Association between Duration of Somatostatin Analogs (SSAs) Use and Quality of Life in Patients with Carcinoid Syndrome in the United States Based on the FACT-G Instrument

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Background and Objectives

- Carcinoid syndrome (CS) results from secretion of bioactive amines, peptides, and polypeptides by functional neuroendocrine tumors (NETs)[1]
  - Symptoms may include diarrhea, flushing, wheezing, and less frequently carcinoid heart disease, characterized by cyanosis and/or peripheral edema[1]
- In one study, among US patients with NET identified between 2000 and 2011, 19% were found to have CS at diagnosis, with common subgroups such as metastatic well-differentiated small bowel NET manifesting CS in over 50% of cases[2]
- Patients with NET and CS often report reduced quality of life (QoL), particularly in areas of fatigue, general health, and physical role limitations; frequent bowel movements and flushing episodes have been shown to be significantly associated with decreased health-related QoL[3]
- The first-line systemic therapy for metastatic NETs frequently includes somatostatin analogs (SSAs) such as octreotide or lanreotide[4]
  - Octreotide, approved in 1988, is indicated for the symptomatic treatment of metastatic carcinoid tumors, targeting severe diarrhea and flushing[5]; lanreotide was approved in 2014 for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic NET to improve progression-free survival[6]
  - SSAs inhibit the secretion of gastrointestinal hormones and alleviate symptoms of CS associated with advanced NETs, such as diarrhea and flushing, and hormonal syndrome[4]
- The objective of this study was to assess the association between the duration of SSA use and QoL among patients with CS symptoms using the validated Functional Assessment of Cancer Therapy-General (FACT-G) instrument

Methods

Data Source

- Patients with CS symptoms in the US were recruited via Neuroendocrine Cancer Awareness Network (NCAN), a patient advocacy group, for an online, anonymous survey between July 21 and October 31, 2016
  - Eligible patients were at least 18 years old, diagnosed with NET and CS by a physician, and received either SSA or non-SSA treatments for CS symptoms control
  - Examples of SSAs included lanreotide, octreotide, and pasireotide. Examples of non-SSAs included cyproheptadine, diphenoxylate-atropine, diphenhydramine, loperamide, ranitidine, and telotristat etiprate
- The survey consisted of demographic characteristics (e.g., gender, age, race), clinical characteristics (e.g., site of NET, time since NET and CS diagnoses, treatments received, CS symptoms such as flushing episodes, bowel movements, and activity levels), and QoL questions from the FACT-G questionnaire
- Data were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act
  - All study materials were approved by the New England Independent Review Board
  - Patients provided their informed consent prior to responding to the survey questions

Statistical Analyses

- FACT-G item subscale (Physical Well-Being [PWB], Social Well-Being [SWB], Emotional Well-Being [EWB], and Functional Well-Being [FWB]) and total scores were calculated using the algorithm from the scoring manual[7]
  - A higher score on FACT-G scales indicates better QoL[7]
- Descriptive analyses assessing patient demographic and clinical characteristics were conducted using means and standard deviations (SDs) for continuous variables and frequencies and proportions for categorical variables
- Multivariable linear regression analyses, adjusting for demographic (gender, age, and race) and clinical characteristics (carcinoid/NET type, number or frequency of symptoms, and current activity level), were performed to assess the association between duration of SSA use and total FACT-G score, as well as FACT-G subscales
- A sensitivity analysis was conducted using a multilevel hierarchical model to adjust for the nested effect of duration of SSA use within duration of time since CS diagnosis
  - Level 1 included SSA duration and patient characteristics
  - Time since CS diagnosis was treated as a random effect in Level 2
- To illustrate the association between duration of SSA use and QoL, duration of SSA use was categorized into quartiles (<2.7, 2.7–4.42, 4.43–8.0, and >8.0 years)
- Statistically significant associations were noted for *P*-values < 0.05

Results

Demographic and Clinical Characteristics

- Of the 117 patients who completed the online survey, the majority were female (77%) and Caucasian (91%), with a mean age of 58.0 years (**Table 1**)

Table 1. Demographic Characteristics

	All Patients (N=117)	
Age (years), mean (SD)	58.0	(9.8)
Female, N (%)	90	(77%)
Race, N (%)[1]		
Caucasian	106	(91%)
Black or African American	6	(5%)
Hispanic or Latino	5	(4%)
Asian/Pacific Islander	0	(0%)
Native American/American Indian	1	(1%)
Other	3	(3%)

SD, Standard Deviation.
[1]Patients were allowed to select multiple responses.

- The most common primary site of NET was ileum (47%), and the mean (SD) time from NET diagnosis to date of survey completion was 8.3 (6.0) years (Table 2)
- The mean time from NET diagnosis to diagnosis of CS was 1.2 years
- The most frequently reported CS symptoms among the six different symptoms queried in the survey included carcinoid diarrhea (97%), flushing (91%), peripheral edema (46%), and wheezing (41%)
- At the time of the survey, 86% had CS symptoms without required bed rest or required bed rest during <50% of the waking day

Table 2. Clinical Characteristics

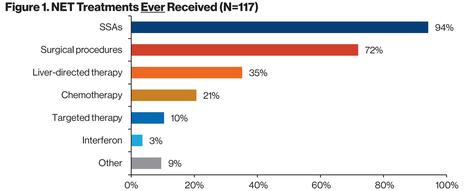
	All Patients (N=117)	
Primary site of NET, N (%)[1]		
Ileum	55	(47%)
Appendix	12	(10%)
Lung	11	(9%)
Stomach	11	(9%)
Duodenum	10	(9%)
Colon	10	(9%)
Jejunum	6	(5%)
Rectum	0	(0%)
Other primary site[2]	30	(26%)
Time from NET diagnosis to survey completion date (years), mean (SD)	8.3	(6.0)
Time from CS diagnosis to survey completion date (years), mean (SD)	7.1	(5.5)
Number of CS symptoms experienced, mean (SD)	3.0	(1.1)
CS symptoms experienced after NET diagnosis, N (%)[1]		
Carcinoid diarrhea	114	(97%)
Flushing	106	(91%)
Peripheral edema	54	(46%)
Wheezing	48	(41%)
Carcinoid heart disease	15	(13%)
Cyanosis	14	(12%)
Current activity level, N (%)		
I have normal activity, without symptoms	11	(9%)
Have symptoms, but do not require bed rest during waking day	70	(60%)
Require bed rest during <50% of waking day	30	(26%)
Require bed rest during ≥50% of waking day	6	(5%)
Unable to get out of bed	0	(0%)

CS, Carcinoid Syndrome; NET, Neuroendocrine Tumor; SD, Standard Deviation.
[1]Patients were allowed to select multiple responses.
[2]Other primary NET sites include patient-submitted mentions of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.

Treatment Characteristics

- Common NET treatments that were ever received included SSAs (94%), surgical procedures (72%), and liver-directed therapy (35%) (**Figure 1**)

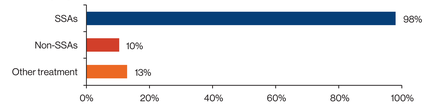
Figure 1. NET Treatments Ever Received (N=117)



CS, Carcinoid Syndrome; NET, Neuroendocrine Tumor; SSA, Somatostatin Analog.
Other NET treatments include: peptide-receptor radionuclide therapy and external beam radiation (outside of liver).

- For CS symptom treatment, the large majority of patients reported receiving SSAs in the past month (98%) (**Figure 2**)
  - A possible explanation as to why a greater percentage of patients reported SSA use for treatment of CS vs treatment of NET (98% vs 94%, respectively) may be that patients understood SSA to be prescribed for CS symptom control only
- The mean duration of CS symptoms treatment with SSAs was 6.1 (SD: 4.7, range: 0.3-21.3) years
  - 43% of patients treated with SSA reported receiving SSA treatment for >5 years

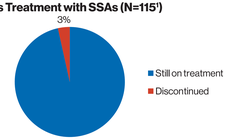
Figure 2. CS Symptoms Treatments Received in the Past Month (N=117)



CS, Carcinoid Syndrome; SSAs, Somatostatin Analogs.
Other CS treatments include patient-submitted mentions of: anti-nausea medication, Cap/Tem chemotherapy, chemo embolization, Creon, Fentora for pain, Lyrica diabetic neuropathy, MIBG, narcotic analgesics, somatuline, surgery, Telestar, tincture of opium, and TSCE.

- Most patients were still receiving CS symptoms treatment with SSAs (97%) at the time of the survey (**Figure 3**)

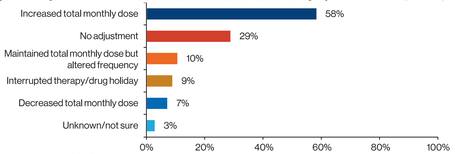
Figure 3. CS Symptoms Treatment with SSAs (N=115[1])



CS, Carcinoid Syndrome; SSA, Somatostatin Analog.
[1]Base: patients treated with SSAs for CS symptoms control.

- The most commonly reported reason for SSA treatment adjustment was increased total monthly dose of SSA (58%), while 29% of patients did not have any treatment adjustment (**Figure 4**)

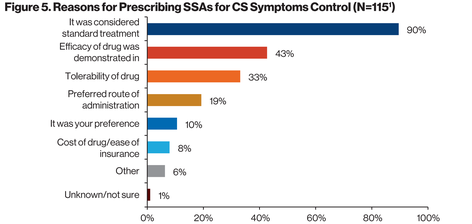
Figure 4. Adjustments Made to Treatment with SSAs for CS Symptoms Control (N=115[1])



CS, Carcinoid Syndrome; SSA, Somatostatin Analog.
[1]Base: patients treated with SSAs for CS symptoms control.

- The most frequently given reason for prescription was that SSA was standard treatment (90%), followed by demonstrated efficacy (43%), and tolerability (33%) (**Figure 5**)

Figure 5. Reasons for Prescribing SSAs for CS Symptoms Control (N=115[1])



CS, Carcinoid Syndrome; SSA, Somatostatin Analog.
[1]Base: patients treated with SSAs for CS symptoms control.

FACT-G Quality of Life Scores

Descriptive analysis

- The mean (SD) FACT-G total score was 67.6 (20.0), which is lower than the general U.S. population score of 80.1 (18.1)[7] (**Table 3**)
- PWB, SWB, EWB, and FWB mean scores were also lower than those of the general U.S. population

Table 3. FACT-G Scores

FACT-G score, mean (SD)	Possible Range	All Patients (N=117)		General U.S. Population[7]	
FACT-G total	0 - 108	67.6	(20.0)	80.1	(18.1)
PWB	0 - 28	17.8	(6.4)	22.7	(5.4)
SWB	0 - 28	18.6	(6.5)	19.1	(6.8)
EWB	0 - 24	16.0	(4.7)	19.9	(4.8)
FWB	0 - 28	15.3	(6.7)	18.5	(6.8)

EWB, Emotional Well-Being; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; PWB, Physical Well-Being; SD, Standard Deviation; SWB, Social Well-Being; US, United States.

Multivariable regression analysis

- After adjustment, the FACT-G total score was significantly (11.3 points; *P*=0.033) higher (better) for patients treated with SSA >8 years (4th quartile) compared to those treated with SSA for <2.7 years (1st quartile). Similar patterns were observed for two FACT-G subscales - PWB and FWB (**Table 4**)

Table 4. Multivariable Predictors of FACT-G Scores

Total patients (N=117)	FACT-G Total		PWB		SWB		EWB		FWB	
Patient characteristics	**Est.**	**P-value**	**Est.**	**P-value**	**Est.**	**P-value**	**Est.**	**P-value**	**Est.**	**P-value**
Male	0.5	0.922	0.1	0.952	0.0	0.998	-0.3	0.812	0.6	0.679
Age (years)	0.2	0.301	0.1	0.291	0.1	0.129	0.0	0.539	0.0	0.878
Race (ref: Caucasian)										
Black or African American	16.7	0.059	4.3	0.124	4.2	0.146	2.6	0.245	5.7	0.055
Hispanic or Latino	2.6	0.798	3.7	0.252	-4.5	0.172	1.6	0.526	1.8	0.597
Other	-5.4	0.566	-1.5	0.608	-0.4	0.884	-1.7	0.478	-1.7	0.582
Clinical/symptom characteristics										
Carcinoid/NET type										
Ileum	7.1	0.129	2.4	0.103	1.8	0.246	1.3	0.278	1.7	0.292
Appendix	1.2	0.851	0.9	0.661	-0.6	0.759	-0.1	0.973	1.0	0.638
Lung	-4.4	0.514	-1.2	0.577	-1.2	0.587	0.0	0.982	-2.0	0.379
Stomach	-6.2	0.357	-2.4	0.265	-0.9	0.668	-1.3	0.453	-1.6	0.473
Duodenum	-2.4	0.742	-4.4	0.056	3.8	0.111	0.1	0.971	-1.8	0.456
Colon	-21.6	0.004*	-5.9	0.012*	-6.5	0.007*	-1.8	0.344	-7.4	0.003*
Jejunum	-3.2	0.711	5.6	0.043*	-5.2	0.064	-1.6	0.482	-2.0	0.488
Other primary site[1]	6.0	0.258	1.6	0.324	2.5	0.145	0.1	0.938	1.7	0.330
Duration of SSA treatment[2] (years, ref: 1st quartile = 0-2.7)										
2nd quartile (2.7–4.4)	-0.2	0.964	0.4	0.810	-0.9	0.598	-0.1	0.918	0.4	0.820
3rd quartile (4.4–8.0)	-5.9	0.296	-0.8	0.639	-3.3	0.077	-0.3	0.858	-1.6	0.408
4th quartile (>8.0)	11.3	0.033*	4.1	0.013*	1.1	0.534	2.3	0.083	3.7	0.034*

Est. (Parameter) Estimate; EWB, Emotional Well-Being; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; NET, Neuroendocrine Tumor; PWB, Physical Well-Being; Ref, Reference (Group); SSA, Somatostatin Analog; SWB, Social Well-Being.
*P<0.05.
[1]Other primary NET sites included patient-submitted responses of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.
[2]Patients who did not receive SSA treatment were categorized into the first quartile.

Sensitivity analysis

- Adjusting for patient demographic and clinical characteristics and treating time since CS diagnosis as a random effect, the hierarchical model showed patients treated with SSA >8 years had significantly higher FACT-G total scores compared to patients treated with SSA for <2.7 years (by 11.7 points; *P*=0.017) (**Table 5**)

Table 5. Hierarchical Model of the Multivariable Predictors of FACT-G Total Score

Total patients (N=117)	FACT-G Total	
Patient characteristics	**Est.**	**P-value**
Male	-0.3	0.951
Age (years)	0.2	0.271
Race (ref: Caucasian)		
Black or African American	15.4	0.076
Hispanic or Latino	1.9	0.860
Other	-4.7	0.559
Clinical/symptom characteristics		
Carcinoid/NET type		
Ileum	7.1	0.134
Appendix	-0.3	0.960
Lung	-7.4	0.255
Stomach	-9.4	0.138
Duodenum	1.3	0.844
Colon	-23.5	<0.001*
Jejunum	-3.0	0.707
Other primary site[1]	5.1	0.326
Time since CS diagnosis to survey date (years) (ref: 0-5)		
>5 to 10	-	-
>10	-	-
Duration of SSA treatment[2,3] (years, ref: 1st quartile = 0-2.7)		
2nd quartile (2.7-4.4)	0.1	0.979
3rd quartile (4.4-8.0)	-6.1	0.292
4th quartile (>8.0)	11.7	0.017*

CS, Carcinoid Syndrome; Est. (Parameter) Estimate; FACT-G, Functional Assessment of Cancer Therapy-General; NET, Neuroendocrine Tumor; Ref, Reference (Group); SSA, Somatostatin Analog.
*P<0.05.
[1]Other primary NET sites included patient-submitted responses of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.
[2]Patients who did not receive SSA treatment were categorized into the first quartile.
[3]Duration of SSA treatment and time since CS diagnosis are highly correlated with a 0.86 Pearson correlation coefficient (P<0.0001).

Limitations

- Recruitment was conducted primarily through NCAN, which may have resulted in a potentially biased sample not fully representative of the heterogeneous NET patient population.
- Potential survival bias may exist – patients who lived with CS longer may be healthier and have better QoL regardless of the treatment received. However, a sensitivity analysis was performed to include both SSA treatment duration and duration of time since CS diagnosis in a hierarchical model to adjust for the nested effect, and the same trends were seen
- All data were self-reported and could have been subject to recall bias
- Results are based on QoL assessment at a single time point

Conclusions

- Almost all patients (98%) taking part in this survey study reported using SSAs for CS symptom control. The mean duration of SSA use was 6.1 years. The most commonly reported CS symptoms were carcinoid diarrhea (97%) and flushing (91%)
- Patients treated with SSAs longer than 8 years had significantly higher (better) FACT-G total score and PWB and FWB subscale scores when compared to patients treated with SSAs for fewer than 2.7 years
- This study suggests that the duration of SSA use was positively associated with QoL benefit among CS patients. This may be explained by long-term effectiveness and tolerability of SSAs. However, there is also the possibility that selection bias favoring patients with more indolent disease (in longer duration group) may have had some effect on the results. Future studies will be needed to distinguish between these possibilities
- The results contribute additional findings on the impact of long-term CS symptoms control with SSAs on QoL using FACT-G

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