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RESEARCH

Time toxicity of lutetium 177 in gastroenteropancreatic neuroendocrine tumours

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Abstract

Objectives: We aim to investigate the time toxicity of patients with gastroenteropancreatic neuroendocrine tumours treated with Lutetium-177 Dotatate in a single institution.

Design: This is a retrospective cohort study.

Methods: All patients with gastroenteropancreatic neuroendocrine tumours treated with Lutetium-177 Dotatate at the Alexander Fleming Institute were included. Our primary endpoint was to evaluate time toxicity, which accounted for every day that the patient had contact with any department of any healthcare institution.

Results: Our cohort included 21 patients with metastatic disease, female sex 86%, and a median age of 55 (IQR 44–63). The primary tumour site was the small intestine in 47.6% of the cases. The median number of previous systemic treatments for advanced disease was two (IQR 2–3). The overall response rate was 19%, and 66.6% had clinical benefit. The median calculated 'time toxicity' was 11 days (IQR 8–18), representing 5.7% of the total treatment duration. The main contributors to time toxicity included infusion days, blood draws, radiological scans, and hospitalisations (median of 4 days for each).

Conclusion: Lutetium-177 Dotatate treatment for gastroenteropancreatic neuroendocrine tumours was associated with low time toxicity, excellent tolerability, a good response and prolonged PFS, of which the median was not reached in the short follow-up we present. Newer treatments with different mechanisms of action provide longer survival and widen the landscape of choices. Understanding new clinical endpoints is important for the transition into a more modern clinical practice, strengthening personalised and patient-oriented strategies.

Keywords: 177 Lu-DOTATATE; peptide receptor radiolabeled therapy; neuroendocrine tumours; delivery of health care; time toxicity

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Introduction

There is a growing necessity to incorporate new endpoints to better assess the impact of modern and costly therapies during the cancer experience. Clinical trials usually incorporate overall survival – and other surrogates – and quality of life (QoL) as the main indicators of the success of a trial therapy (McLeod *et al.* 2019, Bundgaard *et al.* 2022).

The amount of overall survival increased by an investigational technology is generally considered an essential metric by health policymakers, clinical scientists, physicians, and drug developers alike. Contrastingly, it is rarely studied how much 'quality' time is gained by a particular medical treatment. As defined by Gupta and colleagues, this 'quality' time or 'home-day' period represents every treatment interval that was not elapsed in health resource consumption (Fundytus *et al.* 2021, Gupta *et al.* 2022*a*,*b*).

The opposing term, 'time toxicity', comprises all the time involved in coordinating care, including seeking urgent/emergent care for side effects, hospitalisation, and follow-up tests (Gupta *et al.* 2022*a*). Lim and collaborators first described this concept after they evaluated healthcare resource consumption by patients with pancreatic adenocarcinoma who underwent surgical treatment (Lim *et al.* 2022).

There have been efforts to apply time toxicity to a broader spectrum of situations such as the initial treatment lines or early disease management (Nabhan & Feinberg 2017). While assessing cost-effectiveness, studies have indirectly factored in the impact of healthcare on the value associated with different treatments and technologies, and indirectly evaluated time toxicity (Schnipper *et al.* 2016).

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) account for a rare and heterogeneous group of neoplasms with increasing incidence (Pavel *et al.* 2020). Their prognosis is associated with histological grade and primary tumour site (Man *et al.* 2018, Foubert *et al.* 2019).

Well-differentiated tumours are associated with a favourable prognosis even in the advanced setting. There are different treatment strategies that can be sequenced in patients with advanced disease, including watchful observation, local treatments, somatostatin analogues (SSAs), chemotherapy, and targeted therapies (Shah *et al.* 2021). Considering that these options have demonstrated prolonged progression-free survival (PFS) intervals but have not all been directly compared, an adequate assessment of quality-oriented endpoints is essential to balance risks and benefits at the time of decision-making. For these reasons, in this particular cancer type, understanding time toxicity may emerge as a valuable tool for informed decision-making.

Lutetium 177-Dotatate (Lut-177) was approved by the FDA in 2018 for the treatment of GEP-NETs, after demonstrating increased progression-free survival compared to a double dose of octreotide in phase III randomised clinical trials that included patients who had experienced prior disease progression in the advanced setting. Lut-177 was associated with a low incidence of adverse events and an increased time to QoL deterioration (Strosberg *et al.* 2017).

As a result, the possible association of this radionuclide therapy with reduced time toxicity would be of particular interest when assessing treatment-derived utilities in real-world cohorts. To this aim, we examined this new endpoint in a retrospective cohort of patients with advanced GEP-NET who underwent Lut-177 in our institution.

Materials and methods

Study population and design

This retrospective cohort study comprises patients with advanced GEP-NET who received Lut-177 at the Alexander Fleming Cancer Institute (Buenos Aires, Argentina) between January 2019 and July 2023. Institutional guidelines recommend that, prior to Lut-177 initiation, all patients must have a functional study of somatostatin receptors, with an acceptably high uptake of the radiotracer in all target lesions. Patients must also have preserved renal and hepatic function. Lut-177 is routinely administered every 8 weeks during a 24-week time interval.

Krenning score is calculated by comparing the uptake of the radiomarker in the tumour to normal liver uptake. It is used to estimate the positivity of somatostatin receptors as a predictor of response to radionuclide therapy (Bodei *et al.* 2013).

Clinical information, including age, gender, tumour grade, primary tumour, previous treatments for advanced disease, site of metastasis, Krenning and carcinoid syndrome symptoms, was retrieved from medical charts.

Outcomes definitions and treatment characteristics

Time toxicity was defined as the number of days that a patient registered contact with a healthcare institution between the first and last day of Lut-177 treatment. The following contacts were assessed for each included patient: laboratory, computed tomography (CT), other images, general consultations, hospitalisations, emergency consultations (ER), and day centre applications.

For time toxicity calculation, a day with 'time toxicity' was considered if one or more healthcare contacts were recorded for that day. No extra days were considered if more than one event was recorded in a single visit.

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All patients received at least one application of 200 mCi of Lut-177, followed by an infusion of arginine and lysine for renal protection every 2 months for up to four applications. Lut-177 is routinely administered every 8 weeks during a 24-week time interval.

Treatment response was assessed by PET-CT Gallium-68 DOTATATE scan, performed at least 12 weeks after the completion of treatment, or earlier if indicated by a treating physician for any reason. Objective response rate (ORR) was calculated according to RECIST 1.1 criteria assessed by the treating physician. Adverse event grading was reported according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

The primary endpoint of this study was the evaluation of time toxicity, defined as the rate between the days partially or completely in which there was a registered contact with a healthcare institution and the total treatment period with Lut-177. We also evaluated the incidence of adverse events, changes in chromogranin A levels, and the total PFS of our cohort. Descriptive statistics were used to analyse demographics, including medians, proportions, and interquartile ranges when necessary. The Kaplan–Meier method was used for survival estimation.

Results

Patients characteristics

A total of 21 patients were included in the analysis. Patient characteristics are described in Table 1. The median age was 55 (IQR 44–63), and the majority were female (18, 86%). The most common primary tumour sites were the small intestine (10, 47.6%) and pancreas (7, 33.3%). A majority had histologic grade 2 (13, 61.9%). The most common metastatic site was the liver (11, 52.4%), followed by non-regional lymph nodes (10, 47.6%). Less than half of the tumours were functional (9, 42.8%).

Patient characteristics are described in Table 1.

Treatment characteristics and clinical outcomes

Of note, 5 (23.8%) of the patients received somatostatin analogues (SSAs) during Lut-177 treatment for symptomatic control. The median number of previous treatment lines was 2 (IQR 2–3), and all patients received at least one application of Lut-177. The median number of treatment cycles was 4 (IQR 3–4). The median duration of treatment was 194 days (IQR 162.5–215.3).

The overall response rate was 19% ($n = 4$), consisting only of partial responses, and the disease control rate was 47.6% ($n = 10$). Among the ten patients who had chromogranin measures before and after treatment, 7 (70%) cases showed an increase in their concentration after the end of treatment. Patients with either a radiological partial response or a decrease in chromogranin A levels did not experience radiological disease progression at the end of follow-up.

Six patients (28.5%) had at least one treatment-related adverse event to Lut-177. Two patients (9.5%) had grade 1 (G1) increase of alanine or aspartate aminotransferases, 2 (9.5%) G1 neutropenia, 1 (4.75%) G1 acute kidney injury, and 1 (4.75%) case reported G1 alopecia attributed to treatment. There were no G3 or G4 treatment-related adverse events. Two patients (9.5%) had prolonged hospitalisations for non-treatment related complications, including a G3-infected osteonecrosis and a G3 bacteremia.

Outcomes

The median follow-up was 18 months (CI: 95% 9–44), and the PFS at 18 months was 70.7% (CI: 95% 43–100%).

Time toxicity represented 5.7% of the total treatment duration. The median time toxicity was 11 (IQR 8–18) (Fig. 1). The main contributors to time toxicity included infusion days (4 days, IQR (3,4)), blood draws (2 days, IQR (0,4)), CT scans (1 day, IQR (0,1)), other radiological scans (3 days, IQR (2,3)) and hospitalisations (4 days, IQR (0,6)),

Table 1 Patient characteristics.

n (%)	21
Male	14 (66.7%)
Median age (IQR)	55 (44–63)
Primary tumour site	
Small Bowel	10 (47.6%)
Pancreas	7 (33.3%)
Gastric	3 (14.3%)
Feocromocitoma	1 (4.8%)
Functional tumors	9 (42.9%)
Carcinoid syndrome	3 (14.3%)
Grade	
1	3 (14.3%)
2	13 (61.9%)
Carcinomatosis	3 (14.3%)
Primary tumour surgery	
Hemicolectomy	2 (9.5%)
Esplenopancreatectomy	5 (23.8%)
SB resection	6 (28.6%)
Krening score 4	14 (100.0%)
Treatment line in which Lut-177 was indicated	
1	1 (4.8%)
2	8 (38.1%)
3	5 (23.8%)
4	4 (19.0%)
5	1 (4.8%)
Median number of applications	4 (IQR (3,4))

IQR, interquartile range; Lut-177, lutetium 177 dotatate; SB, small bowel.

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representing 2.06%, 1.03%, 0.52%, 1.54% and 2.06 of the total treatment duration, respectively (Fig. 2).

Discussion

A comprehensive cancer treatment approach requires integrating different aspects of patients' daily lives to better understand the journey through a long-term disease and to promote patient-centred care.

The phase III NETTER-1 clinical trial had a deep impact on treatment sequencing for patients with well-differentiated GEP-NETs. This study has demonstrated relevant improvements in traditional clinical endpoints, such as overall survival and quality of life (Foubert *et al.* 2019). Nonetheless, given the high cost derived from this targeted therapy, it is essential to carefully evaluate the impact of radionuclides on the experience of real-world patients, to have a better understanding of its associated risk-benefit ratio.

Our population was in line with the demographic characteristics of the pivotal study NETTER-1 (Foubert *et al.* 2019), except for the higher prevalence of G2 tumours (85.7% vs 44%). The low time toxicity observed in our analysis may be influenced by the characteristics of our included sample, which was associated with good prognostic factors, including a high proportion of patients under 65 years old with low-grade tumours. All the included patients had tumours characterised as Krenning 4, which supports the importance of adequately selecting patients to improve treatment efficacy (Yao *et al.* 2008, Brabander *et al.* 2017).

SSAs infusion represented a significant proportion of time toxicity in our cohort. In the study by Strosberg *et al.*, a significant proportion of patients had functional tumours, most necessitating SSAs during and after Lut-177 treatment (Strosberg *et al.* 2017). Nonetheless, different studies have already shown that Lut-177 was associated with QoL improvement, as well as the duration of disease-related symptoms (Bodei *et al.* 2013). A decrease in symptoms due to tumour response could then also lead to a reduction in SSA usage, which would result in even improved results of time toxicity.

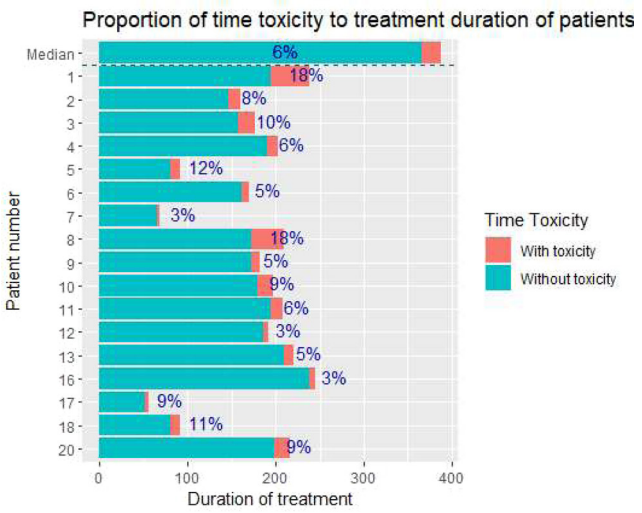

Figure 1

Time toxicity in patients included in the cohort (one patient had no duration of treatment, having only received one dosage before the date of information collection and was therefore not included).

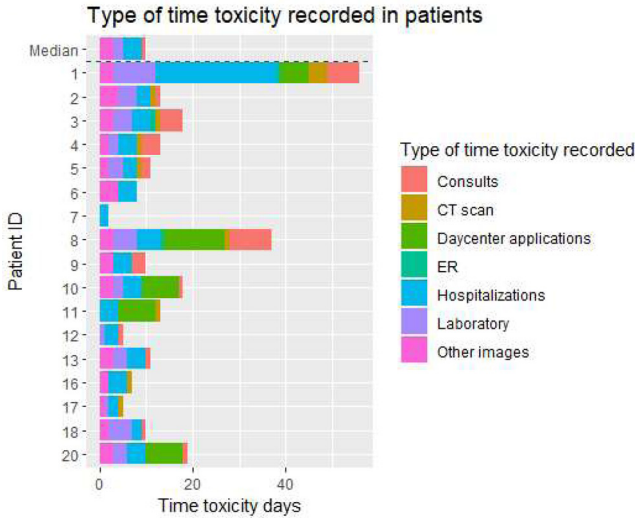

Figure 2

Causes of time toxicity in each included patient (one patient had no duration of treatment, having only received one dosage before the date of information collection and time toxicity information could not be estimated).

The results of our study show a possible management pathway for an ideal patient. The total time toxicity could be reduced if blood draws, medical controls, treatment application, and scans are unified as much as possible, considering necessary precautions such as time between Lut-177 and CT scans to avoid kidney injury. It is important to plan ahead the schedule of studies and treatments to minimise the number of visits and provide a substantial reduction in time toxicity.

We counted the days of medical consultation and SSA injections as time toxicity days, even though with alternative treatments, these days would have been spent in healthcare. We did so because, when accounting for differences in time toxicity, common time spent on every treatment, such as doctor visits or supportive medication, should be considered, given the possibility that in the future, there could be a new treatment requiring less time for such activities. For example, a new SSA that could be used once a year or a new treatment that requires toxicity controls every other week. By considering all components now, future physicians will be able to compare new treatments to the standards.

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Understanding the needs of patients with cancer is a difficult task. Clinical trials usually assess patient-reported outcomes incorporating QoL endpoints. However, other important aspects should also be considered to adequately measure the impact of the quantitative benefits associated with modern technologies.

Time toxicity is one of the emerging endpoints that has been explored by different research groups to fill this gap. In a retrospective matched cohort study, Cox and collaborators have shown that Lut-177 reduced overall costs and increased cost-effectiveness (Cox *et al.* 2021, Smith-Palmer *et al.* 2021, Spada *et al.* 2022). Importantly, the authors reported a statistically significant decrease in the length of hospitalisations due to adverse events or disease-related symptoms.

Treatment utility is often evaluated by reporting its associated change in quality-adjusted life years (QALYs). Smith-Palmer *et al.* used data from the NETTER-1 (Foubert *et al.* 2019), ERASMUS (Brabander *et al.* 2017), A6181111 (Raymond *et al.* 2011), RADIANT-3 (Yao *et al.* 2016*a*) and RADIANT-4 trials (Yao *et al.* 2016*b*) to indirectly compare Lut-177 with the best standard of care (BSC) in GEP-NET. The authors showed a higher gain in QALYs in patients who received Lut-177, accounting for an increase of 1.6 QALYs in all the included patients, and 2.6 QALYs in the subgroup with pancreatic NETs (Smith-Palmer *et al.* 2021).

While the evaluation of QALYs incorporates other methodological assessments to understand the qualitative impact of a treatment, focussing on time toxicity allows for a better understanding how the cancer experience might be influenced by administrative and travel-related burdens, the amount of lab draws and scans needed for patient follow-up, and other aspects that are normally included in QoL measures, such as adverse events and hospitalisations associated with treatments or procedures.

We observed a low time toxicity associated with Lut-177 in patients with advanced GEP-NETs. We consider that documenting this information is fundamental to guide patients regarding their expectations and consequences of cancer treatments, promoting a shared decision-making process, and ultimately, patient empowerment.

Our study is not without limitations. The retrospective nature may have biased our selection criteria for the sample. However, all consecutive patients who were entered in clinical records were included. Considering that usual records are not prepared to capture time toxicity, it is expected that a number of contacts of our population with healthcare institutions may not have been incorporated into our database. Finally, Lut-177 is not universally available in our health system. Consequently, it may be argued that patients with higher incomes might be over-represented in our cohort.

We found a lower rate of grade 3 and 4 adverse events with Lut-177 than previously recorded (Sampaio *et al.* 2016). Only seven instances of grade 1 toxicities were seen. This particularity may be explained by the small sample size and possibly due to selection bias.

Medical decision-making is a complex matter involving more than one possible approach (Glatzer *et al.* 2018). Patients and physicians usually have different priorities when discussing treatment options. Particularly for GEP-NETs, it is expected that multiple treatment options may be available without direct high-quality evidence to support a single right choice. New patient-centred options, such as time toxicity, can help bring patients and oncologists closer together when it comes to evaluating what is the best outcome and therefore which treatment to use in each situation (Shickh *et al.* 2023).

Conclusions

Considering the results of our cohort, treatment with Lut-177 has a good safety profile, a prolonged time to recurrence, and, in a properly selected cohort of patients, a low time toxicity. These findings should encourage physicians to consider the use of Lut-177 in GEP-NET patients and can aid them in decisions regarding therapy sequencing.

This study represents one of the first publications that incorporate time toxicity to understand real-world evidence in patients with advanced GEP-NETs who received radionuclides. More efforts are required from clinical researchers, patient advocates, physicians, and decision-makers to routinely incorporate this novel endpoint in clinical trials, observational studies, and daily work metrics, especially in advanced cancer types that are associated with long disease-related survival.

Declaration of interest
The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
Marcos Bortz: Data collection, main writer, Graphics design, statistical analysis, principal investigator. Andres Rodriguez, Romina Luca, Berenice Freile, Greta Catani, and Federico Esteso: Provided clinical expertise in the management and follow-up of the patients, data collection, patient management and follow-up, collaborated with the PI in conceptualising and designing the study. Federico Waisberg, Diego Enrico: Conducted statistical analysis of the data, final text edition, collaborated with the PI in conceptualising and designing the study. Martina Musumeci, Eliana Vazquez: Patient recruitment, treatment administration, patient follow-up, and data collection. Matías Chacón, Juan Manuel O'Connor, Silvina Racioppi: Oversaw all aspects of the study, including data collection, analysis, and interpretation.

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