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Predictors of Somatostatin Analogs (SSA) Dose Escalations (DEs) Above Recommended Dosing Among Patients with Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) Treated at a Tertiary Referral Center

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Background

- Long-acting SSAs are commonly used to treat symptoms and progression of metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NET) but factors affecting real-world dosing may differ from recommended dosing.

Objectives

- To identify predictors of SSA DEs above recommended dosing among patients with metastatic GEP-NET.

Methods

Study design

- Retrospective cohort study using electronic healthcare database

Data sources

Database from GI Cancer Centers of Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital

- Patients with confirmed GEP-NET recruited between July 2003 and May 2015
- Data collected on demographics, medical history, staging, treatments (current and historical) at first consultation, every 4 months the first year, and yearly thereafter

DFCI's Outpatient Pharmacy Data

- Available data included medication name, date of dispensation, and dose dispensed
- DFCI's Outpatient pharmacy can be linked to institutional database using unique patient identifiers

Study population

- Eligible patients had well-differentiated, metastatic GEP-NETs, were seen ≥2 times at DFCI, and had ≥2 SSAs dispensations

Monthly SSA Exposure Identification

- Dispensations of long-acting SSAs (octreotide or lanreotide) was used to identify the SSA exposure.
- SSAs dispensation frequency categorized into weeks; dispensations +/-3 days considered part of the same week
- Monthly SSAs dosing regimens estimated: (SSAs dose/number of weeks between dispensations) x 4
- Assumed patients with >6 weeks between dispensations discontinued treatment or were treated outside of DFCI/Partners network

Dose Escalation Algorithm

- ≥2 consecutive increases above recommended monthly SSA dosing regimens compared to previous 2 regimens
- If >6 weeks between dispensations, considered SSAs dosing regimens before and after the gap separately

Statistical Analysis

- Compared the baseline characteristics of the SSA dose escalations to those SSA dispensations without a dose escalation within 3 months
- Logistic stepwise regression model (entry p-value 0.15/ stay p-value 0.20) derived considering demographics, disease severity, comorbidities, enrolled in a clinical trial in past 3 months, SSA exposure (initiation in past 3 months, prior SSA dose escalation), prior (past 3 months/ever) surgery, radiation, localized treatment, systemic treatment covariates, and regressed on the binary variable of dose escalation (yes=1/no=0)

Results

- Among 682 metastatic GEP-NETs patients, 340 (49.9%) had >1 octreotide dispensation; lanreotide was not on formulary during the study period and no patients had >1 dispensation
- Mean (SD) follow-up time was 3.0 years (2.0) and median (Q1-Q3) follow-up time was 2.8 years (5.4-14.7)
- The most common highest doses received above >30 mg/month were 40 mg/month (42.8%), 53 mg/month (27.8%), and 80 mg/month (22.2%)
- There were 195 dose escalations (to >30mg/month) among 106/340 (31.2%) patients, range of dose escalation/patient was 1-7. mean (SD): 2.5 (1.5), median (Q1-Q3): 2 (1-3)

Table 1. Characteristics of dose escalation and of comparator group at index date.

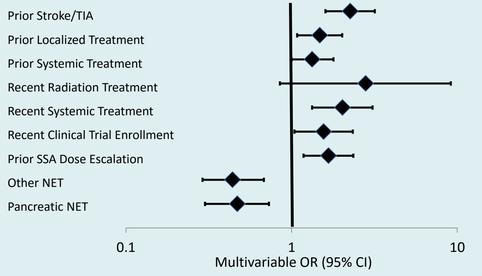
Characteristic	Dose Escalation (N=195)	Comparator Group (N=12,847)	Univariate OR (95% CI)
Age ≥65	34.4%	38.5%	0.84 (0.62 - 1.13)
Women	52.3%	54.8%	0.91 (0.68 - 1.20)
White	94.4%	94%	1.07 (0.58 - 1.97)
Index year ≥2009	59.0%	68.7%	0.66 (0.49-0.87)
Pancreatic NET	13.3%	21.8%	0.45 (0.29 - 0.68)
Midgut NET	73.3%	53.5%	Ref*
Other NET	13.3%	24.7%	0.39 (0.26 - 0.60)
≥5 years since diagnosis of metastatic disease	41.5%	38.7%	1.12 (0.84 - 1.5)
≥2 years since SSA initiation	58.0%	55.9%	1.09 (0.82 - 1.45)
Recent SSA initiation	15.4%	11.9%	1.34 (0.91 - 1.99)
Prior SSA dose escalation	3.1%	6.8%	0.44 (0.19 - 0.99)
Recent clinical trial enrollment	58%	55.9%	1.09 (0.82 - 1.45)
Recent systemic treatment	13.9%	7.4%	2.02 (1.34 - 3.06)

Table 1. Characteristics of dose escalation and of comparator group at index date (continued part 1).

Characteristic	Dose Escalation (N=195)	Comparator Group (N=12,847)	Univariate OR (95% CI)
Recent localized treatment	2.6%	2.6%	1.00 (0.41 - 2.43)
Recent radiation treatment	1.5%	0.5%	2.94 (0.92 - 9.41)
Prior systemic treatment	52.8%	43.8%	1.44 (1.08 - 1.91)
Prior localized treatment	31.3%	21.3%	1.68 (1.24 - 2.28)
Prior radiation treatment	6.2%	6.2%	1.00 (0.55 - 1.80)
Myocardial infarction	19.5%	14.3%	1.46 (1.02 - 2.08)
Heart failure	4.6%	3.6%	1.31 (0.67 - 2.58)
Prior stroke/TIA	26.2%	11.2%	2.82 (2.04 - 3.90)
Kidney problems	14.9%	10.9%	1.44 (0.96 - 2.14)
Diabetes	33.3%	34.6%	0.95 (0.7 - 1.28)
Crohn's/Ulcerative Colitis	6.2%	4.4%	1.44 (0.80 - 2.59)
Cirrhosis/Liver Damage	22.6%	18.4%	1.29 (0.92 - 1.81)

Note: *Ref: reference group for pancreatic and other NET.

Figure 1. Results of the final MV logistic regression.



- Index year ≥ 2009, tumor type, prior SSA DE, recent systemic treatment, prior systemic treatment, prior localized treatment, myocardial infarction, and prior stoke/ITA were identified as the factors associated with DEs in univariate analysis.
- The multivariate logistic regression identified prior stroke/TIA, prior localized treatment, recent systemic treatment, prior SSA dose DEs and tumor type as significant predictors.

Conclusions

- SSA DEs above recommended dosing was common among patients studied, especially among those with midgut NET and greater disease severity.
- The prior localized treatment, recent systemic treatment, and the prior SSA DE are also associated with DEs.

Limitations

This study includes all the potential variables related to dose escalations. However, we acknowledge that some baseline variables of dose escalations and the dispensations of the comparator group share the same value, as they come from the same patient, and these variables might be correlated.

Disclosures

J.J.J. was an employee of Analytica LASER Int. at the time of analysis. **R.C.** and **J.M.** are employees of Analytica LASER Int., which received the research funding from Ipsen. **M.H.K., L.K.B.** and **A.L.** received the research funding from Ipsen. **S.J.P.** is the employee of Ipsen Biopharmaceuticals Inc. **S.G., J.D.** and **A.B.** are employees of Ipsen Pharma SAS.

This study was sponsored by Ipsen

Presented at the NANETS 10th Annual Symposium, Philadelphia, PA, USA, October 19–21, 2017