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Original Article

Safety and tolerability of sequencing somatostatin analogs (octreotide to lanreotide depot) in the treatment of neuroendocrine tumors: an institutional case series

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Abstract: Results from the Controlled study of Lanreotide Antiproliferative Response In NeuroEndocrine Tumors (CLARINET), established lanreotide depot as the first Food and Drug Administration-approved synthetic somatostatin analog (SSA) for treatment of patients with well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (NETs) improving progression-free survival. However, lanreotide use following disease progression, intolerance, or poor carcinoid symptom control with octreotide has not been extensively assessed. We performed a retrospective analysis of NET patients receiving lanreotide at Roswell Park Cancer Institute who were on octreotide long-acting release (LAR) prior to initiation of lanreotide and who received at least 3 doses of lanreotide. Demographics, tumor characteristics, SSA dosing data, serum biomarker levels (chromogranin A [CgA], 5-hydroxyindoleacetic acid [5-HIAA], serotonin), and adverse events (AEs) were obtained. Disease progression was assessed by imaging at 6-month intervals or earlier and by measuring serologic markers. We identified 6 patients aged 59 to 62 years, who had well differentiated NETs of unknown primary and ileocecal/pancreatic/bronchial primaries. Five patients had metastatic disease, 5 had non-functional disease, 2 underwent prior surgical resection, 3 underwent prior liver-directed therapy, and 1 received systemic chemotherapy and targeted therapy. Four patients received prior octreotide of 30 mg, while 2 received 40 mg. Three patients were sequenced to lanreotide due to disease progression, while 1 of each in the remaining cohort were switched due to serologic progression, uncontrolled carcinoid symptoms, and intolerance to octreotide. The average number of lanreotide doses received was 10 (range 3 to 19). Stable or decreased serological markers were seen in most of the patients receiving lanreotide. Stable disease response by imaging studies with a mean duration of response of approximately 15 months was seen with lanreotide in 3 evaluable patients; 2 of whom have ongoing responses. No treatment-related AEs were seen with lanreotide. Lanreotide was well tolerated in this small series of NET patients who had intolerance, poor symptom control, or disease progression while on octreotide. Long-term prospective evaluation would help define efficacy, safety and cost-effectiveness for such a sequencing strategy.

Keywords: Lanreotide depot, octreotide LAR, neuroendocrine tumors, case series, CLARINET trial, synthetic somatostatin analogs, therapeutic sequencing, carcinoid

Introduction

Neuroendocrine tumors (NETs) represent a heterogeneous, sporadically occurring, biologically diverse group of malignancies that arise throughout the body [1]. A variety of systemic symptoms related to secretion of numerous hormones and biogenic amines from these tumor cells can lead to carcinoid syndrome [1-3]. While prognosis varies widely, depending on tumor grade (proliferative rate), stage, and the primary site of origin, more than 50% of patients with NETs have regional or distant metastatic disease at diagnosis [2, 4]. Although NETs are considered rare malignancies, their incidence has markedly increased in recent

Table 1. Patient demographics and tumor characteristics

Patient	Gender/Age (years)	Primary Tumor Location	Metastatic Site(s)	Grade/Histology	AJCC Stage	Functional Status of Tumor
1	Female/62	Bronchial (typical)	None	Low/WD	1	Non-Functional
2	Male/59	Unknown	Pre-sacral mass/groin LNs	Low/WD	4	Non-Functional
3	Male/62	Pancreas	Liver, peritoneum, pleura and RP LNs	Low/WD	4	Non-Functional
4	Male/59	Cecum	Liver, peritoneum	Low/WD	4	Non-Functional
5	Male/60	Unknown primary	Liver and bone	Intermediate/WD	4	Functional
6	Male/61	Ileocecal valve	Liver	Low/WD	4	Non-Functional

Abbreviations: AJCC: American Joint Committee on Cancer; LNs: lymph nodes; RP: retroperitoneal; WD: well differentiated.

Table 2. Octreotide and lanreotide dosing

Patient	Duration of Previous Octreotide Therapy (months)	Last Octreotide dose	Reason for Switching to Lanreotide	Lanreotide Dose	Number of Depot Lanreotide Received
1	16	40 mg	Discomfort with 2 injections of octreotide	120 mg	12
2	36	30 mg	Progressive disease	120 mg	13
3	21	30 mg	Progressive disease	120 mg	9
4	8	30 mg	Serologic progression (CgA and serotonin trending up)	60 mg*	19
5	1	30 mg	Uncontrolled carcinoid symptoms	120 mg	4
6	11	40 mg	Progressive disease	120 mg	3

Abbreviations: CgA: chromogranin A. *Lanreotide dose reduced due to prior octreotide intolerance with diarrhea.

decades [2, 5, 6]. An analysis of the Surveillance, Epidemiology, and End Results database estimated that the incidence of NETs increased approximately 5-fold—from 1.09 to 5.25 cases per 100,000—in the United States between 1973 and 2004 [2].

Lanreotide depot (lanreotide), a synthetic somatostatin analog (SSA) that is indicated in the European Union for the treatment of symptoms associated with NET hormone hypersecretion, has also demonstrated antiproliferative tumor effects in NETs [7]. The CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study is a multinational, double-blind, placebo-controlled phase 3 trial of 204 patients, in which 120 mg of lanreotide (deep subcutaneous injection) or placebo were given every 28 days for 2 years (96 weeks) to locally advanced or metastatic, non-functional, well to moderately differentiated gastroenteropancreatic (GEP) NETs. The primary efficacy endpoint, progression-free survival, was significantly improved in the treatment group as opposed to placebo (median not reached in the lanreotide arm versus 18 months in the placebo group) with a hazard ratio of 0.47, suggesting a 53% reduction in the risk of disease progression or death with the use of lanreotide [7]. This finding assisted in the Food and Drug Administration's (FDA) approval of lanreotide deep subcutaneous injection as the first SSA for the treatment of unresectable, well to moderately differentiated GEP-NETs.

Octreotide long-acting release (LAR [octreotide]), which has similar affinity to somatostatin receptors 2 and 5 [8], is currently indicated in the United States for the treatment of acromegaly and severe diarrhea/flushing episodes associated with metastatic carcinoid tumors [1]; although it has demonstrated anti-proliferative activity in a phase 3 placebo controlled study (PROMID) of advanced midgut NET patients [9]. While the anti-tumor effects of SSA treatments have been well established, tolerability and efficacy of sequential SSA use (octreotide to lanreotide or vice versa) have not been well examined. In an institutional case series, we assessed the tolerability and response rate with lanreotide in NET patients who switched to lanreotide from octreotide due to disease progression, uncontrolled carcinoid symptoms, or intolerance to octreotide.

Methods

Following institutional review board approval, a retrospective search for patients with NETs was conducted within the Roswell Park Cancer Institute (RPCI) database. The database search

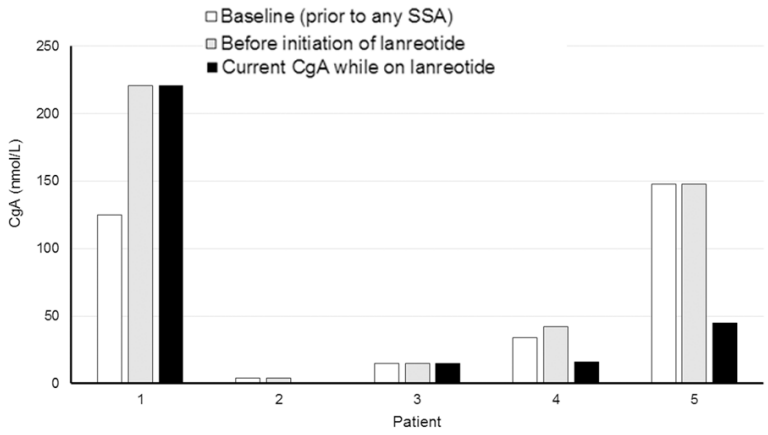

Figure 1. CgA serum levels in nmol/L (reference range 0-5.0 nmol/L). Abbreviations: CgA: chromogranin A; SSA: synthetic somatostatin analog.

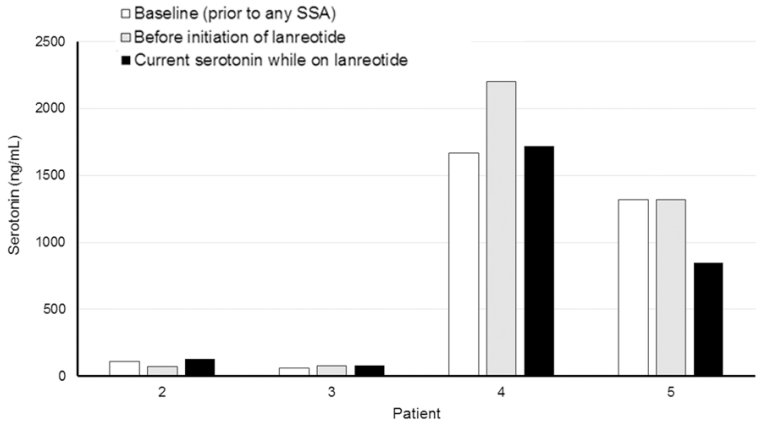

Figure 2. Serotonin serum levels in ng/mL (reference range 21-321 ng/mL). Abbreviation: SSA: synthetic somatostatin analog.

included the terms "lanreotide" and "neuroendocrine tumor." Patients were included in the case series if they received lanreotide for a minimum of 3 doses. The following demographic and baseline tumor information was gathered: Age, sex of the patient; Tumor characteristics including the grade, differentiation, primary site, and site of metastases; Data regarding the duration of previous octreotide treatment, the last octreotide dose, and the indication for the switch to lanreotide; Data regarding prior and concurrent treatments, apart from octreotide; Levels of relevant chemical markers (chromogranin A [CgA], 5-hydroxyindoleacetic acid [5-HIAA], platelet serotonin) from baseline (prior to starting any SSA treatment) to last level prior to starting lanreotide and current levels; Responses while on lanreotide; Adverse events (AEs) with lanreotide.

Disease progression was assessed by computed tomography scan at 6-month intervals or sooner as clinically appropriate, and by serologic markers.

Results

Sixteen NET patients being treated with lanreotide were initially identified; 6 patients (age range 59 to 62; 5 males, 1 female) with well-differentiated NETs who switched from octreotide to lanreotide and received at least 3 doses of lanreotide were identified from 06/2013 to the present. **Table 1** provides the tumor characteristics. Five patients had metastatic disease (to lymph nodes, liver, peritoneum, bone, and pleura). The primary tumor location among 3 of them was the pancreas, cecum, and small intestine, while 2 patients had unknown primary NETs. The remaining patient had a localized typical bronchial carcinoid tumor. All of the patients had non-functional, low-grade (<3% Ki-67 index) disease except for 1 patient who had intermediate-grade (3% to 20% Ki-67 index) tumor and presented with carcinoid syndrome.

Table 2 provides the dosing details of SSAs in these patients. The last dose of octreotide used in 4 of the 6 patients was the standard FDA-approved dose of 30 mg. Two patients received a higher dose of 40 mg octreotide. The starting and maximum dose of lanreotide in 5 patients was 120 mg. One patient was initiated on 60 mg of lanreotide based on clinical judgment due to prior octreotide-related diarrhea, a class adverse effect for SSAs. The average number of lanreotide injections administered to these 6 patients was 10, with a range from 3 to 19.

The reason for switching from octreotide to lanreotide was disease progression on imaging

Table 3. Efficacy and safety with lanreotide

Patient	Prior Treatments Other than Octreotide	Other Treatments Received While on Lanreotide	Response with Lanreotide (by CT Scan)	Duration of Response with Lanreotide	Adverse Events Related to Lanreotide
1	None	None	Stable disease	12 months and continuing	None
2	None	None	Stable disease	13 months	None
3	Everolimus (10 mg); Temozolomide/thalidomide; Temozolomide/capecitabine	Sunitinib (37.5 mg)	NE	NE	None
4	Surgery; RFA of liver metastases	None	Stable disease	19 months and continuing	None
5	SIR-spheres to bilateral liver metastases; Radiation to spine metastases	None	Imaging at 6-month interval is not done yet	4 months and continuing	None
6	Surgery; RFA/SIR-spheres for liver metastases	Bland embolization of liver metastases	NE	NE	None

Abbreviations: CT: computed tomography; NE: not evaluable because patients received other treatments while on lanreotide; RFA: radio-frequency ablation; SIR: selective internal radiation.

(n=3), discomfort with octreotide injections (n=1), serologic progression on octreotide (n=1), and uncontrolled carcinoid symptoms on octreotide (n=1).

The serum levels of the biomarker CgA at baseline (prior to initiation of any SSAs), before initiation of lanreotide and the most recent levels while on lanreotide were available for 5 patients; they are depicted in **Figure 1**. The CgA levels were either stable or decreased with initiation of lanreotide. **Figure 2** depicts the available serum serotonin levels for 4 patients at the same time points. In patients #4 and #5, who had serotonin levels above the reference range, lanreotide use resulted in a decrease from 2202 ng/mL to 1718 ng/mL and from 1321 ng/mL to 850 ng/mL, respectively.

As illustrated in **Table 3**, patient #1 had stable disease as evidenced by imaging studies for over a year and continues to use lanreotide for localized typical bronchial carcinoid symptoms. Patient #2 had a stable response with lanreotide for over a year and then had disease progression to the lymph nodes at which point he was switched to chemotherapy and all future SSAs were discontinued. Neither of these patients received any prior treatments other than octreotide. Patient #4 had a hemicolectomy and radiofrequency ablation of liver metastases prior to initiation of octreotide. He was switched to lanreotide due to serologic progression, which normalized with lanreotide. He received a total of 19 doses of lanreotide to date and continues to experience stable peritoneal disease. The duration of stable disease response in these 3 patients ranged from 12 to 19 months (mean of 14.6 months), with 2 of them having an ongoing response. Patient #3 had clinically aggressive disease requiring several targeted therapies and chemotherapy prior to lanreotide initiation. The patient was started on lanreotide while continuing on sunitinib treatment. He received a total of 9 doses of lanreotide and had stable disease for 4 or 5 months while on combination SSA and targeted therapy. Patients #5 and #6 had prior liver-directed therapy and surgical resection of tumor and were recently switched to lanreotide as detailed in **Table 3**.

There were no serious AEs reported with lanreotide in these patients. Patient #4 who had a history of octreotide-related diarrhea was switched to a lower dose of lanreotide. Diarrhea was not exacerbated by lanreotide in this patient and was well controlled with supportive care. There have been no treatment-related deaths with lanreotide to date. All patients are alive, except for patient #3, who died from disease progression.

Discussion

The sequential use of SSAs has been shown to be effective in acromegaly, especially for patients with treatment failure or side effects [10-12]. However, to date, there have been no prospective published trials assessing the effects of sequential use of SSAs (octreotide to lanreotide or vice versa) in NET treatment, although there have been case reports with small numbers of patients [13, 14]. A phase 2

study of pasireotide (600 to 900 μg subcutaneous twice daily) evaluated 45 patients with advanced NETs and symptoms of carcinoid syndrome that were inadequately controlled by octreotide [15]. Pasireotide controlled diarrhea and flushing in 27% of patients.

In our retrospective case series we showed that octreotide to lanreotide sequencing was well tolerated and was associated with stable biochemical and tumor responses. Most of the patients had stable to decreased serum biomarkers after switching treatment to lanreotide (**Figures 1** and **2**). In 3 evaluable patients, lanreotide produced a stable response (**Table 3**), with a mean duration of response of approximately 15 months (range 12 to 19 months) and 2 of those responses are ongoing. The response results in these 3 patients could be attributed to lanreotide, as they did not require any additional treatments for their disease while receiving lanreotide. Lanreotide was well tolerated with mild AEs of nausea, bloating, and steatorrhea. The CLARINET study reported the most common treatment-related AE of lanreotide was diarrhea, seen in 26% of patients [7]. No treatment-related AEs were noticed with lanreotide in our retrospective analysis.

While the transition from octreotide to lanreotide was well tolerated and appeared safe, the fact that all patients were at or over the maximal recommended dose of octreotide and transitioned to an approved dose of lanreotide should be considered when assessing safety and tolerability. Additionally, this was a retrospective assessment of all patients with NETs who had octreotide to lanreotide sequencing (n=6) at RPCI and efficacy outcome data (including progression-free survival and overall survival) and many lab values, particularly 24-hour urine 5-HIAA, were not available at the time of this analysis, limiting the conclusions that can be drawn. Furthermore, the size of the case study series (6 patients) and duration of some patients' treatment limited the ability to statistically evaluate and interpret the results.

Octreotide doses higher than the FDA-recommended dose of 30 mg are widely used in clinical practice for refractory carcinoid symptoms [16-19], which may necessitate more than 1 intramuscular injection at each visit. The use of prefilled lanreotide syringes may be a convenient and cost effective alternative compared with octreotide in acromegaly and NET patients [20, 21]. These features suggest a potential advantage of lanreotide 120 mg in patients with intolerance to or disease progression with conventional doses of octreotide. Further studies are warranted to establish the safety and potential improved outcomes with sequential SSA use.

Lanreotide was well tolerated in this small series of NET patients who experienced disease progression, intolerance, or poor symptom control with octreotide, producing a stable disease response for a mean duration of approximately 15 months. In sequencing from octreotide to lanreotide, levels of CgA and serotonin serological markers decreased or remained the same. The utility of sequential SSA treatment is potentially important for patients with NETs. Not all patients tolerate or achieve satisfactory efficacy with initial treatment. Additionally, some patients experience a return of symptoms over time [22]. Large prospective studies are needed to define the efficacy, safety, and cost-effectiveness of possible sequencing of SSA agents in NET patients.

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Disclosure of conflict of interest

Dr. Iyer is a consultant for Ipsen and Dr. Fong participated in an advisory panel for lanreotide. The remaining authors do not have financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article. *The authors retain full sole responsibility for the concept, analysis and all content in the final version for submission.*

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