Improvement of Carcinoid Syndrome (CS) Symptoms and Quality of Life in CS Patients Treated with Somatostatin Analogs

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Background and Objectives

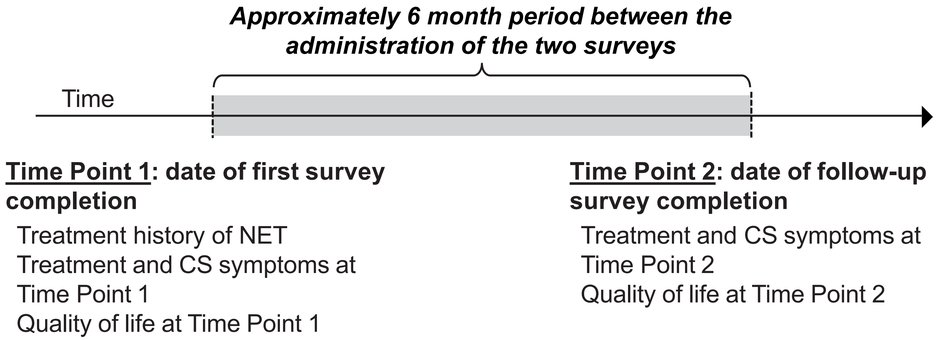
- Carcinoid syndrome (CS) results from the secretion of bioactive amines, peptides, and polypeptides by functional neuroendocrine tumors (NETs)[1]
  - Symptoms may include diarrhea, flushing, wheezing, and less frequently carcinoid heart, cramping, cyanosis, and peripheral edema[1]
- In one SEER study, among US patients with NET identified between 2000 and 2011, 19% were found to have CS at diagnosis[2]
- Among patients with NET and CS, reduced quality of life (QoL) is often reported, specifically in areas of fatigue, general health, and physical role limitations; in particular, symptoms such as frequent bowel movements and flushing episodes have been shown to be significantly associated with health-related QoL[3]
- First-line systemic therapy for metastatic NETs typically includes somatostatin analogs (SSAs) such as octreotide or lanreotide[4], both approved for carcinoid syndrome symptom control
  - 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]
- Currently, there is limited information on the longitudinal impact of CS symptoms and QoL in patients with CS who receive SSAs in a real-world setting
- The objective of this study was to assess the change over time in CS symptoms and QoL, measured by the validated Functional Assessment of Cancer Therapy-General (FACT-G) instrument, among patients with CS

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 that was administered at two time points: Time Point 1 (between July 21, 2016 - October 31, 2016) and Time Point 2 (between February 3, 2017 - April 30, 2017) **(Figure 1)**

Figure 1. Study Design



- 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 symptom control
  - SSAs included lanreotide, octreotide, and pasireotide. 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 sub-domain and total scores were calculated using the algorithm from the scoring manual[7]
  - A higher score on FACT-G scales indicates better QoL[7]
  - FACT-G sub-domains included Physical Well Being (PWB), Social Well Being (SWB), Emotional Well Being (EWB), and Functional Well Being (FWB)
  - FACT-G total score between 3-7 points and FACT-G sub-domains between 2-3 points were considered to meet the minimally important difference (MID) threshold[7]

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Methods (Contd.)

Statistical Analyses (Contd.)

- Descriptive analyses for demographic and clinical characteristics, CS symptoms, treatment duration, and QoL were reported with means and standard deviations for continuous variables and frequencies and proportions for categorical variables
- Comparisons between Time Point 1 and Time Point 2 were conducted using McNemar's test and the Wilcoxon signed rank test
- Total duration of SSA treatment, improvement/worsening in CS symptom severity, and change in QoL scores from Time Point 1 to Time Point 2 were cross-tabulated
  - CS symptom severity was classified as improved or worsened based on the change in response for the symptom on the following scale: severe > moderate > mild > not applicable. For example, a patient who reported moderate diarrhea at Time Point 1 and then mild at Time Point 2 would be classified as improved in diarrhea severity

Results

Demographic and Clinical Characteristics

- Of the 117 patients who completed the survey at Time Point 1, 89 patients also completed the survey at Time Point 2
  - These patients were predominantly female (75.3%) and Caucasian (93.3%) with a mean age of 59.2 years (**Table 1**)
- The mean time from diagnosis of NET to survey completion was 8.6 years and from diagnosis of CS was 7.4 years for patients that completed both Time Point 1 and Time Point 2 surveys (**Table 1**)
- Among 89 patients who completed Time Point 1 and Time Point 2 surveys, 97.8% were treated with SSA (at either Time Point 1 or Time Point 2; **Table 1**)
  - 78 (87.6%) patients were treated with SSA at both Time Point 1 and Time Point 2

Table 1. Patient Demographic and Clinical Characteristics

	(N=89)
Demographic characteristics	
Age (years), mean (SD)	59.2 (9.1)
Male, N (%)	22 (24.7)
Race, N (%)[1]	
Caucasian	83 (93.3)
Black or African American	3 (3.4)
Hispanic or Latino	3 (3.4)
Asian/Pacific Islander	0
Native American/American Indian	0
Other	1 (1.1)
Clinical characteristics	
Primary site of NET, N (%)[1]	
Lung	11 (12.4)
Stomach	6 (6.7)
Duodenum	9 (10.1)
Jejunum	6 (6.7)
Ileum	41 (46.1)
Appendix	8 (9.0)
Colon	8 (9.0)
Rectum	0
Other primary site[2]	25 (28.1)
Time since NET diagnosis (years), mean (SD)	8.6 (6.0)
Time since CS diagnosis (years), mean (SD)	7.4 (5.6)
Treated with SSA at Time Point 1 or Time Point 2, N (%)	87 (97.8)
Treated with SSA at Time Point 1 and Time Point 2, N (%)	78 (87.6)

[1]Respondents were allowed to select multiple responses, so counts and percentages may not sum to the total N or 100%.
[2]Other primary NET sites include typed in mentions of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.

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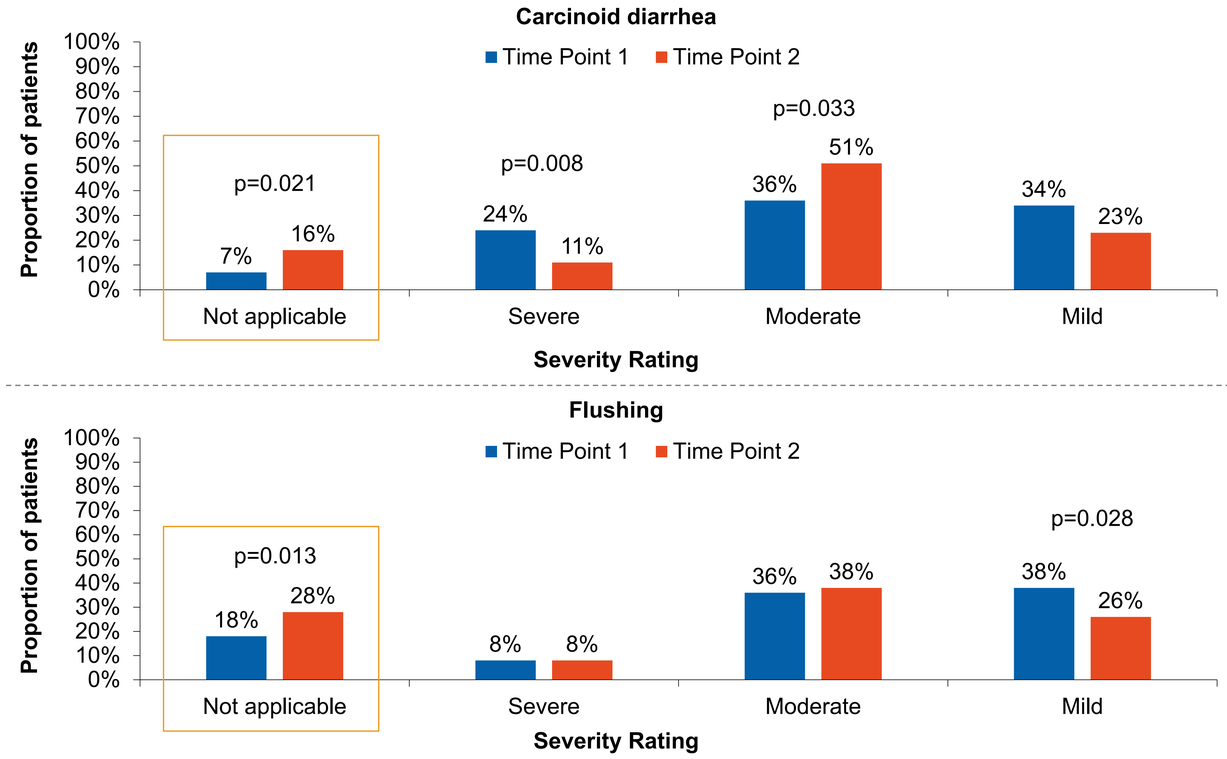
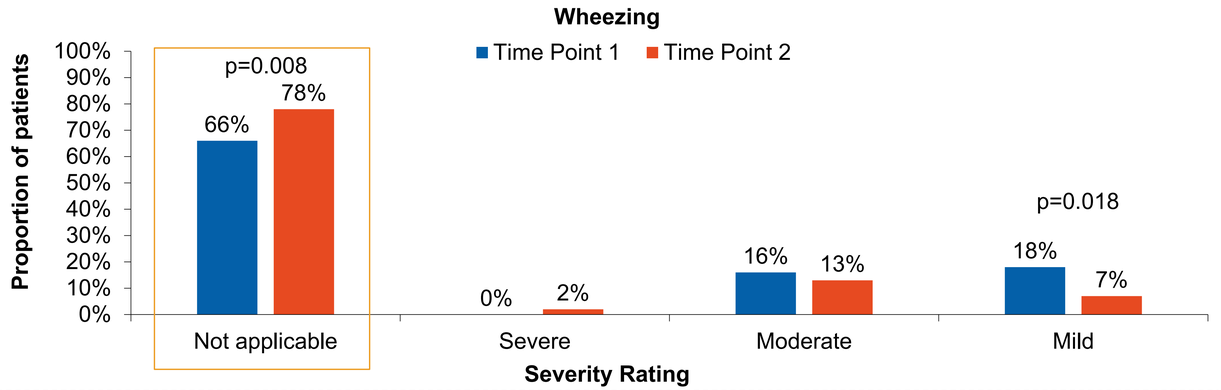
Results (Contd.)

- For CS symptom severity as reported in the past month for both time points, carcinoid diarrhea was selected as 'not applicable' (i.e., not experienced) for 15.7% of patients at Time Point 2 and 6.7% at Time Point 1 (p=0.021), indicating a significant decrease in experience of that symptom (**Figure 2**)
- The same trend was seen for flushing (28.1% vs. 18.0%, p=0.013) and wheezing (77.5% vs. 66.3%) at Time Point 2 compared to Time Point 1 (**Figure 2**)

Figure 2. CS Symptoms Severity Rating Between Time Point 1 and Time Point 2





FACT-G Change in QoL Scores from Time Point 1 to Time Point 2

- The mean (SD) FACT-G total score at Time Point 2 was 67.6 (20.3) which was 0.3 (9.6) points lower than at Time Point 1 (67.9) (**Table 2**)
  - Positive increases were seen in the PWB and EWB sub-domains, while decreases were seen in the SWB and FWB sub-domains
  - Changes in QoL score were below the clinically MID thresholds and they were not statistically different between Time Point 1 and Time Point 2 when assessed overall[8,9]

Table 2. Change in FACT-G Quality of Life Scores between Time Point 1 and Time Point 2

	Range	At Time Point 1	At Time Point 2	QoL Score Change	P-value
FACT-G scores, mean (SD)					
FACT-G total	0 - 108	67.9 (19.3)	67.6 (20.3)	-0.3 (9.6)	0.523
PWB	0 - 28	18.2 (6.2)	18.4 (6.3)	0.3 (3.6)	0.420
SWB	0 - 28	18.4 (6.6)	17.9 (6.6)	-0.5 (3.3)	0.156
EWB	0 - 24	16.1 (4.5)	16.3 (4.8)	0.2 (3.1)	0.746
FWB	0 - 28	15.2 (6.6)	14.9 (6.8)	-0.3 (3.7)	0.305

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Results (Contd.)

SSA Treatment Duration and Change in QoL, CS Symptoms

- Among the 87 patients treated with SSA at either Time Point 1 or Time Point 2, 11 (12.6%) were treated for >0 to 2 years, 37 (42.5%) for >2 to 5 years, and 39 (44.8%) for >5 years (**Table 3**)
- The >0 to 2 year SSA duration group had a mean positive change of 3.7 in their FACT-G total score, which is a potentially clinically relevant improvement that exceeds the lower bound of the MID of 3.0 points (**Table 3**)
- The >2 to 5 year group had no change and the >5 year group had a decrease of 1.2 in their scores (**Table 3**)
- The >0 to 2 year SSA duration group also showed better improvement in flushing severity; 18.2% had improved flushing from Time Point 1 to Time Point 2, compared to 0.0% worsening, while the >2 to 5 and >5 year groups had a smaller or no difference (**Table 4**)
- Diarrhea severity also showed higher rates of improvement than worsening between the two time points, but the trend over SSA duration is not as clear (**Table 4**)

Table 3. Change in FACT-G Scores Stratified by SSA Duration between Time Point 1 and Time Point 2

SSA duration at Time Point 1 (years)	Mean Δ FACT-G Scores					
	N	Total	PWB	SWB	EWB	FWB
>0 to 2	11	3.7*	1.5	0.1	1.6	0.5
>2 to 5	37	0.0	0.6	-0.5	0.1	-0.1
>5	39	-1.2	-0.3	-0.5	-0.1	-0.4

*Score exceed MID of 3.0 points

Table 4. Change in CS Symptom Severity Stratified by SSA duration between Time Point 1 and Time Point 2

SSA duration at Time Point 1 (years)		Flushing severity		Diarrhea severity	
	N	Improved	Worsened	Improved	Worsened
>0 to 2	11	18.2%	0.0%	27.3%	18.2%
>2 to 5	37	21.6%	21.6%	40.5%	18.9%
>5	39	17.9%	12.8%	30.8%	20.5%

CS Symptom Improvement and Change in QoL

- Among patients who indicated improvement in flushing severity (19.1%) in the past month at Time Point 2 as compared to Time Point 1, there was a mean increase of 3.05 in FACT-G total score (**Table 5**), indicating potentially clinically relevant improvement as compared to the lower bound of MID
- Among patients who showed worsening of flushing severity (14.6%), mean FACT-G total decreased by 2.15 points (**Table 5**)
- Patients who indicated improvement or worsening of diarrhea severity showed a mean decrease in FACT-G total of around 1 point (**Table 5**)

Table 5. Change in FACT-G Scores Stratified by Improvement in CS Symptoms

	Mean Δ FACT-G Scores					
	N	Total	PWB	SWB	EWB	FWB
Improvements in CS symptoms in past month						
Flushing severity	17	3.05*	0.71	-0.42	0.82	1.94
Diarrhea severity	31	-1.03	0.61	-0.83	0.16	-0.97
Worsening in CS symptoms in past month						
Flushing severity	13	-2.15	0.77	-0.77	-0.46	-1.69
Diarrhea severity	17	-1.15	0.18	-0.03	-0.76	-0.53

*Score exceeded MID of 3.0 points

Limitations

- All data were self-reported and could have been subject to recall bias
- Potential responder bias may be present as 76% (89/117) patients who completed Time Point 1 survey completed Time Point 2 survey. However, based on comparison of collected demographic and clinical characteristics of patients who responded to both Time Point 1 and 2 surveys, differences in characteristics were not observed
- The sample of patients studied may be heterogeneous in terms of disease characteristics, given no restrictions were placed on disease stage or timing of the survey relative to disease
- Recruitment was conducted primarily through NCAN, which may have resulted in a potentially biased sample not fully representative of the heterogeneous NET patient population. Patients may be highly engaged and motivated care seekers

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Conclusions

- In this study, an innovative study design that included reassessment of patients participating in an online survey was successfully implemented to yield high recapture rates and provide repeated measurements
- There seems to be a trend toward improvement in multiple CS symptoms (i.e., flushing, diarrhea, and wheezing) as illustrated in **Figure 2** with fewer patients exhibiting symptoms at Time Point 2 compared to Time Point 1
- Improvement in flushing resulted in positive benefit in QoL in which FACT-G total score showed small but potentially meaningful improvement exceeding the lower bound of MID of 3.0 points
- Improvement in QoL was most pronounced in the early years (>0-2 years) after SSA treatment initiation with a small but potentially meaningful FACT-G total score improvement exceeding the lower bound of the MID of 3.0 points
- A lesser impact on change in QoL may be observed in later years (>5 years) possibly due to disease progression and late-effects of cancer treatment
- These results contribute to the limited available literature on longitudinal changes in QoL and CS symptoms among CS patients receiving SSAs in the real world setting

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Disclosures

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