



Research Article

Chilean experience using “Theranostics” for treating metastatic neuroendocrine tumors with [¹⁷⁷Lu]Lu DOTA-TATE

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Abstract

Introduction: Well-differentiated, Neuroendocrine Tumors (NET) are highly heterogenic and slow-growing pathologies, characterized by unspecific symptomatology and elevated expression of somatostatin receptors (SSTR). Despite the high incidence of NETs, several patients are diagnosed in advance stages of the disease when surgery is insufficient to treat the pathology. Peptide receptor radionuclide therapy (PRRT) has emerged as a new state-of-the-art treatment for NET-patients in advanced stages.

Results: In this retrospective study, between 2004 and 2018 a total of 66 patients with advanced-stage-NETs, refractory to other therapies, were treated with [¹⁷⁷Lu]Lu DOTA TATE. At the end of the study, 56.1% of the patients were alive and the median overall survival for all patients in the study was 86.3 months. Patients that received doses ≥ 22.2 GBq showed increased overall survival (OS) in comparison with patients that received doses < 22.2 GBq (HR, 0.168; 95%CI 0.12- 0.99; p<0.001), adjusted by gender. Likewise, patients that received doses ≥29.6 GBq had an increased OS (HR, 0.42; 95%CI 0.19-0.94, p<0.05).

Conclusion: Although several studies have shown that PRRT is an effective alternative for advanced NET, patients in South America have no regular access to PRRT. Our study proves that [¹⁷⁷Lu]Lu-DOTA-TATE effectively increases the survival of patients with metastatic NET and provides an excellent alternative in terms of cost-efficiency for South American countries.

Introduction

The worldwide incidence of neuroendocrine tumors (NETs) is rising [1-9]. NETs mainly affect the gastrointestinal tissue [1-3, 10], and are considered slowly progressing cancers characterized by a wide variety of unspecific symptoms with different levels of tumor differentiation and prognosis [11]. Unfortunately, the slow progression and the broad spectrum of clinical presentation of NETs lead to unawareness and late diagnose, resulting in limited therapeutic options for patients

[2,3]. Nevertheless, during the last decades, peptide receptor radionuclide therapy (PRRT) has emerged as a treatment option for patients with metastatic NET that exhibit high expression of somatostatin receptors (SSTR) [12]. SSTR bind somatostatin (SST), a paracrine 14 amino acid neuropeptide secreted by cells of the pancreas, the gastrointestinal tissue and the brain [13]. Thus, we can target SSTR-overexpressing cancer cells of middle or low grade neuroendocrine carcinomas (classified by the WHO as G1 and G2) with SST peptides analogues labelled with therapeutic radioisotopes such as yttrium-90 or lutetium-177.

Although PRRT is widely used in a subgroup of advanced NETs (G1/G2, Ki-67<20%), it is not a standard procedure in Chile and other countries in South America. For example, the public health system (Ricarte Soto law N° 20.850) only covers everolimus and sunitinib to treat patients with non-operable metastatic G1/G2-NETs [14]. In this retrospective analysis, we present data from 66 patients with metastatic NETs that have been treated with [¹⁷⁷Lu]Lu-DOTA-TATE between 01/2004 and 06/2018. All patients had histopathological confirmation of metastatic NETs with overexpression of SSTR-2, as confirmed by [⁶⁸Ga]Ga-DOTA-TATE PET/CT or [¹¹¹In]In-DTPA-[D-Phe1]-Octreotid (OctreoScan®) SPECT/CT. All patients were in palliative care without further treatment options and matched commonly accepted inclusion criteria [15].

Results

All patients were treated with [¹⁷⁷Lu]Lu-DOTA-TATE at PositronMed, and the retrospective study was approved by the regional ethics committee board (Servicio de Salud Metropolitano Oriente, permit number 20191203) and in accordance to the Declaration of Helsinki, Good Clinical Practices, and Chilean regulations. The survival was calculated using the Kaplan-Meier method and the survival functions between the different groups were done using the log-rank test. Our analysis showed that the median overall survival (OS) for all patients in the study was 86.3 months, and the 5-year survival rate was 55.29% (95% CI, 40.9%–67.5%) (Figure 1A). 83.3% of the patients presented gastroenteropancreatic neuroendocrine tumors (GEP-NET). The median age at diagnosis was 53.98 years (range 13–79), and 57.6% of the patients were male. Within the GEP-NET group, 58.8% presented gastrointestinal tumors, 30.9% presented pancreatic tumors, and in 10.9% of the cases, the tumors were of rectal origin. Patients with NETs from other tissues than the gastroenteropancreatic tissue were registered as others. Patients with GEP-NET exhibited a higher OS than patients affected by other NETs types, but the number of patients in the others-NET group was rather low (9 patients). There was no statistical difference in OS between tumor grade (G1 and G2), age, or gender, although we did observe that female had slightly higher OS (Figure 1B). To determine whether a certain cumulative dose of [¹⁷⁷Lu]Lu-DOTA-TATE could increase the OS, we grouped patients that received less than 22.2 GBq (23 patients) and compared the OS to those that received ≥ 22.2 GBq (43 patients). Patients that received a cumulative activity ≥ 22.2 GBq had a significantly higher OS than patients that received < 22.2 GBq ($p < 0.001$) (Figure 1C).

The Cox proportional hazard model, adjusted by gender, showed that patients receiving doses of 22.2 GBq or more reduced by a 83% the expected hazard as compared to patients that received fewer doses (Hazard Ratio (HR)=0.168; 95%CI 0.12–0.99; $p < 0.001$) at any given time during the study. When we analyzed the OS of female (n= 12) and male (n=11) patients that received < 22.2 GBq, we observed that females had a median survival of 45.8 versus 19.7 in males ($p < 0.05$; HR=0.352; 95%CI, 0.15–0.83) (Figure 1D). However, this difference was not evident in the group receiving ≥ 22.2 GBq (Figure 1E).

Our data further indicate that patients that received over 29.6 GBq had a higher OS than patients that received less ($p < 0.05$) (Figure 1F) (HR, 0.42; 95%CI 0.19–0.94).

Discussion

This retrospective study summarizes our experience with the Theranostic agent [¹⁷⁷Lu]Lu-DOTA-TATE to treat patients affected by NET (G1 or G2). Our results support the notion that patients with advanced metastatic NETs benefit from PRRT therapy with [¹⁷⁷Lu]Lu-DOTA-TATE. The median survival for G1 and G2 patients is 124 and 64 months, respectively. However, G1/G2 patients with advanced disease and distant metastasis show a median survival of only 33 months [2]. Our results showed that patients treated with [¹⁷⁷Lu]Lu-DOTA-TATE had a median survival of 87.6 months with no statistical differences in median survival between patients with G1 or G2, although we had only a few cases of G1 (8 cases).

The median survival improved significantly in patients that received a cumulative dose of ≥ 22.2 GBq of [¹⁷⁷Lu]Lu-DOTA-TATE. In fact, for patients that received a cumulative dose of ≥ 22.2 GBq the estimated median survival was not reached, whereas for patients that received a cumulative dose < 22.2 GBq, the median survival was 32.2 months. If a therapeutic response by imaging or based on biomarkers can be observed following [¹⁷⁷Lu]Lu-DOTA-TATE treatment [16–18], a further increase of the cumulative dose should also increase the survival time. Not surprisingly, the median survival time of patients that received a cumulative dose of ≥ 29.6 GBq was also not reached, whereas patients that received a cumulative dose < 29.6 GBq showed a median survival time of 45.8 months. Cross-sectional imaging, such as CT, is considered the standard follow-up analysis. However, levels above the normal upper limit of chromogranin A (CgA) and alkaline phosphatase (ALP) have been associated with shorter survival in patients with metastatic NETs [19]. Unfortunately, CgA was not initially available in the country, which made it impossible to measure this biomarker in all our patients. Furthermore, since CD3+ cell infiltration and levels of circulating regulatory T cells are associated with recurrence-free survival and prognosis, it would be interesting to include these biomarkers in future studies [20,21].

As gender affect OS [2,16], we analyzed the difference between females and males. We noticed, that in the group that received a cumulative dose < 22.2 GBq, females showed a significantly higher median survival than males. However, the difference in median survival between gender disappeared in patients that received a cumulative dose of ≥ 22.2 GBq.

Side-effects of PRRT with [¹⁷⁷Lu]Lu-DOTA-TATE may include myelotoxicity or nephrotoxicity due to the relatively high uptake in kidneys [22]. Although the risk of nephrotoxicity is rather low and cases are rare, the risk can be further reduced by co-administration of renal-protective agents [12]. Hematological toxicity usually occurs 4 to 6 weeks after therapy and is usually mild and reversible. Therefore, it is crucial to select patients with relatively normal bone marrow and renal functions to reduce the occurrence of severe side effects. In our study population, we observed in 13% of

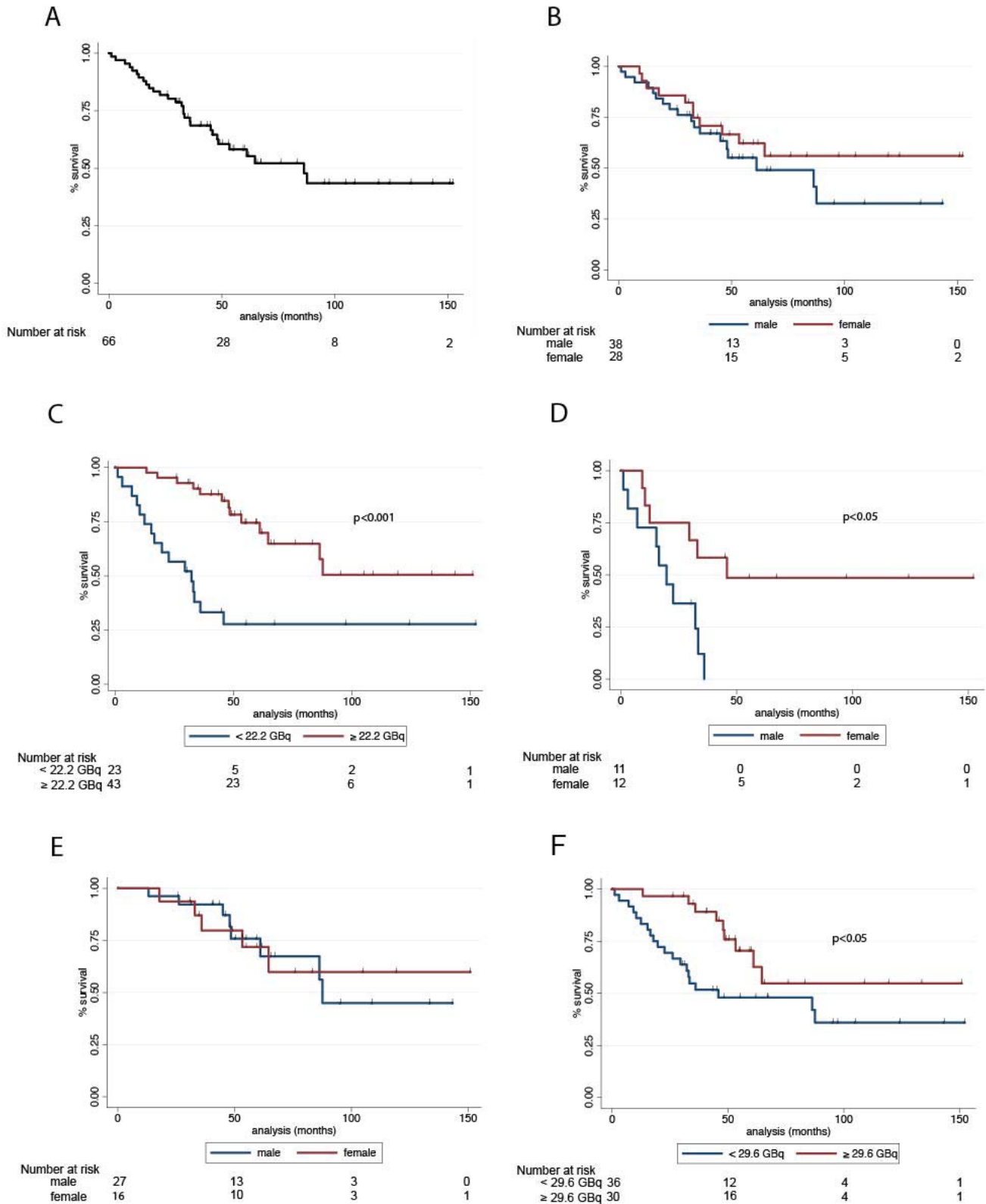


Figure 1: Kaplan–Meier survival curves. (A) Patients analyzed retrospectively (n=66) showed a median overall survival of 86.3 months. (B) Comparison between male (blue line) and female patients (red line). At the bottom of every Kaplan–Meier curve is indicated the number of patients at risk over time. (C) Comparison between patients that received total doses <22.2 GBq (blue line) and patients that received ≥22.2 GBq (red line) (Log Rank test $p < 0.001$). (D) Comparison between male (blue line) and female (red line) patients that received total doses <22.2 GBq and patients that received ≥22.2 GBq (Log Rank test $p < 0.05$). (E) Comparison between male (blue line) and female (red line) patients that received total doses ≥22.2 GBq (Log Rank test $p = 0.92$). (F) Comparison between patients that received total doses <29.6 GBq (blue line) and patients that received ≥29.6 GBq (red line) (Log Rank test $p < 0.05$). At the bottom of every Kaplan–Meier curve is indicated the number of patients at risk over time.



the patients a carcinoid syndrome following treatment with diarrhea, vomiting, increase of weight, hepatomegaly and bone pain as the most prevalent side effects. Nevertheless, these were transitory and patients improved within a short period of time after the therapy.

A limitation of our study is the fact that patients were referred from different medical institutions throughout the country. As a consequence, clinical follow-up was not available for all patients due to the limited availability of imaging or access to their local health institution.

Our results have important implications: firstly, we provide data for more than 14 years of PRRT with [¹⁷⁷Lu]Lu-DOTA-TATE to treat patients affected by metastatic NETs, contributing to the recently published register of NET patients in Chile [23]. The Chilean and Argentinian registers show a high incidence of GEP-NETs, which is in line with our study and others [1,24]. However, this is not the case for the Brazilian population in which GEP-NET is the second most frequent NET [25]. Therefore, it is important to characterize our populations if we want to design strategies for early detection and improve treatments outcomes. Secondly, Pinto et al. reported a high proportion of metastatic patients in the Chilean register. The study proposed different factors such as the bias of the register itself (led by an oncologist or oncologists), late diagnose and economic factors that limit the access to preventive care, early diagnosis and treatment [23]. Our study shows that, patients with access to [¹⁷⁷Lu]Lu-DOTA-TATE, may benefit from increased survival and quality of life, as other studies have also shown [16,26–29]. Thirdly, the access and cost of the treatment depend on several factors such as availability, treatment duration, number of doses required, individual patient conditions and reimbursement. Moreover, since NET is a rare disease and different diagnostic and therapeutic protocols are applied depending on the individual condition of the patient (personalized medicine), the experience of the medical staff is of utmost importance. Today, only a few centers have the necessary experience to treat NET patients and administer PRRT treatments, highlighting the urgent need of suitable training programs for the Theranostic field.

Conclusion

Although the availability of PRRT is limited to a few specialized centers, our results suggest that [¹⁷⁷Lu]Lu-DOTA-TATE is an excellent alternative in term of cost-effectiveness, especially considering the current situation in Chile and other South American countries.

Conflict of interest

All authors contributed to the study conception and design. Amaral H, Pruzzo R, Fernández R, and Coudeu I treated the patients, performed the PET/CT ¹⁸F-FDG scans and collected the data. All the authors analyzed the data and the first draft of the manuscript was written by Cristian Soza-Ried and Horacio Amaral. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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