Outcomes of first-line long-acting octreotide treatment in non-functional, advanced gastroenteropancreatic neuroendocrine tumors

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Summary

Purpose: Benefits of somatostatin analogues have been mostly studied in mixed samples of patients including both functional and non-functional neuroendocrine tumors. This study aimed to examine the response of patients with non-functional metastatic or inoperable gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that received first-line treatment with the somatostatin analogue octreotide LAR.

Methods: The medical records of 23 patients with locally inoperable or metastatic non-functional neuroendocrine tumors who received octreotide LAR (long acting release) treatment were retrospectively reviewed for clinical data and disease course. All patients had received first-line octreotide LAR 30 mg for 4 weeks. Progression free survival (PFS) and overall survival (OS) were the primary and secondary endpoints, respectively.

Results: All patients were followed for a median of 47 months. Mean PFS and OS were 25.0±3.4 months (95% CI: 18.4-31.5) and 71.3±9.5 months (95% CI: 52.7-89.9), respectively, with an estimated 5-year OS of 58%. Patients with ≤25% of hepatic tumor load had better PFS when compared to patients with >25% hepatic tumor load (32.2±6.2 vs 19.4±2.7 months, p=0.043). During treatment, the following adverse events developed: skin reaction (N=1, 4.3%), cholestasis (N=1, 4.3%), grade 1 diarrhea (N=1, 4.3%), and newly onset diabetes (N=3; 13.0%).

Conclusion: Octreotide LAR seems to be an effective treatment option with acceptable tolerability for patients with well-differentiated non-functional GEP-NETs. Survival benefits warrant further testing in future large-scale prospective trials.

Key words: gastroenteropancreatic neuroendocrine tumor, LAR, non-functioning tumor, octreotide, survival

Introduction

Neuroendocrine tumors (NETs) is a group of slowly progressing neoplasms originating from the diffuse neuroendocrine system, which have secretory granules and are able to secrete various peptide hormones and biological amines. GEP-NETs present as functioning or non-functioning tumors depending on the presence or absence of characteristic hormonal symptoms. In a recent international GEP-NET registry study with 1005 patients, 71.1% of patients had non-functional tumors . Genetic etiology has also been suggested; for example, mutations of MEN1, DAXX or ATRX, and mTOR pathway genes have been associated with pancreatic NET tumorigenesis . The incidence of GEP-NETs is on the increase and has tripled over the past 30 years.

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Patients with localized GEP-NETs are usually treated surgically. Surgical operations range from conservative approach to extended resection, depending on the size and localization of the tumor. However, most tumors are metastatic at the time of diagnosis owing to the indolent nature of the disease .

The prognosis of NETs depends mainly on the proliferative activity of the tumor. For example, the median survival in well to moderately well differentiated (grade 1-2) metastatic disease is 33 months, but it is only 5 months in patients with poorly differentiated carcinomas. The corresponding 5-year survival rates are 35% and less than 5%, respectively .

The development of somatostatin analogs (SSAs) has profoundly affected the management and outcome of patients with metastatic GEP-NETs. They were initially developed for the palliative treatment of patients with carcinoid syndrome; then they were shown to possess antiproliferative activity. They bind to SSTR2 and SSTR5, resulting in similar efficacy of symptom control in patients with carcinoid syndrome in NETs . SSAs are still the mainstay of therapy in patients with well-differentiated GEP-NETs and are efficient in terms of both growth inhibition and control of hormonal syndromes. Currently, octreotide and lanreotide are the two commercially available SSAs.

Lanreotide and octreotide have been used to control symptoms that result from the release of peptides and neuroamines; however, octreotide is the most studied SSA in NETs. Octreotide is a synthetic octapeptide SSA with a half-life of 90-120 min when administered subcutaneously and a pharmacodynamic action lasting up to 8-12 hrs . Octreotide acts on many pathways resulting in inhibition of tumor angiogenesis and of growth factors including growth hormone, insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide and secretin, thus exhibiting antiproliferative effects in NETs . In octreotide acetate LAR formulation, the active ingredient is encapsulated in microspheres of a slowly dissolving polymer. This provides a steady-state kinetics and predictable pharmacokinetic profile when injected intramuscularly once every 28 days .

To date, benefits of somatostatin analogues have been mostly studied in mixed samples of patients with functional or non-functional NETs. This retrospective study aimed to examine the PFS and OS of patients with non-functional GEP-NETs that received first-line somatostatin analogue octreotide LAR.

Methods

Patients

The patient medical records with neuroendocrine tumors that received treatment between 2006 and 2010 at the Oncology Institute, Istanbul University, were investigated. Unresectable, locally advanced or metastatic, non-functioning, somatostatin receptor-positive GEP-NETs with grade 1 or 2 and Ki-67 proliferative index <10 that received first-line octreotide LAR treatment were included in this study. No patient had received any medical treatment before octreotide LAR including interferon, chemotherapy, radionuclide ablation or any embolization. All patients had normal levels of urinary 5-hydroxyindole acetic acid. Ki-67 index of proliferation was evaluated by two pathologist (Y.K. and M.G.).

Outcome estimation

All patients had received octreotide LAR 30 mg for 4 weeks (Sandostatin LAR, Novartis) until progression. The main outcome endpoint was PFS according to RECIST criteria . OS was the secondary endpoint. PFS was defined as the time period between the first administration of octreotide and progression or death. OS was defined as the time period between the first administration of octreotide and death. Patients were followed-up by computerized tomography, MRI and somatostatin receptor scintigraphy (SRS) where appropriate, every 4-6 months after treatment.

Statistics

The Statistical Package for Social Sciences (SPSS) version 15.0 was used for data analysis. Descriptive statistics were presented as appropriate. Kaplan-Meier method was used for survival analysis and differences were compared with log-rank test. p values <0.05 were considered as statistically significant.

Results

Table 1 shows the demographic and clinical characteristics of the patients. All patients had grade 1 or 2 tumors (Ki-67 proliferation index <10).

All patients received treatment until disease progression.

During the course of the disease, ascites developed in 2 patients (8.7%). During octreotide treatment, the following adverse events developed: skin reaction (N=1, 4.3%), cholestasis (N=1, 4.3%), grade 1 diarrhea (N=1, 4.3%), newly onset diabetes (N=3, 13.0%, one being grade 3). No ma-

Table 1. Patient and tumor characteristics (N=23)

Characteristics	N (%)
Sex (M/F)	9/14
Age at diagnosis, median, years (range)	56 (23-80)
Ki-67 status (%)	
Ki-67 ≤ 2	7 (30.4)
Ki-67 3-10	16 (69.6)
Origin of the primary tumor	
Pancreas	10 (43.5)
Stomach	4 (17.4)
Midgut-Hind gut	9 (39.1)
Metastasis at diagnosis	20 (87.0)
Locally advanced disease at diagnosis	3 (13.0)
Hepatic tumor volume (%)	
≤25	10 (43.5)
>25	13 (46.5)

Figure 1. Kaplan-Meier curve for progression free survival..

jor side effects were noted. Radiological responses were as follows: no complete response; 4 partial responses (17.4%) and 14 cases with stable disease (60.9%).

Twenty-three patients were followed for a median of 47.9 months (range 8.2-111.7). Mean PFS and OS were 25.0±3.4 months (95% CI:18.4-31.5) (median 22.4 months) and 71.3±9.5 months (95% CI: 52.7-89.9) (median 70.1 months), respectively, with an estimated 5-year OS of 58%. Figures 1 and 2 show Kaplan-Meier curves for PFS and OS, respectively.

Patients with metastasis with ≤25% of hepatic tumor volume had better mean PFS when compared to patients with >25% hepatic tumor volume (32.2±6.2 vs 19.4±2.7 months, log rank p=0.043). However, these two groups did not differ with regard to OS (62.3±9.9 vs 70.1±12.5 months, log rank p=0.916).

Discussion

To date several studies with varying methodologies have provided support for the use of somatostatin analogues in GEP-NETs . The CLARINET study was the first randomized study specifically showing efficacy of a somatostatin analogue (lanreotide) in non-functional GEP-NETs. On the other hand, the randomized PROMID study showed the efficacy of octreotide in midgut tumors. The present study is the first to examine octreotide as
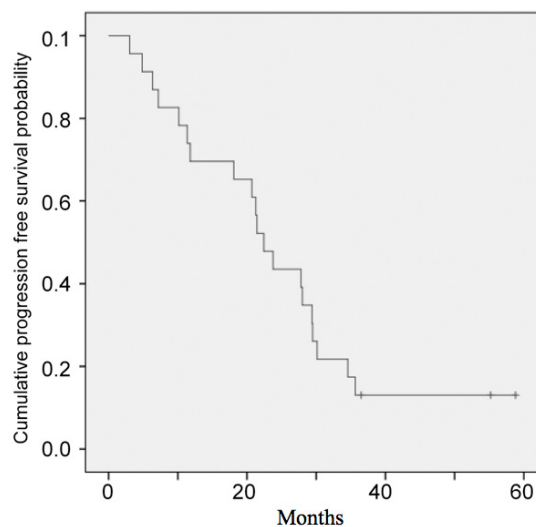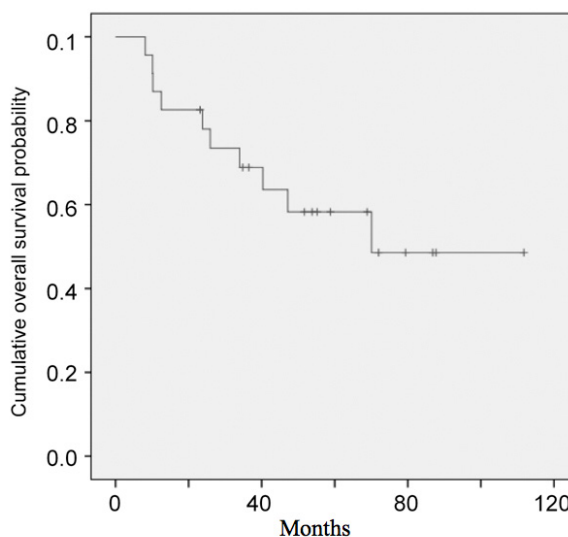

Figure 2. Kaplan-Meier curve for overall survival.

first-line treatment of non-functional variant of these tumors.

The two currently available somatostatin analogues, namely octreotide and lanreotide, are of the same drug class, but they differ in certain aspects. The affinity of octreotide for SST2 receptors is 30% higher than lanreotide. It has a moderate affinity for SST2 receptors, which is still 63% higher than that of lanreotide. Octreotide has a long-acting formulation and lanreotide has a prolonged-release formulation. Astruc et al. compared *in vivo* release profiles of these formulations and found substantial differences with regard to their single-dose pharmacokinetic profiles. Oct-

reotide LAR had and initial transient increase in concentration on the first day, then concentrations decreased and remained low on days 2 to 6, followed by an increase towards plateau levels between days 6 to 30 and then a steady decrease started. Prolonged-release lanreotide on the other hand, reached peak concentration on the first day, which was followed by a consistent decrease thereafter. This pharmacokinetic profile of prolonged-release lanreotide suggests that patients receiving this agent would be exposed to drug levels higher than the therapeutic target, to maintain effective concentration for 28 days. In line with this profile, adverse events were more common among the subjects that received prolonged-release lanreotide than octreotide LAR. Nausea for example was observed in 30% of subjects in the former group; however, none of the subjects in the latter group experienced nausea. Thus, octreotide LAR may have better gastrointestinal tolerance.

Several recent studies have tested the efficacy and safety of lanreotide in GEP-NETs. In the retrospective study by Palazzo et al. , patients received lanreotide monotherapy and the study mainly examined the factors effecting the antitumor efficacy of the treatment. Although retrospective, it was the first large study to investigate the somatostatin analogue efficacy in this patient group. Half of the patients had functional tumors and a great proportion had received prior non-surgical treatment. That study included patients with relatively favorable prognostic profile with 78% of available Ki-67 values equal to or smaller than 5%. A quarter of patients had negative somatostatin receptor scintigraphy. However, these patients were given lanreotide and PFS was not affected, as expected. In that study, the median follow-up time was 21 months, which is relatively short for GEP-NETs. A median PFS of 29 months was achieved. This greater-than-expected PFS may be explained by the overall favorable prognostic features of the patients: 78% having a Ki-67 index ≤5% and 53% having hepatic tumor load ≤25%. In the first prospective study by Martin-Richard et al., lanreotide autogel was used, and 87% of the patients had GEP-NETs with even lower proliferation index than in the Palazzo study. Surprisingly, a low median PFS of 12.9 months was obtained. In that study, most patients were not treatment-naïve. The latest study with lanreotide, the CLARINET study, included only non-functional GEP-NETs and proved the efficacy of somatostatin analogues in this subgroup of patients. That study included 204 patients with well or moderately well differentiated (Ki67 < 10%) non-functioning GEP-NETs that were not treatment-naïve. After two years of treatment, PFS was improved when compared to placebo; however, the median PFS could not be reached in the treatment arm. At the study end, 62% and 22% of lanreotide-treated patients and placebo treated patients did not progress or died, respectively. On the other hand, groups did not differ with respect to OS, probably because of the long life expectancy for patients with slow-growing tumors. Lanreotide showed favorable safety/tolerability profile. Treatment-related adverse events occurred in 50% of the lanreotide groups compared to 28% of the placebo group. The most common adverse event was diarrhea.

Rinke et al. tested the efficacy of octreotide LAR in exclusively treatment-naïve midgut GEP-NETs in a randomized design study (PROMID). Patients with functional or non-functional tumors were included. Hepatic load of the patients was below 10%, thus representing a good prognostic profile. The median time to tumor progression was 14.3 months and 6.0 months in the octreotide LAR and placebo groups, respectively, thus demonstrating antiproliferative efficacy. The PROMID study differs from CLARINET in several aspects: only midgut tumors and only patients with low hepatic load were included. Another study by Panzuto et al. included patients that received lanreotide autogel or octreotide LAR in somatostatin receptor scintigraphy positive patients and disease stabilization was achieved in a median of 26.5 months. In that study, 64% of the patients had non-functional tumors and 87% were not treatment-naïve.

The findings of this study regarding PFS are in line with the findings of the previous CLARINET study with lanreotide, supporting the beneficial effects of somatostatin analogues in non-functional GEP-NET tumors. However, in the CLARINET study, hepatic tumor load did not appear to be a significant determinant of treatment outcome, whereas in this study difference in PFS between patients ≤25% vs >25% hepatic tumor load was found.

The main limitations of this study are its retrospective non-randomized design and the relatively small sample size.

The findings of this study suggest that octreotide LAR seems to be an effective treatment option with acceptable tolerability for patients with well-differentiated non-functional GEP-NET's. Long-term large-scale comparative studies are warranted to support its benefits, particularly in

terms of PFS.

Ethical standard

All procedures performed in studies involving human participants were in accordance with

the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

References

1. Modlin IM, Champaneria MC, Bornschein J, Kidd M. Evolution of the diffuse neuroendocrine system--clear cells and cloudy origins. Neuroendocrinology 2006;84:69-82.

2. Yalcin S, Glasberg S, Abali H. Gastroenteropancreatic neuroendocrine tumors (GEPNET) registry: update from international collobaration. Ann Oncol 2014;25(Suppl 4):iv398.

3. Jiao Y, Shi C, Edil BH et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science 2011;331:1199-203.

4. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063-3072.

5. Modlin IM, Oberg K, Chung DC et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61-72.

6. O'Toole D, Ducreux M, Bommelaer G et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. Cancer 2000;88:770-776.

7. Chadha MK, Lombardo J, Mashtare T et al. High-dose octreotide acetate for management of gastroenteropancreatic neuroendocrine tumors. Anticancer Res 2009;29:4127-4130.

8. Costa F, Gumz B. Octreotide – a review of its use in treating neuroendocrine tumours. Eur Oncol Haematol 2013;9:1050-1059.

9. Bauer W, Briner U, Doepfner W et al. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982;31:1133-1140.

10. Florio T. Molecular mechanisms of the antiproliferative activity of somatostatin receptors (SSTRs) in neuroendocrine tumors. Frontiers Biosci 2008;13:822-840.

11. Susini C, Buscail L. Rationale for the use of somatostatin analogs as antitumor agents. Ann Oncol

2006;17:1733-1742.

12. Astruc B, Marbach P, Bouterfa H et al. Long-acting octreotide and prolonged-release lanreotide formulations have different pharmacokinetic profiles. J Clin Pharmacol 2005;45:836-844.

13. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-216.

14. Panzuto F, Di Fonzo M, Iannicelli E et al. Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma. Ann Oncol 2006;17:461-466.

15. Palazzo M, Lombard-Bohas C, Cadiot G et al. Ki67 proliferation index, hepatic tumor load, and pretreatment tumor growth predict the antitumoral efficacy of lanreotide in patients with malignant digestive neuroendocrine tumors. Eur J Gastroenterol Hepatol 2013;25:232-238.

16. Martin-Richard M, Massuti B, Pineda E et al. Antiproliferative effects of lanreotide autogel in patients with progressive, well-differentiated neuroendocrine tumours: a Spanish, multicentre, open-label, single arm phase II study. BMC Cancer 2013;13:427.

17. Caplin ME, Pavel M, Cwikla JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. NEJM 2014;371:224-233.

18. Rinke A, Muller HH, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656-4663.

19. Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur J Endocrinol 2002;146:707-716.