Treatment patterns and outcomes in metastatic neuroendocrine tumors: results from a retrospective community oncology database

Maxine D. Fisher[1], Sonia Pulgar[2], Matthew H. Kulke[3], Susan Pitman Lowenthal[2], David Cox[2], Paul J. Miller[1], Mark S. Walker[1], Lee S. Schwartzberg[4]

[1]Vector Oncology, Memphis, TN, USA; [2]Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA; [3]Program in Neuroendocrine and Carcinoid Tumors, Dana-Farber Cancer Institute, Boston, MA, USA; [4]The West Clinic, Memphis, TN, USA

Introduction

- Neuroendocrine tumors (NETs) are a slow-growing, heterogeneous group of neoplasms that arise in many different bodily organs[1]
- Although NETs are relatively rare, their prevalence has been rapidly increasing; data from the Surveillance, Epidemiology and End Result (SEER) registry indicate that the incidence of NETs in the US increased 5-fold from 1973 to 2004
- The World Health Organization subdivided NETs into grades based on a proliferation index in which G1 is a well-differentiated tumor, G2 is moderately-differentiated, and G3 is poorly-differentiated[2]
  - The European Neuroendocrine Tumor Society felt there was a need for a further tumor-node-metastasis (TNM) classification[3] in which:
    - T – The primary tumor is classified on size and site-specific features/ clinicopathological correlations
    - N – Tumor is classified by the level of metastasis to regional lymph nodes
    - M – Tumor is classified by level of distant metastasis
- Diagnoses of NETs are typically made relatively late, and 21% of patients with G1 malignant NETs, 30% of those with G2, and 50% of those with G3 or G4 malignant NETs had synchronous distant metastatic NETs (mNETs) at the time of diagnosis[4]
- Although somatostatin analog (SSA) treatment for mNETs has been shown to increase symptom control and reduce tumor progression,[5] little is known about how SSAs are being used in real-world community oncology settings
- The objective of the present study was to describe recent and current treatment patterns in mNET patients treated in the community oncology setting

Methods

Study setting and population

- Data were collected from the Vector Oncology Data Warehouse (VODW), a comprehensive cancer patient database comprising demographic, medical, treatment, and patient-reported outcome variables for US patients
  - The VODW contains electronic medical record (EMR) data, billing systems data, and a repository of Patient Care Monitor data
- Structured Query Language (SQL) was used to identify patients for the study, with eligibility verified by Clinical Research Nurse (CRN) review and variables abstracted by CRNs onto case report forms (CRFs) and entered into a secure database for analysis

Inclusion and exclusion criteria

- Patients from the VODW were eligible for inclusion if they had a diagnosis of mNET and were ≥18 years of age at the time of diagnosis
- Included patients were treated from 11/1996-5/2015
- Patients with metastatic solid tumors other than mNETs were excluded

Procedures for extraction of data

- SQL queries identified patients within the VODW who had evidence of mNET diagnosis and a screening list was populated; from that list patients were screened in random order to ensure that the sample was a probabilistically representative sample of the candidates
- Information related to demographics, infused treatments, staging, and other clinical data were extracted, and CRNs examined the medical records of each eligible patient for selection
- Dates were documented for all systemic therapy from mNET diagnosis to end of medical record; the occurrence and dates of disease progression were recorded for analysis of progression-free survival (PFS); and type of therapy administered, tumor grade, and occurrence/date of treatment emergent adverse events (TEAEs) of interest were logged

Regimens and lines of therapy

- A regimen was defined as ≥1 anti-cancer agent given in combination in which:
  1) All agents started ≤30 days from the start of the first agent, unless the start of an agent >30 days after the first agent was prespecified as part of the treatment plan
  2) No agent was discontinued and replaced by another ≤30 days after the first agent
  3) No agent was held and resumed after 42 days
- First-line therapy was defined as the first regimen the patient received after diagnosis of mNET, and subsequent lines were defined as regimen-based lines of therapy in which each sequential regimen was a new line of therapy (regardless of reason for regimen change)

Statistical methods

- Descriptive statistics were generated for all study variables
- Treatment pattern was defined as the systemic therapies delivered starting from diagnosis with mNET through end of the medical record
- Kaplan Meier survival analysis was used to examine PFS, in which the earlier of any documented disease progression or death was considered the terminal event

Results

Demographic and clinical characteristics

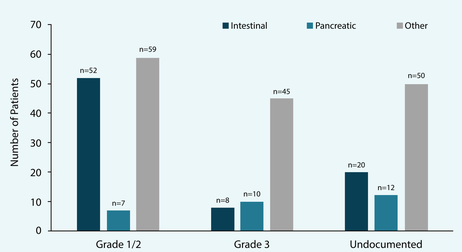
- A total of 263 patients with mNETs were included in the present analysis, with a median age of 65.0 years, an even split between sexes (50.6% female), the majority (73.4%) were Caucasian in race, and the region of residence for most of the sample (75.7%) was the southern US (**Table 1**)
- Of those patients with documented primary tumor site (n=132; one patient had >1 site), location of the primary tumor was intestinal (jejunal/ileal/colon/ duodenal/appendix) for 67 (50.8%) patients, pancreatic for 19 (14.4%) patients, and other (bronchopulmonary/gastric/rectal/thymus/stated as unknown/ undocumented) for 47 (35.6%) patients
  - A statistically significant difference was observed between tumor location categories for age (p=0.023; Kruskal-Wallis test), with the lowest median age of 61.0 years in the pancreatic group, followed by 63.0 years in the intestinal group, and 68.0 years for those in the location other group
- **Figure 1** displays tumor subtype by tumor grade for the entire population

Table 1. Demographic characteristics by tumor grade.

Variable	Tumor grade: Grade 1/ Grade 2 n=118	Grade 3 n=63	Not documented n=82	Overall N=263
Age, mean (SD), years	63.4 (12.9)	64.2 (13.3)	65.8 (12.5)	64.3 (12.9)
Female, n (%)	67 (56.8)	31 (49.2)	35 (42.7)	133 (50.6)
Race, n (%)				
White	87 (73.7)	48 (76.2)	58 (70.7)	193 (73.4)
Black or African American	27 (22.9)	9 (14.3)	21 (25.6)	57 (21.7)
Hispanic or Latino	2 (1.7)	2 (3.2)	2 (2.4)	6 (2.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.4)
Asian	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.4)
Not documented	2 (1.7)	3 (4.8)	0 (0.0)	5 (1.9)
BMI, mean (SD), kg/m^2	26.6 (5.8)	29.2 (8.4)	27.7 (5.0)	27.6 (6.3)

BMI, body mass index; SD, standard deviation.

Figure 1. Tumor subtype by grade.



Intestinal, jejunal/ileal/colon/duodenal/appendix; Other, bronchopulmonary/gastric/rectal/thymus/ stated as unknown/undocumented; Grade 1/2, well-differentiated tumor; Grade 3, poorly differentiated tumor.

- Most patients (80.6%) were diagnosed with Stage IV disease at the time of the initial diagnosis, with the first documented tumor subtype approximately equal between primary (50.2%) and metastatic (47.9%) (**Table 2**)
- At Stage IV diagnosis, the most common sites of distant metastasis were liver (73.4% of patients), followed by lymph node (31.6%), and bone (13.3%)
- Carcinoid symptoms or syndrome were documented for 43% of patients

Table 2. Clinical characteristics.

Variable, n (%)	Overall N=263
Stage of disease at initial diagnosis	
Stage IV	212 (80.6)
Stage III	9 (3.4)
Stage II	3 (1.1)
Stage I	1 (0.4)
Other	1 (0.4)
Undocumented	37 (14.1)
First documented tumor subtype[a]	
Primary tumor	132 (50.2)
Metastatic tumor	126 (47.9)
Undocumented	5 (1.9)
Primary tumor grade, n (%)	
G1: Well-differentiated	47 (58.0)
G2: Moderately-differentiated	8 (9.9)
G3: Poorly-differentiated	26 (32.1)
Total	81
Metastatic tumor grade, n (%)	
G1: Well-differentiated	48 (48.5)
G2: Moderately-differentiated	15 (15.2)
G3: Poorly-differentiated	36 (36.4)
Total	99
Overall tumor grade	
G1: Well-differentiated	95 (36.1)
G2: Moderately-differentiated	23 (8.7)
G3: Poorly-differentiated	62 (23.6)
Unknown	83 (31.6)
Sites of distant metastasis at Stage IV diagnosis	
Liver	193 (73.4)
Lymph node	83 (31.6)
Bone	35 (13.3)
Lung	34 (12.9)
Brain	4 (1.5)
Chest wall	2 (0.8)
Pleura	1 (0.4)
Other	84 (31.9)
Undocumented	0 (0.0)
Mention of carcinoid symptoms/syndrome	
Any carcinoid symptoms/syndrome	114 (43.3)
Carcinoid syndrome[b]	102 (38.8)
Carcinoid symptoms[b]	27 (10.3)

[a]The record was checked for documentation of tumor subtype and grade. If documented for a primary tumor, that subtype or grade was recorded. If not, and documentation for a metastatic tumor existed, that subtype or grade was recorded. If neither existed in the record, the subtype or grade was recorded as undocumented.

[b]Categories are not mutually exclusive.

Treatments administered

- The most commonly used therapeutic class were SSAs, specifically octreotide long-acting release (LAR) (n=153, 58.2%)
  - Approximately 1/3 of patients on octreotide (n=53, 34.2%) received above-label dosing, defined as cumulative dose >30 mg every 4 weeks
  - For the patients who received octreotide, 72 (46.5%) had a documented treatment change and, of those, 62 patients' treatment change was an alteration in octreotide dose (most often due to uncontrolled symptoms)
- The next most common therapeutic classes used were cytotoxics (n=92, 35.0%) and targeted therapies (mammalian target of rapamycin [mTOR] inhibitors and tyrosine-kinase inhibitors [TKIs]; n=29, 11.0%)
- For every line of treatment (1-5), the regimen most commonly used was octreotide (**Table 3**)

Table 3. Regimen distribution by treatment line.

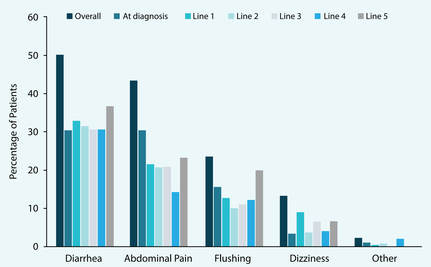
Line	Treatment pattern	Patients in line, n	Patients in regimen, n (%)
1	Octreotide	219	128 (58.4)
	Carboplatin, etoposide		50 (22.8)
	Carboplatin, etoposide, filgrastim		5 (2.3)
	Cisplatin, etoposide		5 (2.3)
2	Octreotide	140	85 (60.7)
	Carboplatin, etoposide		8 (5.7)
	Everolimus, octreotide		5 (3.6)
	Topotecan		5 (3.6)
3	Octreotide	91	60 (65.9)
	Carboplatin, paclitaxel		5 (5.5)
	Everolimus, octreotide		4 (4.4)
4	Octreotide	49	33 (67.3)
	Carboplatin, paclitaxel *		2 (4.1)
5	Octreotide	30	20 (66.7)
	Everolimus, octreotide *		2 (6.7)

*All other treatment patterns used in n=1 patient.

Physical symptoms

- The most frequently observed symptoms overall were diarrhea (n=132, 50.2%), abdominal pain (n=114, 43.4%), flushing (n=62, 23.6%), and dizziness (n=35, 13.3%) (**Figure 2**)
  - Little variation was seen in the frequency of each symptom from start of treatment through each line of therapy

Figure 2. Physical symptoms overall, at diagnosis, and by line of treatment.



Progression-free survival

- Overall median PFS from start of line 1 was 9.9 months (**Table 4**)

Table 4. Kaplan Meier analysis of PFS from start of regimen-based line of treatment by tumor grade.

	Grade: Grade 1/2	Grade 3	Not documented	Overall
Line 1	12.1 (8.1, 22.8)	4.5 (2.5, 8.1)	11.8 (6.8, 17.5)	9.9 (7.5, 11.9)
Events/subjects	50/95	30/56	33/68	113/219
Line 2	6.7 (5.4, 15.7)	3.8 (2.3, 9.3)	9.7 (3.7, 13.8)	6.7 (5.1, 9.9)
Events/subjects	32/62	21/32	25/46	78/140
Line 3	8.7 (3.3, 24.2)	2.10 (1.5, 3.7)	7.4 (4.3, 20.8)	5.9 (3.3, 9.9)
Events/subjects	19/41	17/20	21/30	57/91
Line 4	5.4 (1.9, --)	5.6 (1.7, 8.9)	13.6 (4.6, 46.8)	6.94 (4.0, 13.6)
Events/subjects	8/22	9/12	8/15	25/49
Line 5	6.5 (0.5, 22.8)	3.5 (1.0, 10.5)	5.6 (2.1, --)	5.8 (3.0, 10.5)
Events/subjects	6/12	4/6	8/12	18/30

Events/subjects, total number of events/total number of subjects within the specified line of treatment.

PFS, progression-free survival.

Data by line are median (95% confidence intervals) in months.

Conclusions

- Results from this analysis indicate that most patients were diagnosed with Stage IV disease at the time of their initial diagnosis, and the site of distant metastasis for most patients was the liver
- The most commonly used therapeutic class of drugs to treat patients with mNETs was SSAs, specifically octreotide, with 34% receiving above-label dosing
- Diarrhea and abdominal pain were the most frequently observed symptoms, and little variation was seen in the frequency of these symptoms from treatment start through all observed lines of therapy
- Median PFS from start of line 1 treatment was 9.9 months for all patients
- Data from this analysis of patients with mNETs in a community oncology setting provide a real-world view of patient characteristics, treatment patterns, and outcomes for this patient population

References

1. Klimstra DS, et al. *Pancreas.* 2010;39:707-12.
2. Oberg K, Castellano D. *Cancer Metastasis Rev.* 2011;30(suppl 1):3-7.
3. Rindi G, et al. *Virchows Archiv.* 2006;449:395-401.
4. Yao JC, et al. *J Clin Oncol.* 2008;26:3063-72.
5. Susini C, Buscail L. *Ann Oncol.* 2006;17:1733-42.

Acknowledgments

This study is funded by Ipsen Biopharmaceuticals, Inc. Development, editorial, design, and production support was provided by MedVal Scientific Information Services, LLC and was funded by Ipsen Biopharmaceuticals, Inc.

Presented at the 2015 North American Neuroendocrine Tumor Society Symposium, October 15-17, 2015, Austin, TX