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Clinical Benefits of Above-Standard Dose of Octreotide LAR in Patients With Neuroendocrine Tumors for Control of Carcinoid Syndrome Symptoms: A Multicenter Retrospective Chart Review Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine tumor • Carcinoid syndrome symptoms • Somatostatin analogs • Flushing • Diarrhea • Above-standard dose

ABSTRACT

Background. Octreotide LAR is used in patients for control of carcinoid syndrome (CS) and other symptoms of hormone hypersecretion. The aim of this study was to examine reasons for octreotide LAR dose escalation and observe CS symptom improvement in patients with neuroendocrine tumors (NETs) who underwent octreotide LAR dose escalation at three cancer referral centers.

Methods. Medical records for patients with diagnosis of carcinoid or pancreatic NET who had received one dose or more of octreotide LAR above 30 mg every 4 weeks from 2000 to 2012 were reviewed. Reasons for dose escalation and symptomatic outcomes were abstracted for each patient 3 months prior to and up to 12 months following the dose escalation.

Results. Of the evaluated 239 NET patients, 53% were male, mean age at first dose escalation was 60 years (standard deviation [SD]: 11 years), and mean time from octreotide LAR initiation to first dose escalation was 1.7 years (SD: 2.0 years). The primary reasons reported for dose escalation were carcinoid or hormonal syndrome (62%) or radiographic progression (28%). The most common dose changes at the first dose escalation were 40 mg every 4 weeks (71%) and 60 mg every 4 weeks (18%). Of 90 patients in whom flushing was reported prior to first dose escalation, 73 (81%) were reported to have experienced improvement or resolution of their symptoms following the dose escalation. Of 107 patients who were reported to have experienced diarrhea before the first dose escalation, 85 (79%) were reported to have experienced improvement or resolution after first dose escalation.

Conclusion. The goal of improved symptom control is a common reason for dose escalation of octreotide LAR. This study suggests that escalation to above the standard dose of octreotide LAR of 30 mg every 4 weeks may result in improved CS symptom control. ***The Oncologist*** 2014;19:930–936

Implications for Practice: The goal of improved symptom control is a common reason for dose escalation of octreotide LAR above 30 mg every 4 weeks. Patients may experience improved symptom control following dose escalation above the standard doses.

INTRODUCTION

Neuroendocrine tumors (NETs) originate from neuroendocrine cells in the digestive tract, pancreas, lung, and liver. According to results from the Surveillance, Epidemiology, and End Results (SEER) database, there were 5.25 new cases per 100,000 persons in 2004 in the U.S. [1]. The primary clinical manifestation of functional intestinal NETs is carcinoid syndrome (CS), which occurs in approximately 8%–35% of patients with well-differentiated NETs, most typically in the small intestine, with incidence ranging from 1.7% to 18.4% [2]. The release of bioactive substances is a marker of CS [2]. The most prominent of these substances is serotonin, which is metabolized to 5-hydroxyindoleacetic acid (5-HIAA). Chromogranin A (CgA) is a secretory product of most NETs and is used as a marker for tumor burden [3]. CS manifests through four key symptoms: flushing (occurs in 94% of patients with CS), diarrhea (78%), cardiac disease caused by valvular heart lesions (53%), and abdominal pain or cramping (51%) [4, 5].

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First-line systemic therapy for metastatic NETs frequently comprises somatostatin analogs (SSAs) such as octreotide or lanreotide, which inhibit the secretion of gastrointestinal hormones [6]. SSAs alleviate symptoms of CS, including diarrhea and flushing, and hormonal syndromes associated with advanced pancreatic NETs [7]. Emerging evidence demonstrates that SSAs also significantly inhibit tumor progression in patients with well-differentiated NETs [8, 9].

The doses of octreotide LAR approved by the U.S. Food and Drug Administration (FDA) range from 10 mg to 30 mg every 4 weeks [10]. In clinical practice, however, higher doses and dose frequencies are often prescribed to patients who experience refractory CS (e.g., flushing and diarrhea) or uncontrolled CS symptoms. In a survey study conducted by Anthony et al. in 2004, 20%–40% of patients in the clinical practice received octreotide LAR doses higher than the FDA-approved maximal dose to adequately control symptoms or to suppress tumor progression [11]. However, this study did not further investigate the underlying reasons why physicians chose to prescribe higher doses. Another retrospective study reported on dose or frequency increases of octreotide LAR among NET patients, using the SEER-Medicare database. In this study, Xu et al. found that approximately 38% of patients received doses greater than 30 mg every 4 weeks [12]. Additional evidence of the administration of higher doses of octreotide LAR in the clinical practice setting was examined in a longitudinal database created by the National Comprehensive Cancer Network (NCCN) [13]. In the NCCN database, 82 patients (40%) with carcinoid NETs and 15 patients (23%) with pancreatic NETs received above-label doses of octreotide LAR, primarily to treat uncontrolled symptoms [13].

Furthermore, previous studies have reported CS symptom resolution or improvement observed among patients with progressive disease (i.e., symptomatic progression of CS symptom or tumor progression) with higher doses of octreotide LAR [14–16]. However, these studies were either conducted at one clinical center or had a small study population, which limits the generalizability of the study findings. To further understand the extent of prescription of octreotide LAR above the standard dose across multiple cancer centers, the present study evaluated treatment patterns for octreotide LAR, reasons for administering an above-standard dose, and the relationship between the administration of an above-standard dose of octreotide LAR and CS symptom improvement.

Materials and Methods

Study Design

A multicenter retrospective medical record review of patients with a confirmed diagnosis of carcinoid or pancreatic NET was conducted during the period of November 2012 through May 2013 at three large cancer referral centers (Dana-Farber Cancer Institute, Moffitt Cancer Center and Research Institute, and Robert H. Lurie Comprehensive Cancer Center of Northwestern University). The study protocol was approved by the institutional review board committees of the three cancer referral centers. NET patients who received care during the period between January 1, 2000, and December 31, 2012 were assessed for eligibility.

Patient Selection Criteria

To be eligible, patients had to be at least 18 years of age; have a confirmed diagnosis of advanced NET; have received at least one dose of octreotide LAR on or after January 1, 2000, with at least one dose escalation and/or dose-frequency escalation above the standard dose of 30 mg every 4 weeks; and be actively treated at one of the three tumor referral centers during the study period. Patients with poorly differentiated or high-grade tumors were excluded from the study.

Data Collection

A standardized case report form was developed to be used for the abstraction of data from patient medical charts. Information was collected on patient demographics, medical history, CS symptoms and other conditions associated with NET, octreotide LAR treatment patterns including dose and frequency of administration of octreotide LAR, reasons for octreotide LAR initiation and dose escalation, concomitant medications, serum CgA and 24-hour urine 5-HIAA laboratory values, and tumor progression or response. Octreotide LAR dose administration was standardized to a dosage on a basis of every 4 weeks (e.g., 30 mg every 3 weeks was converted to 40 mg every 4 weeks). Medical chart abstraction was completed using a web-based case report form. No identifiable patient information was collected, as per the Health Insurance Portability and Accountability Act.

Dose escalation was defined as an increase in the dosage or dose frequency of octreotide LAR above the standard octreotide LAR dose of 30 mg every 4 weeks. Subsequent dose escalations resulting in a consecutive increase in dosage or dose frequency relative to the prior dosage or dose frequency were recorded. The date of the first octreotide LAR dose escalation for each patient marked the beginning of the study observation period. Comorbidities and medical treatment history were assessed during the 6-month period immediately prior to the initial dose escalation. For the assessment of CS symptoms, clinical information was abstracted 3 months immediately prior to the first dose escalation episode and up to the earliest of 12 months after dose escalation, occurrence of death, loss to follow-up, or subsequent dose escalation. Safety data were not collected and assessed in this study. Data collection was completed in May 2013. Figure 1 depicts the study design scheme.

Statistical Analysis

Descriptive statistics were computed for all eligible patients. Continuous data were expressed as mean $\pm$ SD and median. Categorical data were reported as percentages. The main clinical outcome was change in hormonal symptoms to assess the effectiveness of an above-standard dose of octreotide LAR in controlling CS symptoms. Among patients who reported flushing or diarrhea as CS symptoms prior to dose escalation, the proportion of patients whose symptoms resolved or improved after dose escalation and the proportion of patients for whom CS symptoms remained the same or worsened were reported. As a sensitivity analysis to control for potential confounding from concomitant treatments received, patients who initiated another treatment (e.g., liver-directed therapy or interferon-α) 30 days before or after the first dose escalation were excluded from the analysis. Data management and

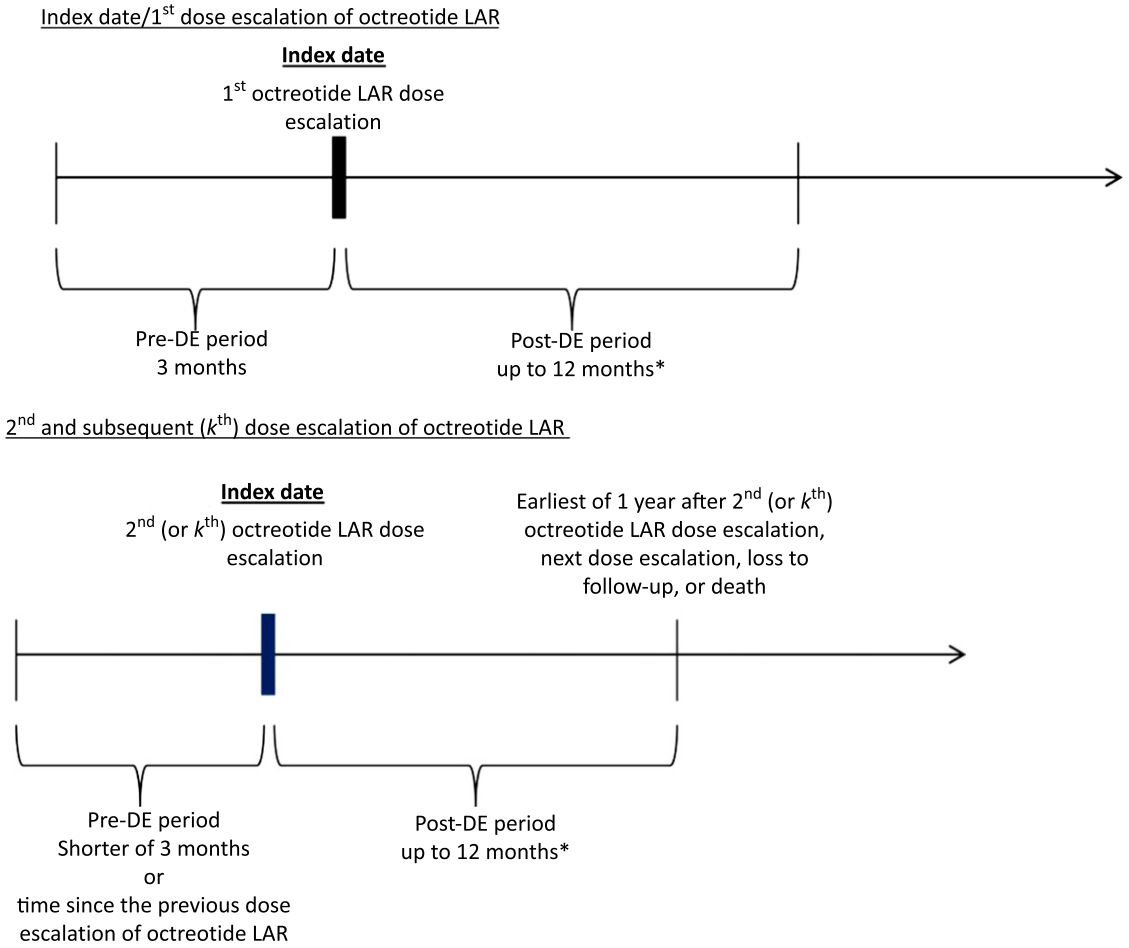

Figure 1. Study design scheme.

∗, The actual length of the post-DE period used in the comparative evaluation varies based on the timing of the next dose escalation, loss to follow-up, or death.

Abbreviation: DE, dose escalation.

statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, http://www.sas.com).

Results

Medical records for 239 NET patients who received octreotide LAR above the standard dose of 30 mg every 4 weeks were reviewed. Table 1 presents the patient demographics. Among the evaluated patients, 53% were male, 89% were non-Hispanic white, and mean age at initial dose escalation of octreotide LAR was 60 years (SD: 11 years). Death was recorded for 118 patients (49%) and was primarily caused by tumor progression (64%). Carcinoid and pancreatic NETs were diagnosed in 212 patients (89%) and 27 patients (11%), respectively. Of the patients diagnosed with carcinoid tumor, the most commonly reported primary sites were in the small bowel (n = 76, 36%) and ileocecal valve (n = 72, 34%). Moreover, 203 patients (85%) were observed to have hormonal syndrome at the time of NET diagnosis, with CS being the most prevalent type (93%).

The median initial octreotide LAR dosage received was 20 mg every 4 weeks (range: 10–53.3 mg every 4 weeks). The mean time between NET metastatic diagnosis and initiation of octreotide LAR was 1.1 years (SD: 2.2 years). Presence of carcinoid syndrome was the most common reason reported for the initiation of octreotide LAR (69%). Other nonmutually exclusive reasons reported were antiproliferative effect (29%), noncarcinoid syndrome (e.g., weight loss, fatigue, and pain; 11%), somatostatin receptor expression (10%), radiographic progression of disease (14%), and biomarker elevations (5%). Only two patients received octreotide LAR as part of a clinical trial. These patients were included in the analyses.

Approximately 74% of patients (n = 177) received NET-directed concomitant treatment during the observational period (i.e., time period after the first dose escalation and up to 12 months after dose escalation). Liver-directed therapy consisting of various embolizations and radiofrequency ablation was the most common concomitant treatment and was administered to 97 patients (55%). Other concomitant treatments administered included interferon-α, radiation therapy, targeted therapy (e.g., everolimus and sunitinib), temozolomide, bevacizumab, capecitabine, streptozotocin, fluorouracil, and doxorubicin.

All patients evaluated in this study received at least one dose of octreotide LAR above the standard dose of 30 mg i.m. (intragluteally) every 4 weeks. Among the 239 patients, 36% received a second dose escalation during the observation period. Third, fourth, and fifth and sixth dose escalations were observed in 8%, 2%, and less than 1% of patients, respectively.

Table 1. Demographic and clinical characteristics of NET patients

Characteristic	Total NET patients ($N = 239$)
Age at NET diagnosis, years, mean (SD)	57 (11)
Center, *n* (%)	
Dana-Farber	101 (42)
Moffitt	92 (39)
Northwestern	46 (19)
Male, *n* (%)	127 (53)
Non-Hispanic white, *n* (%)	212 (89)
Type of tumor, *n* (%)	
Carcinoid	212 (89)
Pancreatic NET	27 (11)
Primary site of tumor among carcinoid, *n* (%)[a]	
Small bowel	76 (36)
Ileocecal	72 (34)
Bronchial (lung)	7 (3)
Other[b]	17 (8)
Unknown primary site	45 (21)
Patients with confirmed metastasis, *n* (%)	234 (98)
Site of metastasis among patients with confirmed metastasis, *n* (%)[c]	
Liver	191 (82)
Lymph nodes	50 (21)
Secondary soft tissue site	30 (13)
Gastrointestinal organs	27 (12)
Other (reproductive organs, bone, breast, lung)	40 (17)
Patients with hormonal syndrome at NET diagnosis, *n* (%)	203 (85)
Carcinoid syndrome, *n* (%)	188 (93)
Other (insulinoma, gastrinoma, glucagonoma, VIPoma) , *n* (%)	15 (7)

[a]Primary site of tumor categories do not sum up to 100% because categories were not mutually exclusive.
[b]Other primary site of tumor includes colorectal, jejunal, gastric, duodenal, and mesenteric.
[c]Percentages do not sum up to 100% because events were not mutually exclusive.
Abbreviations: Dana-Farber, Dana-Farber Cancer Institute; Moffitt, Moffitt Cancer Center and Research Institute; NET, neuroendocrine tumor; Northwestern, Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The mean time from octreotide LAR initiation to the first dose escalation was 1.7 years (SD: 2.0 years). The primary reasons reported for dose escalation were carcinoid or hormonal syndrome (62%) or radiographic progression (28%). The most common dose changes at the first dose escalation were 40 mg every 4 weeks (51%), 30 mg every 3 weeks (18%), and 60 mg every 4 weeks (18%). The highest first dose escalation was 80 mg every 4 weeks and was observed in three patients (i.e., prior dosage was 30 mg every 4 weeks for 2 patients and 40 mg every 4 weeks for 1 patient). One patient who had a total of 6 dose escalation episodes received 160 mg every 4 weeks of octreotide LAR at the sixth dose escalation. Table 2 provides the distribution of octreotide LAR dosage administered by dose escalation episode.

Evidence of symptoms related to NET was examined through a medical record review for all patients prior to dose escalation of octreotide LAR. Table 3 reports the number of patients with CS 3 months prior to octreotide LAR dose escalation and provides the proportion of patients with CS symptoms for all dose escalations. Prior to the first dose escalation, CS symptoms were reported for 147 patients (62%) within the 3 months. Among all NET patients, symptoms included flushing (12%), diarrhea (18%), or a combination of flushing and diarrhea (31%).

CS symptom improvement was recorded in the medical record among patients who reported CS symptoms prior to a dose escalation of octreotide LAR and had a known clinic visit after dose escalation. Of the 90 patients for whom flushing was reported prior to the first dose escalation, 73 (81%) were reported to have experienced improvement or resolution of their symptoms following the dose escalation. Of the 107 patients for whom diarrhea was reported prior to the first dose escalation, 85 (79%) were reported to have experienced improvement or resolution of their symptoms following the dose escalation. To control for potential confounding from concomitant treatments received, patients who initiated another treatment (e.g., liver-directed therapy or interferon-α) 30 days before or after the first dose escalation were excluded from the analysis. Similar results (resolution or improvement after dose escalation; 80% flushing and 77% diarrhea) were observed when patients who received these concomitant treatments were excluded. Table 4 is focused on only the patients who reported CS symptoms and summarizes the findings of CS symptom improvement for subsequent dose escalations.

Discussion

This multicenter retrospective chart review study evaluated octreotide LAR dose escalation and possible effects on carcinoid symptoms in a large sample of NET patients across three major cancer referral centers in the U.S. The results suggest that an above-standard dose of octreotide LAR may result in improved CS symptom control among NET patients with CS symptoms prior to dose escalation. Comparable findings were observed when potential confounders such as concurrent treatments around the time of dose escalation were accounted for. This multicenter study result is consistent with another retrospective chart review study that was conducted at one cancer referral center, Moffitt Cancer Center and Research Institute, and all patients at Moffitt who met the eligibility criteria were part of this current study [16]. Strosberg et al. reported that among 41 patients with diarrhea, 63% reported improvement of diarrhea after the first dose escalation of octreotide LAR [16]. The authors also reviewed charts for the 39 patients with flushing and found that 56% of these patients experienced improvement after first dose escalation of octreotide LAR [16].

Results from this study are consistent with evidence in the published literature suggesting that an above-standard dose of octreotide LAR may provide improvement of CS symptoms and supporting the administration of these higher doses for the control of CS symptoms [14, 15]. Chadha et al. performed a retrospective chart review of patients with gastroenteropancreatic NET who received octreotide LAR between June 1, 2002, and September 30, 2007, at Roswell Park Cancer Institute

Table 2. Distribution of octreotide LAR treatment regimen by dose escalation episode

	Dose escalation episodes, *n* (%)						
Octreotide LAR dose administration[a,b]	**Initial (*n* = 239)**	**Dose prior to first increase[c] (*n* = 239)**	**First (*n* = 239)**	**Second (*n* = 86)**	**Third (*n* = 20)**	**Fourth (*n* = 5)**	**Fifth (*n* = 2)**
Temporarily off octreotide LAR[d]	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown dosage[e]	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dose every 4 weeks							
10 mg	9 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
20 mg	115 (48)	23 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
25 mg[f]	4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
27 mg	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
30 mg	107 (45)	209 (87)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
40 mg[g]	3 (1)	3 (1)	170 (71)	6 (7)	3 (15)	0 (0)	0 (0)
50 mg	0 (0)	0 (0)	4 (2)	5 (6)	0 (0)	0 (0)	0 (0)
53 mg	1 (0)	0 (0)	19 (8)	41 (48)	3 (15)	3 (60)	1 (50)
60 mg	0 (0)	0 (0)	42 (18)	28 (33)	3 (15)	0 (0)	0 (0)
67 mg	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
70 mg	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
80 mg	0 (0)	0 (0)	3 (1)	1 (1)	9 (45)	1 (20)	0 (0)
107 mg	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	1 (20)	0 (0)
120 mg	0 (0)	0 (0)	0 (0)	1 (1)	1 (5)	0 (0)	0 (0)
133 mg	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)

[a]Octreotide LAR dose administration was standardized at a dosage on a basis of every 4 weeks. Fifty-eight observations of patients who were temporarily off octreotide LAR treatment were not reported in this table because these patients participated in a clinical trial or were placed on a lower octreotide LAR dosage.
[b]One patient with a sixth dose escalation episode reported a dosage of 160 mg every 4 weeks.
[c]Dose reported after octreotide LAR treatment initiation and prior to the first dose escalation.
[d]Two patients from the Dana-Farber Cancer Institute were temporarily off treatment prior to the first dose escalation.
[e]One patient from the Dana-Farber Cancer Institute was transferred from another center and the dosage prior to the first dose escalation was unknown.
[f]Imputation using the overall mean dose and mean frequency was performed for observations that had missing initial dose or frequency because the patient had received care elsewhere. Four observations were imputed. The actual value used for imputation was 24.5 mg every 4 weeks.
[g]Among the 170 individuals prescribed 40 mg every 4 weeks at the first dose escalation, 44 patients were prescribed with a dosage of 30 mg every 3 weeks, 122 patients were prescribed with a dosage of 40 mg every 4 weeks, and 4 patients were prescribed with 20 mg every 2 weeks.

Table 3. Carcinoid syndrome status 3 months before dose escalation

	Dose escalation episodes, *n* (%)				
Symptom status	**First (*n* = 239)**	**Second (*n* = 86)**	**Third (*n* = 20)**	**Fourth (*n* = 5)**	**Fifth (*n* = 2)**
Patients reporting CS	147 (62)	57 (66)	13 (65)	2 (40)	2 (100)
Symptoms reported[a]					
Flushing only	29 (12)	11 (13)	2 (10)	0 (0)	2 (100)
Diarrhea only	42 (18)	20 (23)	2 (10)	1 (20)	0 (0)
Flushing and diarrhea	74 (31)	26 (30)	9 (45)	1 (20)	0 (0)
Hypoglycemia[b]	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown CS status	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No CS[c]	92 (38)	29 (34)	7 (35)	3 (60)	0 (0)

[a]CS symptom categories reported 3 months prior to dose escalation were mutually exclusive events.
[b]One patient from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University reported hypoglycemia as a CS symptom.
[c]No flushing or diarrhea was selected when the patient chart explicitly stated that no flushing or diarrhea was observed. If no information was provided, "unknown" was selected.
Abbreviation: CS, carcinoid syndrome.

[14]. The authors found that high dose of octreotide LAR was well tolerated, and no toxicities were reported among the 30 patients (~56%) who required octreotide LAR above the dose of 20–30 mg every 4 weeks [14]. In a multicenter open-label study, Ferolla et al. examined the effect of 30 mg every 3 weeks of octreotide LAR on tumor progression, serum markers, and CS symptoms [15]. This study enrolled 28 patients who had received 30 mg every 4 weeks of octreotide LAR and were given 30 mg every 3 weeks of octreotide LAR for a median duration of 30 months. Ferolla et al. reported that 40% of cases had

Table 4. Carcinoid syndrome status after dose escalation

DE	3 months before DE, n	Up to 12 months after DE[a], n (%)	
		Resolved or improved	Remained the same or worsened
First[b]			
Flushing	90	73 (81)	17 (19)
Diarrhea	107	85 (79)	22 (21)
Second			
Flushing	27	21 (78)	6 (22)
Diarrhea	38	24 (63)	14 (37)
Third			
Flushing	10	6 (60)	4 (40)
Diarrhea	10	7 (70)	3 (30)
Fourth			
Flushing	1	0 (0)	1 (100)
Diarrhea	0	0 (0)	0 (0)
Fifth			
Flushing	1	1 (100)	0 (0)
Diarrhea	0	0 (0)	0 (0)

[a]Patients with unknown CS symptoms assessment status in the post-DE period were excluded from the analysis.
[b]CS symptom categories were not mutually exclusive events.
Abbreviations: CS, carcinoid syndrome; DE, dose escalation.

complete normalization of symptoms (e.g., flushing, diarrhea, and bronchospasm), and partial symptomatic control was observed in the remaining 60% [15].

Guidelines from the North American Neuroendocrine Tumor Society published in 2013 recommend increased dosage or more frequent doses of SSAs to control refractory CS [17]. In the 2013 consensus report on the use of SSAs, the committee recommended that physicians treating NET increase the dose and/or frequency of SSAs in an attempt to control refractory CS, with a note that no prospective study has been conducted [17]. For these patients, standard dosing may not be sufficient to obtain symptom control; therefore, an above-standard dose of SSA may be considered as an attempt to control CS symptoms associated with NET. Additional recommendations (e.g., National Comprehensive Cancer Network) and consensus reports have recommended considering an increase of dosage or dose frequency of octreotide LAR for refractory CS symptoms [18–20].

This study is subject to some limitations stemming primarily from its retrospective nature. First, the frequency of physician visits and assessments varied by patient, and that may have had some impact on the recording of CS symptom status within the predefined observation period of the study. Second, because all data were collected solely from physicians' notes in patients' medical charts, occurrences of CS symptoms and their status over time may be underreported. Third, information on the status of flushing or diarrhea (e.g., resolution or improvement) was not substantiated by quantitative measures and could be contaminated by recall or reporting bias from the patient or the physician. Finally, results reported in this study are based on data collected at three cancer referral centers and may not reflect practice patterns observed at other institutions.

Conclusion

Our study suggests that the goal of improved symptom control is a common reason for dose escalation of octreotide LAR above 30 mg i.m. (intragluteally) every 4 weeks and that patients may experience improved symptom control following dose escalation above the standard doses. Prospective studies to confirm the effect of higher doses of octreotide LAR above 30 mg i.m. (intragluteally) every 4 weeks on symptoms are warranted.

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Disclosures

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For Further Reading:

James C. Yao, Diane Reidy Lagunes, Matthew H. Kulke. Targeted Therapies in Neuroendocrine Tumors (NET): Clinical Trial Challenges and Lessons Learned. ***The Oncologist*** 2013;18:525–532.

Implications for Practice:

With the approval of two new drugs, everolimus and sunitinib, for the treatment of patients with well-differentiated pancreatic neuroendocrine tumors, we are witnessing a shift from case series and single-arm studies toward prospective, randomized controlled clinical trials and evidence-based therapy in the neuroendocrine tumor field. However, the clinical development of these agents highlights the potential challenges awaiting other new drugs in this area. Focusing on the strengths, weaknesses, and limitations inherent in trial design can help identify pitfalls and potentially hasten the approval of drugs successfully developed to treat patients with neuroendocrine tumors.