Original Article

Real world use of lanreotide in neuroendocrine tumors

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Background: Treatment for metastatic neuroendocrine tumors (NETs) is often with somatostatin analogues (SSA) such as lanreotide in the first-line setting. Real world use of lanreotide in Canada is not well studied.

Methods: We performed a retrospective chart review of 69 patients to study real world use of lanreotide at our centre.

Results: Lanreotide was the first-line of systemic treatment in 60 patients. Watch-and-wait was a common strategy and was seen in 31 patients. SSA switch strategy was seldom applied. Majority of patients on lanreotide had low-grade NETs. Standard starting dose of lanreotide 120 mg every 28 days was used in 66 patients. Dose escalation to 120 mg every 21 days occurred in 7 patients. The primary intention for treatment was tumor control in 32 patients, and both tumor and symptom control in 34 patients. Median time on treatment was 21.6 months.

Conclusions: Overall, our findings were in keeping with current guidelines. It will be interesting to assess how clinical practice evolves in the future and to determine the role of dose escalation for disease control.

Keywords: Lanreotide; neuroendocrine; real world use; somatostatin analogue

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Introduction

Neuroendocrine tumors (NETs) are a heterogenous group of tumors that arise from neuroendocrine cells that are located diffusely throughout the body. Majority of NETs arise from the gastrointestinal tract and present with metastases. NET management is complex in that both tumor growth and hormone production must be addressed. Though rare, the incidence of NETs is rising with annual incidence rate of 6.98 per 100,000 persons in 2012 in USA. This was a 6-fold increase from 1973 (1). Canada has seen more than double the increase in the incidence rate over 15 years (2).

Due to its indolent nature, NETs are most commonly metastatic at presentation and when well differentiated, many can live for years (2). Characteristics like tumor morphology, mitotic count and Ki-67 are instrumental in predicting disease course and clinical behavior.

Multidisciplinary management is indicated for optimal outcome. Once metastatic, medical therapy is the mainstay of treatment. Somatostatin analogs (SSAs) such as octreotide and lanreotide are preferred in the first-line setting for well to moderately differentiated tumors that are not progressing quickly. In the PROMID trial, octreotide was found to significantly lengthen time to tumor progression in metastatic midgut NETs (3,4). Similarly, CLARINET study demonstrated improved progression free survival (PFS) with lanreotide in enteropancreatic NET patients (5). Given this evidence, SSAs are useful in not only controlling symptoms associated with carcinoid syndrome but are also

prescribed for their anti-proliferate properties.

Staying on SSAs for as long as they are effective is desirable given that other systemic options including targeted agents, chemotherapy and Peptide Receptor Radionuclide Therapy (PRRT) are often associated with additional toxicity in comparison to SSAs. Multiple international guidelines support the use of SSA in the first-line setting for well to moderately differentiated gastroenteropancreatic NETs (6,7).

Lanreotide has many advantages, including Ipsen patient injection support program, and the formulation being a subcutaneous injection where patients can be taught to self-inject. In addition to that, lanreotide is a preferred option over Octreotide in various settings such as extra midgut or higher grade NETs. The patient profile, optimal use, and sequencing of the lanreotide depot remains undefined. As well, there is limited data available for NET-treating physicians on how to use SSA-switch strategy if patients are not tolerating their initial SSA.

Recognizing the paucity of Canadian data on real world use on lanreotide, we conducted a single-centre retrospective analysis to study the use of lanreotide in the management of NETs at our institution. The Ottawa Hospital Cancer Centre (TOHCC) is a centralized tertiary care cancer centre which provides comprehensive medical, radiation, and surgical oncological care serving a population of over 1.3 million in Eastern Ontario.

The primary aim was description of lanreotide prescribing patterns for metastatic NETs. Secondary objectives were description of NET patients on lanreotide, including demographic and clinical features, NET treatment history, and as well as subsequent line of treatment. Time on treatment with lanreotide was also assessed. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1182/rc).

Highlight box

Key findings

- In management of metastatic NETs, use of lanreotide at a large tertiary care Canadian centre is in keeping with current guidelines allowing for introspection and practice affirmation.

What is known and what is new?

- Lanreotide is used for its anti-proliferative properties in the first-line setting for grade 1 and 2 NETs originating from various tumour sites.
- Real world use of lanreotide entailed use of 120 mg every 28 days and dose escalation was seldom employed.

What is the implication, and what should change now?

- Dose escalation of lanreotide post progression maybe considered in select patients as per CLARINET FORTE trial that confirmed that this strategy is well tolerated.

Methods

Study design

This study was a single centre, retrospective, observational evaluation of the management of patients with NETs treated with Somatuline® Depot (lanreotide) at TOHCC.

Participants

All patients aged ≥18 years diagnosed with NET who were initiated on lanreotide therapy at TOHCC were eligible for study enrollment. Patients were excluded if lanreotide was used for indications other than NET.

Data sources and measurements

Data sources for this study included medical records from the TOHCC for patients who were treated with Somatuline® Autogel® for NETs up until July 1, 2020 which was the cut off point for data collection. The earliest documented use was July 2014 and all patients in this study had NET pathologically confirmed.

Patients received treatment at the discretion of the medical oncologist, with no protocol-directed interventions. The lines of treatment were defined as treatment received by the patient after a diagnosis of NET. A new line of treatment was considered as the initiation of a new treatment. Lanreotide use after initiation of additional systemic therapy was defined as lanreotide use post progression.

Disease status was measured radiographically using conventional imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), biochemically using tumor markers such as chromogranin A (CgA) and clinically. Due to retrospective nature of the study, Response Evaluation Criteria in Solid Tumors (RECIST) criteria was not used to measure radiographic response.

Octreotide receptor status was measured using somatostatin receptor scintigraphy (SSRT) scan and

Table 1 Patient characteristics

Characteristics	Total n=69
Sex, n, %	
Female	22, 32
Male	47, 68
Age at diagnosis, year	
Mean (range)	63 (35–93)
Geographic setting, n, %	
Inside Ottawa metropolitan area*	35, 51
Outside Ottawa metropolitan area	34, 49
Survival status, n, %	
Alive	42, 61
Deceased	24, 35
Cancer-related death	18, 26
Non-cancer related death	6, 9
Lost to follow-up	3, 4

*, inside Ottawa metropolitan area was defined as city of Ottawa and neighboring suburbs.

Gallium-68 positron emission tomography (Ga-67 PET) scan. The results were categorized as positive, negative, or mixed as reported by the radiologist. Mixed described disease where some lesions showed somatostatin receptor positive disease while other lesions showed somatostatin receptor negative disease.

The duration of treatment with lanreotide was calculated. The duration of treatment was defined as the last patient encounter while on lanreotide minus clinic visit date when decision to start lanreotide was definitively made. For patients who died while on treatment with lanreotide, the date of death was used to estimate the end of treatment period.

The treatments were grouped by therapy class for the treatment pattern analysis as watch and wait, SSA, nuclear radiotherapy, external radiotherapy, targeted therapy, chemotherapy, surgery, and locoregional and ablative therapy.

Statistical analysis

No formal sample size calculation was performed. The sample size was driven by the number of eligible patients available. We enrolled all NET patients treated with lanreotide as the intention-to-treat population. All data were analyzed descriptively using Stata software package version 16. Analysis of patient characteristics included demographics, disease characteristics, systemic therapies. Continuous data were analyzed as mean and standard deviation, while categorical data were analyzed as absolute and relative frequencies.

Ethical statement

The study was approved by the Ottawa Health Science Network Research Ethics Board (No. IRB00002616) and performed in accordance with the ethical standard of the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Results

Patient characteristics

Overall, 69 patients met all the inclusion and exclusion criteria. Baseline patient and disease characteristics are outlined in *Table 1*. Within our cohort, 47 (68%) were male and the mean age of diagnosis was 63 (SD =12) years. By July 2020, which was the end of our follow up period, 24 (35%) patients were deceased, and cancer-related mortality was seen in 18 (26%) patients.

Disease characteristics

Disease characteristics are detailed in *Table 2*. The most common sites for primary disease were ileum and pancreas with 24 (35%) and 22 (32%) patients, respectively. Forty-three (62%) patients presented in metastatic setting. The most common sites of spread were the liver and lymph nodes at 49 (33%) and 46 (31%) occurrences, respectively. We found that 58 (84%) patients had either grade 1 or 2 disease.

Forty-three (62%) patients received an SSRT scan during the course of their disease. Of these patients, 37 (54%) patients were found to have positive SSRT disease. Four (6%) patients lacked uptake and two (3%) patients showed mixed uptake. Twenty-six (38%) did not receive an SSRT scan. We found that 18 (26%) patients received Ga-68 PET scan all of whom had uptake except for one (1%) patient who had mixed receptor status. Only 40% of patients who received Ga-68 PET scan had also received SSRT scan. Patients were also assessed for symptoms of

Table 2 Disease characteristics

Characteristic	Metastases, n, %
Primary location, n=69	
Lung	3, 4
Pancreas	22, 32
Stomach	2, 3
Duodenum	3, 4
Jejunum	1, 1
Ileum	24, 35
Caecum	1, 1
Colon	1, 1
Rectum	1, 1
Other	6, 9
Unknown	5, 7
Frequency of metastases location, n=149	
Liver	49, 33
LN or lymphatic system	46, 31
Lung	6, 4
Bone	16, 11
Peritoneum	14, 9
Other	18, 12
Tumour grade, n=69	
Well-differentiated grade 1	29, 42
Well-differentiated grade 2	29, 42
Well-differentiated grade 3	2, 3
Poorly differentiated grade 3	1, 1
Unknown	8, 12
Ki-67 index (%), n=69	
<2	16, 23
2–20	23, 33
>20	2, 3
Not available	28, 41
Mitotic rate (figures per 10 high power field), n=69	
<2	14, 20
2–20	3, 4
Not available	52, 75

Ga68 PET, gallium-68 positron emission tomography; LN, lymph node.

Table 3 Systemic therapies displayed in relation to lanreotide use

Treatment	Before lanreotide treatment, n, %	After lanreotide treatment, n, %
Octreotide LAR	4, 6	1, 1
Chemotherapy	3, 4	4, 6
External radiation therapy	6, 9	0
PRRT	1, 1	6, 9
Targeted therapy	1, 1	10, 14
Locoregional and ablative therapies	2, 3	0

LAR, long-acting release; PRRT, Peptide Receptor Radionuclide Therapy.

carcinoid disease. Diarrhea and flushing were noted in 17 (25%) and 28 (28%) cases, respectively.

Treatment characteristics

Watch-and-wait (WW) strategy before starting lanreotide was used in 31 (45%) patients of whom seven (10%) had pancreatic NET, 12 (17%) had small bowel NET and 12 patients (17%) had NET originating from other sites. Within the same WW population, 14 patients (20%) had Ki-67 <2%, 13 (19%) had Ki-67 2–20% and one patient (1%) had Ki67 >20%. Three patients (4%) did not have Ki-67 index reported. On an average, the time from diagnosis to administration of systemic treatment was 3.4 (0.4–18.4) years in our cohort.

Lanreotide was the first line of systemic treatment in 60 (87%) patients, second line in 5 (7%), and third line or later in 4 (6%) patients. Treatments received in relation to lanreotide use are shown in *Table 3*. Other than two patients (3%) who received locoregional and ablative therapies, there were no instances of administration of additional systemic therapy during treatment with lanreotide. Surgical resection occurred in 39 (57%) patients.

Where used, chemotherapy regimens included cisplatin/carboplatin and etoposide, or capecitabine and temozolomide. Targeted agents included sunitinib, everolimus and pazopanib. Locoregional and ablative therapies included chemoembolization, radiofrequency ablation, transarterial embolization and TheraSphere Yttrium microbeads.

The octreotide long-acting release (LAR) to lanreotide switch strategy was seen in two (3%) patients, and vice

Table 4 Characteristics of lanreotide therapy

Characteristic	n, %
Starting dose (mg), n=69	
120	66, 96
Indications for dose escalation, n=7	
Tumor progression	5, 7
Symptom control	1, 1
Indication not documented	1, 1
Method of administration, n=69	
Self-injection	2, 3
Injection program	64, 93
Not available	3, 4

Table 5 Characteristics of discontinuation of lanreotide

Characteristic	n, %
Lanreotide discontinued, n=69	
Yes	32, 46
No	37, 54
Reason for discontinuation, n=32	
Progression	18, 26
Side effects	7, 10
Other*	7, 10
Type of progression leading to discontinuation, n=25	
Progression of previous lesions	8, 32
New lesions	1, 4
Clinical	13, 52
Biochemical	3, 12
Lanreotide continued post-progression, n=27	
Yes	19, 28
No	8, 12
Side effects leading to discontinuation, n=10	
Diarrhea	3, 30
Hyperglycemia	2, 20
Abdominal pain	2, 20
Other**	3, 30

*, other reasons included competing co-morbidities such as liver failure, renal failure, cognitive dysfunction etc.; **, other events included fatigue, arrythmia, and constipation.

versa was observed in one (1%) patient. SSA switch strategy was defined as consecutive use of octreotide LAR and lanreotide. Three (4%) patients required the use of short-acting octreotide rescue medication in our study cohort. As expected, these patients had functional disease. Of the five patients (7%) who received both lanreotide and octreotide LAR along their treatment course, three (4%) had carcinoid syndrome.

Lanreotide use

A standard starting dose of lanreotide 120 mg every 28 days was administered to 66 (96%) patients as seen in *Table 4*. In 3 (4%) patients, lanreotide starting dose was lower than the standard dose of 120 mg every 28 days. Two (3%) of these patients were eventually dose escalated to the standard dose. Dose escalation beyond the standard dose to 120 mg every 21 days occurred in 7 (10%) patients which was the highest dose observed in our study cohort. Dose interruption was seen in 5 (7%) patients. The Ipsen home injection program was documented to be used by 64 (93%) patients to receive their treatment.

Lanreotide was started for progressive disease in 31 (45%) patients and for stable disease in 11 (16%) patients. In 27 (39%), disease trajectory was not established prior to treatment initiation. The primary intention for use was tumour control in 32 (46%) patients, symptom and tumour control in 34 (49%) patients, and only symptom control in three (4%) patients. Lanreotide discontinuation occurred in 32 (46%) patients. As seen in *Table 5*, the most common reason for discontinuation was disease progression seen in 18 (26%) patients which was characterized as clinical, radiographical and/or biochemical in nature. Clinical progression seen in 13 (52%) patients was most common given that it included patients who progressed to the point of cancer-related death as was noted in 7 (28%) patients. Seven (10%) patients discontinued treatment due to a combination of ten reported side effects as shown in *Table 5*. CgA was available in 45.8% (36.4–61.5%) instances to guide clinical decision making.

For the overall population, patients were maintained on lanreotide for a median time of 21.6 (0–35.2) months. Lanreotide was continued post progression in 11 (16%) patients. Six (9%) of these patients had functional disease. Other patients were continued on lanreotide due to reasons such as frailty, patient preference, contraindications to other therapies, and good safety profile associated with lanreotide.

Discussion

We conducted a single academic centre, retrospective analysis studying the real world practice of lanreotide use for NETs. We found that the majority of our patients were started on lanreotide in the first-line setting in keeping with Canadian guidelines which recommend SSA in first-line setting for gastrointestinal NET (GI-NET) that is either non progressive, or progressing and treatment naive (8). European guidelines also recommend use of SSAs in first line setting with preferential recommendation for Lanreotide over Octreotide for pancreatic NET (panNETs) by European NET Society (9,10). Similarly, North American guidelines recommend SSA as first-line for advanced panNETs that are SSRT imaging positive (6) which fits our study population. SSRT negative panNETs are rare and treatment approach is not clear (6). In our well-differentiated population, it was rare that patients were SSRT negative. This is reassuring given in real-life practice, often physicians will start SSA as they wait for this imaging test when patients are metastatic and progressing. Of note, our population had a lower number of Ga-68 PET imaging as part of their staging. This is explained by the fact this study spanned a time frame where access to Ga-68 PET in Canada was very limited.

In terms of disease monitoring, SSRT scan was usually only performed once during disease course to document somatostatin receptor status. Conventional imaging modalities like CT and MRI were used for routine monitoring. Biochemical markers such as CgA were used in less than half of patients and its use has fallen out of favour in clinical practice. Dam *et al.* found CgA to be an unreliable marker of tumor progression with sensitivity of only 36% (11).

We commonly used the standard dose of lanreotide 120 mg every 28 days and the intention for use was mainly either tumor control or both tumor and symptom control. This is in keeping with results of CLARINET study which showed significant improvement in PFS compared to placebo in metastatic enteropancreatic NET. CLARINET study included patients with grade 1–2 tumors (5). This was consistent with the use of lanreotide at our centre where only a minority of our patients had high grade NET.

Most of our patients had NETs originating from midgut or pancreas. This was also consistent with CLARINET study which showed clinical benefit in enteropancreatic tumors. Rarer NETs treated with lanreotide at out centre included Merkel cell and thymus NET. This has been previously described in the literature (12).

About 25% of our patients progressed on lanreotide with a median time on treatment of 21.6 months for the overall study cohort. We compared our results with original CLARINET trial in which the median PFS of the lanreotide arm was not reached with 65% patients being progression free at two years (5). The overall median PFS of the patients in lanreotide arm of the core CLARINET study and then continued on it in the open label extension study was 38.5 months and varied with tumor origin (13). It was not surprising that our time on treatment of 21.6 months was less given that our real world data did not report PFS. Nonetheless we showed a robust time on treatment.

Lanreotide was approved for treatment of NETs in Canada in 2014 and we studied its use at our centre since then till July 2020. As a result, we had the benefit of capturing its use as an anti-tumor agent in early phase of its use. Very few patients were dose escalated to lanreotide 120 mg every 21 days as the highest dose used in our cohort. This is certainly interesting given the recent CLARINET FORTE study (14) in which increased lanreotide frequency, from every 28 days to every 14 days, was studied in patients with progressive pancreatic or midgut NET. Patients had grade 1–2 tumors and had progressed on at least 24 weeks of standard regimen of lanreotide. With dose escalation, there was PFS of 8.3 and 5.6 months in patients with progressive midgut and pancreatic NETs, respectively. Post-hoc subgroup analysis of panNETs showed PFS of 8.0 months with Ki67 ≤10%. No new safety signals were identified at the higher dose and quality of life was acceptable. It will be interesting to see how clinical practice surrounding use of lanreotide evolves in the near future.

WW strategy is used to delay the onset of unwanted side effects and to prevent exhaustion of all treatment possibilities. CLARINET study saw that progression was significantly delayed in the group receiving lanreotide even when the majority of patients on this trial were non-progressing at initiation (5). In keeping with numerous guidelines, WW strategy for NET treatment is used in real-life practice. We found that roughly half of our patients were managed in this manner. This approach was more common in slow growing tumors with Ki-67 index <20%. We showed that this is a reasonable approach for panNET and does not appear to be associated with tumor grade. Therefore, we hypothesize that other factors such as pace of disease and disease burden are driving this decision. WW

approach was also endorsed by Mendis *et al.* who reported a median time duration of 23.6 months prior to lanreotide initiation (15). For octreotide LAR group, median time to treatment initiation was 9.6 months. This was likely due to changes in practice over time as octreotide group likely represented earlier patient cohort. Their study span was 1990 to 2015.

SSA switch strategy was seldom used at our centre. British Columbia Cancer Agency reported higher use of SSA strategy (15). Rather it was seen that introduction of other treatment modalities such as targeted therapy or nuclear radiation therapy was instead initiated at our centre which is keeping with current Canadian guidelines (8).

Limitations of our study include its single-centre retrospective design, which may not be generalizable to other populations. However, eligibility was reflective of all patients treated with lanreotide at our centre since Health Canada approval. Another limiting factor was the sample size. However, we must consider that NET is a rare disease with incidence in rising and the study provides insight into the profile of first patients treated with lanreotide in Canada. External validity and generalisability of results were not an aim of the study. Yet, patient level data contributes to understanding local practice patterns, of which Canadian use of SSAs for low grade NETs is lacking. The carry-over effect is a possible effect of the internal validity in observational studies. However, since lanreotide was intended as first line therapy, carry-over effects are not relevant.

Conclusions

Overall, the use of lanreotide at our academic centre is in keeping with current guidelines. Lanreotide is being used for its antiproliferative properties in majority of cases. It is most often used in first line setting. Standard dose of 120 mg every 28 days is the most common dose being used and dose escalation is seldom seen. It will be interesting to see if practice changes given the results of the CLARINET FORTE study showing meaningful PFS with dose-escalation while maintaining a known safety profile.

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Footnote

Reporting Checklist: The authors have completed STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1182/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1182/coif). TA is a consultant for Ipsen and involved in enrolling patients in clinical trials. MV is a consultant for Amgen, a speaker for Merck and is involved in enrolling patients in clinical trials. RG is a member of advisory board for Ipsen, Pfizer, Eisai, Roche, Bayer, AAA and Apobiologix. She is a speaker for Merck, Viatris, Pfizer and Amgen. She received independent educational grants from Pfizer and Eisai and Apobiologix. She is also involved in enrolling patients in clinical trials. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ottawa Health Science Network Research Ethics Board (No. IRB00002616) and performed in accordance with the ethical standard of the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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