT), represents a novel therapy indicated for second-line use in somatostatin positive midgut and pancreatic NETs that offers targeted delivery of radionuclides to the tumour, such as ^{177}Lutetium ([^{177}Lu]Lu-DOTA-TATE, Lutathera®) and ^{90}Yttrium equivalents. Treatment guidelines provide recommendations regarding the use of the treatment options in the subsequent lines of treatment [18–20].

Lutathera® was associated with significantly improved progression-free survival (PFS) and immature overall survival (OS) was prolonged versus octreotide LAR, as well as positive response rates and significant health-related quality of life (HRQoL) benefits. Survival benefits were corroborated by large real-world PRRT studies [21,22]. In the CLARINET study, involving predominantly stable patients, lanreotide was shown to significantly improve PFS but not OS and HRQoL versus placebo and, similarly, everolimus and sunitinib, improved PFS with no HRQoL deterioration versus placebo [13,23,24]. Chemotherapy regimens were most efficacious for high-grade NETs but associated with higher adverse event rates. However, there is a paucity of head-to-headtrial data in the published literature making direct conclu-sions about relative efficacy and safety profiles challenging.

Key data on the efficacy and safety of [^{177}Lu]Lu-DOTA-TATE in the review came from the NETTER-1, open-label, phase 3, randomised, controlled trial [^{177}Lu]Lu-DOTA-TATE versus octreotide LAR 60 mg in 230 patients with progressive, somatostatin receptor-positive midgut NETs previously treated with octreotide. PFS after 20 months was significantly improved with [^{177}Lu]Lu-DOTA-TATE therapy (65.2% of patients, 95% confidence interval [CI] 50.0–76.8) versus octreotide LAR 60 mg (10.8%, 95% CI 3.5–23.0) [25]. The overall response rate (complete and partial) was 18% in the [^{177}Lu]Lu-DOTA-TATE group versus 3% in the octreotide group ($P < 0.001$). In the planned interim analysis of overall survival, 14 deaths occurred in the [^{177}Lu]Lu-DOTA-TATE group compared with 26 in the control group ($P = 0.004$). Sub-group analysis showed that benefits were consistently observed irrespective of prognostic and stratification factors. These data, in combination with other studies showing benefits in PFS and fewer treatment-related adverse events in relation to more conventional systemic therapies, led to regulatory approvals for [^{177}Lu]Lu-DOTA-TATE from the Food and Drug Administration and the European Medicines Agency in 2018 [26,27].

Health-related quality of life (HRQoL) was also assessed in the NETTER-1 trial using the EORTC QLQ-C30 questionnaire and the time-to-deterioration (TTD) methodology, whereby investigators generated a Kaplan–Meier TTD curve with a log-rank statistical comparison between the two randomised study groups to compare HRQoL [28]. The analysis showed a clinically and statistically significant improvement in TTD of global heath (hazard ratio [HR 0.41]), physical functioning (HR 0.52), and role functioning (HR 0.58) with [^{177}Lu]Lu-DOTA-TATE compared with octreotide. There were also significant improvements in TTD of symptoms, including diarrhoea (HR 0.47), pain (HR 0.57) and fatigue (HR 0.62). There were no HRQoL domains where a benefit for octreotide was observed. The endocrine scale of the EORTC QLQ-C30 did not show a difference for the treatment arms [28].

Khan et al. (2021) also described in this issue of the journal a matching-adjusted indirect treatment comparison of [^{177}Lu]Lu-DOTA-TATE, everolimus and sunitinib. In the analysis, the single-arm ERASMUS study was used to infer the effectiveness of [^{177}Lu]Lu-DOTA-TATE in gastro-intestinal NETs patients relative to best supportive care and everolimus, and its effectiveness in pancreatic NETS patients relative to best supportive care, sunitinib and everolimus. Across all of the analyses reported, [^{177}Lu]Lu-DOTA-TATE demonstrated superior effectiveness in extending PFS and OS relative to everolimus and sunitinib, as well as best supportive care. The authors note that the observed magnitude of effect sizes and their consistency across comparators indicates that [^{177}Lu]Lu-DOTA-TATE appears to be a more effective treatment option than everolimus, sunitinib or best supportive care in GEP-NETs, but caution is needed given the non-randomised nature of the comparisons and the associated potential for residual confounding that could not be accounted for in the study.

In the second paper in this issue of the journal, the cost-effectiveness of [^{177}Lu]Lu-DOTA-TATE in the treatment of GEP-NETS was evaluated for the UK setting based on the results of Khan et al. (2021) matching-adjusted indirect treatment comparison. The analysis used a three-state partitioned survival model (pre-progression, post-progression and death) with UK-specific HRQoL utility data and published UK costs (accounted from a National Health Service perspective) to evaluate costs and clinical outcomes over a 20-year time horizon. The study provides evidence that [^{177}Lu]Lu-DOTA-TATE is likely to be cost-effectiveness versus everolimus, sunitinib and best supportive care assuming a willingness to pay threshold of GBP 30,000 per QALY gained. These base case findings were supported by deterministic and probabilistic sensitivity analysis. In financially stringent times, a favourable cost per QALY gained for optimal treatment is in the interest of health care providers and patients.

There are new early data regarding the potential for genetic biomarkers to predict for individual patients the PRRT efficacy and potential adverse events before a treatment decision is made, as well as for monitoring patients during and after

PRRT. Recently, the PRRT prediction quotient has been developed using transcriptomics and grading. Based on mathematical modelling, this is a blood-based eight gene assay with an overall accuracy of 95% regarding responses to PRRT in NETs, and this deserves further prospective evaluation [29,30]. Assaying the phosphorylated histone variant H2AX (γ-H2AX) is a recognised technique for monitoring the effect of external-beam ionising radiation on DNA making use of peripheral blood lymphocytes (PBLs). γ-H2AX in PBLs is thus of interest as a potential biomarker of myelotoxicity [31]. Further understanding and development of such strategies is important and may aid the selection of patients, as well as identification of those patients in need of more intense monitoring.

As the first radiopharmaceutical to get regulatory approval for the treatment of GEP-NETs, the evidence published to date and summarised, in part, in this issue of the journal suggests that [^{177}Lu]Lu-DOTA-TATE may have considerable potential to improve outcomes for patients with unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive GEP-NETs. Moreover, the development of targeted molecular therapies like [^{177}Lu]Lu-DOTA-TATE provides an opportunity to offer more personalised cancer treatment as radiopeptides can be tailored to the unique biologic characteristics of the patient and the molecular properties of the tumour. The highly selective delivery of radiopeptides can be readily adapted to target different types of tumour cells, while limiting radiation exposure to healthy tissue, offering great potential for well-tolerated and highly efficacious treatments for many malignancies. The NET experience acts as a paradigm for other malignancies, for example, current clinical trials in prostate cancer with Lu-177 PSMA, offering hope for a net benefit not just for NET patients but also for patients with other types of tumours overexpressing a particular biological entity, e.g. receptor or protein serving as a high-affinity target for therapy.

Disclaimer

This article is part of a supplement supported by Advanced Accelerator Applications (AAA), a Novartis company.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Professor Martyn Caplin has received speaker and research honoraria from Advanced Accelerator Applications International, Ipsen, Novartis and Pfizer.

REFERENCES

[1] Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumours and carcinomas. Neoplasia 2017;19(12):991–1002.

[2] Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumours in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.

[3] Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumours in the United States. JAMA Oncol 2017;3:1335–42.

[4] Basuroy R, Srirajaskanthan R, Ramage JK. Neuroendocrine tumours. Gastroenterol Clin North Am 2016;45(3):487–507.

[5] Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumours. CA Cancer J Clin 2018;68(6):471–87.

[6] Rodrigues Â, Castro-Poças F, Pedroto I. Neuroendocrine rectal tumours: main features and management. GE Port J Gastroenterol 2015;22(5):213–20.

[7] Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumours (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008;19. 1727–173.

[8] Öberg K, Knigge U, Kwekkeboom D, Perren A, ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii124–v130.

[9] Shah MH, Goldner WS, Halfdanarson TR, et al. Neuroendocrine and adrenal tumours, version 2.2018. Featured updates to the NCCN guidelines. J Natl Compr Cancer Netw 2018;16(6):693–702.

[10] Reubi JC, Schonbrunn A. Illuminating somatostatin analog action at neuroendocrine tumour receptors. Trends Pharmacol Sci 2013;34(12):676–88.

[11] Ruszniewski P, Valle JW, Lombard-Bohas C, et al. Patient-reported outcomes with lanreotide Autogel/Depot for carcinoid syndrome: an international observational study. Dig Liver Dis 2016;48(5):552–8.

[12] Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. J Clin Oncol 2009;27(28):4656–63.

[13] Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumours. N Engl J Med 2014;371(3):224–33.

[14] Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumours. N Engl J Med 2011;364(6):501–13.

[15] Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumours. N Engl J Med 2011;364(6):514–23.

[16] Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387(10022):968–77.

[17] Garcia-Carbonero R, Rinke A, Valle JW, et al. Antibes consensus conference participants. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms. Systemic therapy 2: chemotherapy. Neuroendocrinology 2017;105(3):281–94.

[18] Version 1.2020 NCCN clinical practice guidelines in oncology: neuroendocrine and adrenal tumours – NCCN evidence blocks. July 10, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine_blocks.pdf.

[19] Pavel M, O'Toole D, Costa F, et al. Consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms

(NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103(2):172–85.
[20] Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31(7):844–60.
[21] Brabander T, Van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA0, Tyr3] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumours. Clin Cancer Res 2017;23(16):4617–24.
[22] Baum RP, Kulkarni HR, Singh A, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with (90)Yttrium and (177)Lutetium in 1048 patients with neuroendocrine neoplasms. Oncotarget 2018;9(24):16932–50.
[23] Pavel ME, Singh S, Strosberg JR, et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1411–22.
[24] Vinik A, Bottomley A, Korytowsky B, et al. Patient-reported outcomes and quality of life with sunitinib versus placebo for pancreatic neuroendocrine tumours: results from an international phase III trial. Target Oncol 2016;11(6):815–24.
[25] Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumours. N Engl J Med 2017;376:125–35.
[26] US Food and Drug Administration. Lutathera (lutetium Lu 177 dotatate) Injection. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208700Orig1s000TOC.cfm. [Accessed 18 March 2019].
[27] European Medicines agency. Lutathera; 2018. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera#product-information-section. [Accessed 28 February 2019].
[28] Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumours treated with ^{177}Lu-dotatate in the phase III NETTER-1 trial. J Clin Oncol 2018;36(25):2578–84.
[29] Bodei L, Kidd M, Modlin IM, et al. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumours. Eur J Nucl Med Mol Imag 2016;43(5):839–51.
[30] Bodei L, Kidd MS, Singh A, et al. PRRT genomic signature in blood for prediction of ^{177}Lu-octreotate efficacy. Eur J Nucl Med Mol Imag 2018;45(7):1155–69.
[31] Denoyer D, Jackson P, Lobachevsky P, et al. Analysis of 177Lu-DOTA-octreotate therapy–induced DNA damage in peripheral blood lymphocytes of patients with neuroendocrine tumours. J Nucl Med 2015;56(4):505–11.

Martyn E. Caplin
Royal Free Hospital, Pond Street, London, NW3 2QG, UK
E-mail address: m.caplin@ucl.ac.uk

13 October 2020

https://doi.org/10.1016/j.ejcsup.2021.06.001