Above-Label Doses of Octreotide-LAR in Patients With Metastatic Small Intestinal Carcinoid Tumors

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ABSTRACT

BACKGROUND: Octreotide LAR is indicated for treatment of malignant carcinoid syndrome and has been studied at doses of 10 to 30 mg intramuscularly every 4 weeks. In clinical practice, higher doses are often prescribed for patients who experience refractory carcinoid syndrome (flushing and/or diarrhea) or tumor growth while on the maximum label-recommended dose.

METHODS: We performed a retrospective, longitudinal review of octreotide LAR administration at a tertiary institution to determine the frequency of above-label dosing and outcomes.

RESULTS: Three hundred thirty-eight patients were considered evaluable, among whom 100 (30%) underwent at least 1 increase in dose or frequency of octreotide-LAR above the standard label dose. The most common maximum doses were 40 mg every 4 weeks ($n = 37$ patients), 60 mg every 4 weeks ($n = 34$), and 30 mg every 3 weeks ($n = 18$). The indications for dose increase were worsening carcinoid syndrome ($n = 60$), radiographic progression ($n = 33$), and rising urine 5-HIAA ($n = 6$). Of the patients whose doses were increased for refractory carcinoid syndrome, 62% ($n = 34$) experienced improvement in diarrhea, and 56% ($n = 28$) experienced improvement in flushing.

CONCLUSIONS: In conclusion, octreotide LAR is commonly prescribed in doses or schedules above the recommended dose and frequency. Patients with refractory carcinoid syndrome appear to experience a clinical benefit from this change. Prospective data may be used to further evaluate this strategy.

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Metastatic neuroendocrine tumors (NETs) of the distal small intestine and cecum (embryonic midgut) commonly produce serotonin and other vasoactive products, including prostaglandins and tachykinins.¹ Secretion of these substances into the systemic circulation produces symptoms such as flushing, diarrhea, and cardiac valvular fibrosis, otherwise known as the malignant carcinoid syndrome.^{2,3} The human hormone somatostatin was found to be a potent inhibitor of serotonin release in patients with metastatic midgut NETs.⁴ However, the therapeutic application of native somatostatin was limited by its short half-life. Synthetic somatostatin analogues (SSAs) have been developed to prolong somatostatin's duration of activity. Oc-

treotide and lanreotide are two commercially available SSAs that bind with high affinity to somatostatin receptor subtype 2 (sst₂) and with moderate affinity to sst₅.⁵ In a landmark phase II study, subcutaneous octreotide was found to inhibit serotonin production and palliate the carcinoid syndrome in most patients treated at a dose of 150 μ g 3 times daily.⁶ During the past decade, a long-acting repeatable (LAR) depot formulation of octreotide has been available that enables monthly intramuscular dosing. Octreotide LAR was tested at doses ranging from 10 to 30 mg every 4 weeks.⁷ In this trial, up to 40% of patients needed rescue doses of short-acting octreotide for symptom control, independent of the monthly LAR dose. There was no evidence of cor-

relation between the octreotide LAR dose and symptomatic improvement in flushing or diarrhea; however, suppression of urine 5-HIAA appeared to be inferior in the 10-mg study arm compared with that in the 20- or 30-mg arms. As a result, the FDA label recommends a starting dose of 20 mg, with titration to 30 mg in patients with suboptimally controlled symptoms.

The highest dose of octreotide LAR tested prospectively in patients with metastatic NET is 30 mg every 4 weeks.⁷ This dose and schedule, while clinically active, is not the maximum tolerated dose. Sub-

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Table 1 Demographics and tumor characteristics

Characteristic	n	%
Age, y		
Median	60	
Range	21–83	
Sex		
Male	166	49
Female	172	51
Race		
White	300	89
African American	18	5
Other*	20	6
Carcinoid syndrome		
Present at baseline	100	32
Present subsequently	133	43
Absent	77	25
Tumor grade		
Low	246	73
Intermediate	41	12
High	1	0
Unspecified	50	15
Presenting symptoms		
Abdominal pain	149	44
Diarrhea	153	45
Flushing	138	41
Bowel obstruction	69	20
GI bleeding	20	6
Nausea and/or Vomiting	13	4
Wheezing	7	2
Incidental Diagnosis		
Yes	56	17
No (symptomatic)	281	83
Elevated 5-HIAA		
Yes	269	83
No	54	17
Carcinoid heart disease		
Present at baseline	20	6
Present subsequently	13	5
Location of metastases at baseline		
Liver	297	88
Mesentery	179	53
Peritoneum	78	23
Retroperitoneum	43	13
Ovaries	25	7
Bone	10	3

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stantially higher doses (eg, 90 mg every 4 weeks⁸) have been investigated in other malignant diseases and found to be tolerable. In clinical practice, above-label doses are often prescribed for patients with metastatic NETs who show suboptimal control of carcinoid syndrome (flushing and/or diarrhea) or tumor growth while on the maximum label dose.⁹ Moreover, dose escalations for patients with refractory symptoms are recommended by several key organizations, including the National Comprehensive Cancer Network (NCCN) consensus guidelines¹⁰ and the North American Neuroendocrine Tumor Society (NANETS).¹¹

To test the efficacy of this therapeutic strategy, we performed a retrospective, longitudinal review of octreotide LAR administration at a tertiary institution. The specific goals of this study were to determine the frequency of above-label dosing and outcomes associated with dose increases after initiation of octreotide.

METHODS

A retrospective chart review was performed of cases from a database of all patients with metastatic midgut (jejunal, ileal, or cecal) NETs seen at the Moffitt Cancer Center between 2000 and 2010. Data abstraction included severity of baseline carcinoid syndrome (frequency of flushing and diarrhea), baseline levels of urine 5-hydroxyindoleacetic acid (5-HIAA) and serum chromogranin A (CgA), starting dose and frequency of octreotide, reason for initiation of octreotide (carcinoid syndrome, radiographic disease progression, antiproliferative effect, or other), and response to treatment (severity of flushing, diarrhea, and urine levels of 5-HIAA and serum CgA). All subsequent escalations of the dose and frequency of octreotide were documented, along with the reasons for dosing change and the responses to dose escalation.

The definition used for an above-label dose of octreotide LAR included any regimen that exceeded 30 mg every 4 weeks. Thus, 30 mg every 3 weeks was considered above-label; however, 20 mg every 3 weeks (equivalent to 26.6 mg every 4 weeks) was not considered above-label. All patients were counted as having an above-label dose once it exceeded 30 mg every 4 weeks after initiation of octreotide. Eight

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Characteristic	n	%
Lung	8	2
Breast	6	2
Primary reason for initiation of octreotide		
Carcinoid syndrome	220	65
Antiproliferative	103	30
Radiographic progression	14	4
Unknown	1	1

* Hispanic, Asian/Pacific Islander, or Native American.

Figure 1. CONSORT diagram illustrating reasons for dose escalations of octreotide LAR.

patients were excluded for having an above-label dose at initiation of treatment. A patient was considered to have 2 or more dose escalations if the above-label doses occurred consecutively. Because of the retrospective nature of this study, quantitative measurements of changes in flushing and diarrhea were not typically available. We therefore considered any documentation of symptomatic improvement associated with treatment changes as a clinical response. We did not attempt to measure the effect of octreotide dose changes on radiographic tumor measurements, given the lack of a standardized schedule or method of imaging before and after dose changes. Statistical analysis was conducted using Stata SE 10.0 software (Stata, College Station, TX). All tests were 2-sided, and statistical significance was declared at $P < .05$. Institutional approval was obtained for the study.

RESULTS

Patient Characteristics

We identified 458 patients with metastatic NETs who had a proven or suspected midgut primary site. Nearly all patients (99%) received octreotide therapy during their disease course. Among these patients, 338 had sufficient longitudinal follow-up at Moffitt Cancer Center to enable data abstraction for this study. The median age at onset of octreotide therapy was 60 years (range, 21–83). The male-to-female ratio was 1:1 (166 men and 172 women). One hundred sixty-eight patients (50%) had flushing, 214 (63%) had diarrhea, and 14 (4%) had carcinoid heart disease at baseline. Reasons for initiation of octreotide LAR included control of carcinoid syndrome in 220 (65%) patients, antiproliferative effect in 103 (30%) patients, and radiographic progression in 14 (4%) patients.

The patient and tumor characteristics are summarized in Table 1.

Dose Escalations

One hundred (30%) patients were found to have received doses and/or frequency of octreotide LAR above the standard label dose of 30 mg every 4 weeks. The reasons for dose escalation included symptomatic progression of carcinoid syndrome ($n = 60$), radiographic progression ($n = 33$), and rising urine 5-HIAA levels ($n = 6$; Figure 1). The most common maximum doses were 40 mg every 4 weeks ($n = 37$), 60 mg every 4 weeks ($n = 34$), and 30 mg every 3 weeks ($n = 18$; Table 2). Twenty-six patients underwent more than 1 dose escalation, including 23 with 2 escalations and 3 with 3 escalations. Ten patients received an above-label dose and then were decreased back to the standard dose.

Response to 1 Dose Escalation

Of the 74 patient who had 1 dose escalation, responses were evaluated among the 47 patients in whom octreotide was increased above the label levels due to suboptimal control or progression of carcinoid syndrome. Of these patients, 41 had documented diarrhea at the time of dose escalation and 39 had flushing. Among the patients with diarrhea, 26 (63%) reported some degree of improvement after dose escalation, 1 (2%) had further progression of diarrhea, and 4 (10%) had no change. Of the patients with flushing, 22 (56%) experienced improvement, 2 (5%) had progression, and 5 (13%) had no change (Figure 2).

Response to 2 Dose Escalations

Of the 23 patients who had 2 dose escalations, responses to the second dose escalation were evaluated in the 11 patients in whom octreotide was increased because of suboptimal control or progression of carcinoid syndrome. All 11 of these patients had documented diarrhea at the time of dose escalation, and 9 had flushing. Among the patients with diarrhea, 7 (64%) reported some degree of improvement after dose escalation and none (0%) had further progression of diarrhea documented. Of those with flushing, 5 (56%) experienced improvement, and none (0%) had documented progression.

Table 2 Maximal octreotide-LAR doses stratified by number of dose escalations

One Dose Escalation		Two Dose Escalations		Three Dose Escalations	
(mg q wk)	n	(mg q wk)	n	(mg q wk)	n
30 q 3	18	30 q 3		30 q 3	
30 q 2		30 q 2	2	30 q 2	
40 q 4	36	40 q 4	1	40 q 4	
40 q 3		40 q 3		40 q 3	
50 q 4	2	50 q 4		50 q 4	
50 q 3		50 q 3	1	50 q 3	
60 q 4	16	60 q 4	18	60 q 4	
60 q 3	1	60 q 3		60 q 3	2
70 q 4	1	70 q 4		70 q 4	
90 q 4		90 q 4	1	90 q 4	
90 q 3		90 q 3		90 q 3	1

Figure 2. Symptomatic responses to initial above-label dose escalation among patients with suboptimal control of carcinoid syndrome.

DISCUSSION

Patients with carcinoid syndrome who have suboptimal control of symptoms frequently receive above-label doses of octreotide LAR in clinical practice. Indeed, the National Comprehensive Cancer Network (NCCN) recommends initiation of octreotide LAR at doses of 20 to 30 mg every 4 weeks with upward titration of doses for symptom control.¹⁰ Moreover, several ongoing and planned randomized clinical trials used high-dose octreotide LAR in the control arm.¹² However, there are no prospective studies evaluating doses or frequencies of administration in excess of 30 mg every 4 weeks, and very little retrospective data have been published in support of this practice. Therefore, we sought to investigate patterns of octreotide LAR administration at a tertiary referral center for NETs,

with a focus on metastatic carcinoid tumors of the jejunum and ileocecum (midgut).

We found that approximately 30% of patients with metastatic midgut carcinoid tumors treated at our institution underwent dose escalations beyond the label dose of 30 mg every 4 weeks. The primary indication for dose escalation was suboptimal control of the carcinoid syndrome, particularly flushing and diarrhea. Among these patients, a majority (63% of patients with diarrhea, 56% of patients with flushing) reported some degree of improvement after initial upward titration of octreotide LAR. However, the precise magnitude of benefit was difficult to ascertain on medical chart review. The data were also insufficient to ascertain whether escalation of octreotide LAR affected the velocity of tumor progression.

This study was designed to collect information on real-world clinical practice and outcomes but was limited by its retrospective design. Quantitative measurements of flushing and diarrhea before and after dose changes were not available from the retrospective charts in most cases. Instead, we primarily relied on generic statements such as “patient reports improvement in diarrhea and flushing,” to document response to dose titration. Such statements, however, may be prone to various biases, including recall and response biases on the part of the patient and reporting bias on the part of the treating physician. Prospective studies, utilizing detailed patient diaries for carcinoid symptoms when feasible, may provide additional information about the magnitude of improvement in these symptoms after dose escalation.

The results of this single-institution study are reflective of the practice patterns of a limited number of physicians. It is unclear whether similar titrations of octreotide LAR occur in other academic institutions or in community practices. A planned database analysis of NETs treated at 7 NCCN institutions will provide additional information on octreotide dosing in a broader population of patients. Even larger registries, such as SEER-Medicare, may allow for evaluation of national practice patterns, but are unlikely to provide detailed information on treatment response.

SUMMARY

Our institutional analysis of 338 patients with metastatic midgut carcinoid tumors demonstrated that above-label doses of octreotide LAR are commonly prescribed, primarily for patients with suboptimal control of their carcinoid syndrome. Most of these patients appeared to derive symptomatic benefit from this strategy. Prospective studies may further validate these findings.

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Disclosures of Potential Conflicts of Interest

Dr. Jonathan Strosberg has served on advisory boards for Novartis. Dr. Larry Kvols served on the Novartis Speakers Bureau.