Treatment Outcomes in Patients With Metastatic Neuroendocrine Tumors: Retrospective Analysis of a Community Oncology Database

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INTRODUCTION

- Although neuroendocrine tumors (NETs) are relatively rare, data from the Surveillance, Epidemiology and End Result registry indicate an approximate 5-fold increased incidence of NETs in the United States from 1973 to 2004[1]
- Various classifications of NETs exist; the World Health Organization and the European Neuroendocrine Tumor Society subdivide 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]
- Low-grade (well differentiated) and high-grade (poorly differentiated) NETs behave very differently with low-grade tumors described as relatively indolent in nature and high-grade NETs as highly aggressive; therapy, likewise, can differ substantially between these tumor categories[2]
- Data describing the clinical characteristics and treatment experience of patients with metastatic NETs (mNETs) have been somewhat limited with a focus on the institutional treatment setting[3]
- Recently, we presented demographic characteristics and overall treatment patterns in patients diagnosed with mNETs from a retrospective database analysis of community oncology practices[4]
- The objective of the present study was to further describe treatment outcomes for patients with mNETs treated in the community oncology setting, with a focus on G1/G2 tumors

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 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 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
- 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 or the end of the observation period; the occurrence and dates of disease progression were recorded for analysis of progression-free survival (PFS) as determined by treating physician; type of therapy administered, tumor grade, and occurrence/date of physical symptoms attributed to hormone hypersecretion were logged (eg, diarrhea, flushing, abdominal pain, dizziness)
- Dates of death were recorded in the clinical record and linked to the Social Security death index

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
- Unless the record indicated a planned delay in the start of an agent, the addition of a new agent to an existing therapy >30 days after start of the regimen constituted a change of regimen
- First-line therapy was defined as the first regimen the patient received after diagnosis of mNET; 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 demographic and clinical variables, including means, standard deviations, medians, minimums and maximums for continuous variables and frequencies, and percentages for categorical variables
- Treatment pattern was defined as the systemic therapies delivered starting from diagnosis with mNET through the end of the medical record or the end of the observation period
- Kaplan-Meier survival analysis was used to examine overall survival (OS), from time of mNET diagnosis or initiation of first-line therapy, and PFS from the start of each line of therapy, in which the earlier of any documented disease progression or death was considered the terminal event

RESULTS

Demographic and Clinical Characteristics

- The database included a total of 263 patients with mNETs, of which 118 patients had G1/G2 tumors (**Table 1**)
- The median duration of follow-up was 22 months (range 0.1-193.9)
- Statistically significant differences were observed between tumor grade categories for many clinical characteristics (**Table 1**)
- 30.4% (80/263) of patients had intestinal tumors, 11.0% (29/263) had pancreatic tumors, and 58.6% (154/263) had other/unknown tumors

Table 1. Demographic and Clinical Characteristics by Tumor Grade

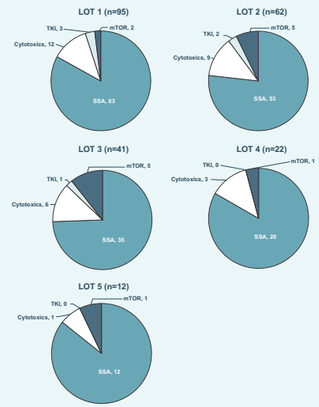
	Grade				
Variable	G1/G2 (n=118)	G3 (n=63)	Undocumented (n=82)	Overall (N=263)	*P*-value[a]
Age, mean (SD), years	63.4 (12.9)	64.2 (13.3)	65.8 (12.5)	64.3 (12.9)	0.4386
Female, n (%)	67 (56.8)	31 (49.2)	35 (42.7)	133 (50.6)	0.1417
Race, n (%)					0.7571
White	87 (73.7)	48 (76.2)	58 (70.7)	193 (73.4)	
Other/unknown	31 (26.3)	15 (23.8)	24 (29.3)	70 (26.6)	
BMI, mean (SD), pounds/inch[2]	26.6 (5.8)	29.2 (8.4)	27.7 (5.0)	27.6 (6.3)	0.0953
Stage of Disease at Initial Diagnosis, n (%)[a]					0.0190
IV	102 (86.4)	51 (81.0)	59 (72.0)	212 (80.6)	
III	5 (4.2)	2 (3.2)	2 (2.4)	9 (3.4)	
II	2 (1.7)	1 (1.6)	0	3 (1.1)	
I	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.4)	
Other	0	0	1 (1.2)	1 (0.4)	
Undocumented	9 (7.6)	8 (12.7)	20 (24.4)	37 (14.1)	
First Documented Tumor Subtype, n (%)[b]					0.5070
Primary tumor	63 (53.4)	28 (44.4)	41 (50.0)	132 (50.2)	
Metastatic tumor	54 (45.8)	34 (54.0)	38 (46.3)	126 (47.9)	
Undocumented	1 (0.8)	1 (1.6)	3 (3.7)	5 (1.9)	
Collapsed Overall Tumor Subtype, n (%)[b]					
Intestinal[a]	52 (44.1)	8 (12.7)	20 (24.4)	80 (30.4)	<0.0001
Pancreatic	7 (5.9)	10 (15.9)	12 (14.6)	29 (11.0)	0.0573
Other[a]	61 (51.7)	45 (71.4)	51 (62.2)	154 (58.6)	0.0309
Primary Tumor Grade, n (%)					
G1: Well differentiated	47 (85.5)	0	--	47 (58.0)	
G2: Moderately differentiated	8 (14.5)	0	--	8 (9.9)	
G3: Poorly differentiated	0	26 (100.0)	--	26 (32.1)	
Metastatic Tumor Grade, n (%)[a]					<0.0001
G1: Well differentiated	48 (76.2)	0	--	48 (48.5)	
G2: Moderately differentiated	15 (23.8)	0	--	15 (15.2)	
G3: Poorly differentiated	0	36 (100.0)	--	36 (36.4)	

BMI, body mass index; SD, standard deviation.
[a]Values derived from a Kruskal-Wallis test for continuous variables and a chi-square or Fisher's Exact test for categorical variables. In instances for which exact computations required a great amount of time and memory, *P*-values were estimated by Monte Carlo simulation.
[b]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, any 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. For reporting collapsed tumor subtype, the following groupings were used: Intestinal=jejunal/ileal/colon/duodenal/appendix; other=bronchopulmonary/gastrorectal/thymus/stated as unknown/undocumented. Three patients with documented metastatic tumor subtype had both jejunal/ileal/colon and other as the first documented. For inclusion in models, these patients will be categorized as jejunal/ileal/colon.

Treatments Administered

- 83.3% (219/263) of patients received 1 line of therapy, 52.9% (139/263) received 2 lines of therapy, 34.6% (91/263) received 3 lines of therapy, 18.6% (49/263) received 4 lines of therapy, and 11.4% (30/263) received 5 lines of therapy
- 87.4% (83/95) of patients with G1/G2 tumors in line 1 received somatostatin analog treatment and 12.6% (12/95) received cytotoxic therapy (**Figure 1**)

Figure 1. Lines of Therapy (Collapsed Regimens[a]) for Patients with G1/G2 Tumors (n=118)



LOT, line of therapy; mTOR, mammalian target of rapamycin; SSA, somatostatin analog; TKI, tyrosine kinase inhibitor.
[a]Note: Data expressed as "n" rather than percent as categories were not exclusive.

- Among patients with G1/G2 tumors, for every line of therapy (1-5), the regimen most often used was octreotide (**Table 2**)

Table 2. Distribution of Treatment Regimens Received by >1 Patient by Treatment Line for Patients with G1/G2 Tumors (n=118)

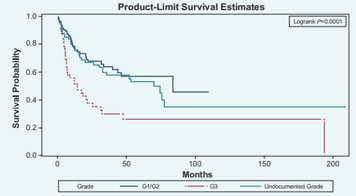
Line	Treatment Pattern	Patients in Regimen, n (%)
1 (n=95)	SSA	78 (82.1)
	Carboplatin, etoposide	5 (5.3)
	Carboplatin, etoposide, filgrastim	2 (2.1)
	Sunitinib	2 (2.1)
2 (n=62)	SSA	47 (75.8)
	Everolimus	2 (3.2)
	Everolimus, SSA	2 (3.2)
3 (n=41)	SSA	29 (70.7)
	Everolimus, SSA	4 (9.8)
	Carboplatin, paclitaxel	2 (4.9)
4 (n=22)	SSA	17 (77.3)
5 (n=12)	SSA	10 (83.3)

SSA, somatostatin analog.

Overall Survival

- While the focus of this analysis is on G1/G2 tumors, outcomes for patients with G3 tumors were also available and presented
- Among patients with G1/G2 tumors (n=118), the median OS from the start of first-line therapy was 83.4 months (**Figure 2**)

Figure 2. Kaplan-Meier Analysis of OS by Tumor Grade From Start of First-Line Therapy (n=219)

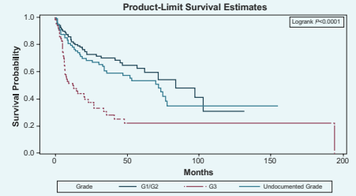


	Grade			
OS	G1/G2	G3	Undocumented	Overall
No. of Events / No. of Subjects	34/95	37/56	32/68	103/219
Mean (months)	54.91[a]	59.61[a]	48.88[a]	85.19[a]
SD	3.97	12.50	4.08	8.28
Median (months)	83.41	13.97	69.57	47.54
95% CI of Median	[39.45, --]	[6.48, 25.08]	[32.45, --]	[31.69, 77.49]
Minimum, Maximum	0.13, 109.81	0.85, 193.68	1.08, 209.23	0.13, 209.23

Logrank χ^2 (2)=18.8, *P*<0.0001
CI, confidence interval; OS, overall survival; SD, standard deviation.
The time origin was the start of first-line therapy.
[a]Mean is biased downward because there are censoring times greater than the largest event time.

- For patients for whom tumor grade was undocumented (n=80), median OS from time of diagnosis was 71.5 months (**Figure 3**)

Figure 3. Kaplan-Meier Analysis of OS From Diagnosis of mNET, by Tumor Grade (n=261)

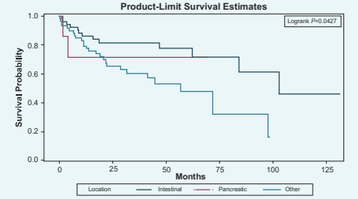


	Grade			
OS	G1/G2	G3	Undocumented	Overall
No. of Events / No. of Subjects	41/118	44/63	39/80	124/ 261
Mean (months)	66.89[a]	52.76	49.42[a]	82.24
SD	4.52	11.18	3.70	7.28
Median (months)	83.93	12.43	71.51	56.94
95% CI of Median	[62.30, --]	[6.58, 23.08]	[33.83, 77.85]	[35.87, 74.83]
Minimum, Maximum	0.46, 131.47	0.10, 193.91	0.72, 155.61	0.10, 193.91

Logrank χ^2 (2)=30.7, *P*<.0001
CI, confidence interval; OS, overall survival; SD, standard deviation.
Note: Two patients have missing survival time due to unknown date of mNET diagnosis
[a]Mean is biased downward because there are censoring times greater than the largest event time.

- For patients with G1/G2 tumors, the median OS from the time of diagnosis of mNET was 102.8 months for those with intestinal tumors and 56.9 months for those with other/unknown tumors (**Figure 4**)

Figure 4. Kaplan-Meier Analysis of OS From Diagnosis of mNET by Tumor Location for Patients With G1/G2 Tumors (n=118)



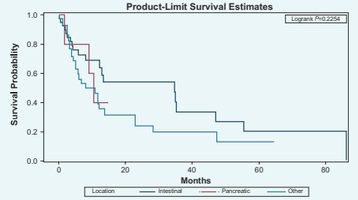
	Location			
OS	Intestinal	Pancreatic	Other	Overall
No. of Events / No. of Subjects	13/52	2/7	26/59	41/118
Mean (months)	78.83[a]	3.75[a]	53.81[a]	66.89[a]
SD	6.14	0.43	6.41	4.52
Median (months)	102.81	--	56.94	83.93
95% CI of Median	[83.93, --]	[1.78, --]	[28.64, 97.55]	[62.30, --]
Minimum, Maximum	1.22, 131.47	1.78, 69.76	0.46, 98.27	0.46, 131.47

Logrank χ^2 (2)=6.31, *P*=0.0427
CI, confidence interval; OS, overall survival; SD, standard deviation.
[a]Mean is biased downward because there are censoring times greater than the largest event time.

Progression-Free Survival

- For patients with G1/G2 tumors, the median PFS from the start of therapy for those with intestinal (n=42), pancreatic (n=6), and other/unknown tumors (n=47) was 34.6 months, 10.4, and 8.1 months, respectively (**Figure 5**)

Figure 5. Kaplan-Meier Analysis of PFS by Tumor Location From Start of First-Line Therapy for Patients With G1/G2 Tumors (n=95)



	Location			
PFS	Intestinal	Pancreatic	Other	Overall
No. of Events / No. of Subjects	20/42	3/6	27/47	50/95
Mean (months)	34.45	8.41[a]	16.45[a]	27.03
SD	6.75	1.84	3.07	4.18
Median (months)	34.59	10.42	8.09	12.10
95% CI of Median	[12.16, 46.88	[1.78, --]	[4.87, 13.64]	[8.09, 22.82]
Minimum, Maximum	0.03, 86.10	0.69, 14.73	0.03, 64.47	0.03, 86.10

Logrank χ^2 (2)=2.98, *P*=0.2254
CI, confidence interval; PFS, progression-free survival; SD, standard deviation.
The time origin was the start of first line of therapy.
[a]Mean is biased downward because there are censoring times greater than the largest event time.

- Median PFS for patients with G1/G2 tumors by regimen-based line of therapy (1-5, respectively) was 12.1 (n=95), 6.7 (n=62), 8.7 (n=41), 5.4 (n=22), and 6.5 (n=12) months (**Table 3**)

Table 3. Kaplan-Meier Analysis of PFS From Start of Regimen-Based Line of Treatment by Tumor Grade

	Grade			
	G1/G2	G3	Undocumented	Overall
Line 1	12.10 (8.09, 22.82)	4.50 (2.47, 8.05)	11.77 (6.84, 17.52)	9.93 (7.46, 11.87)
Events/Subjects	50/95	30/56	33/68	113/219
Line 2	6.67 (5.36, 15.72)	3.75 (2.30, 9.34)	9.73 (3.72, 13.84)	6.67 (5.06, 9.90)
Events/Subjects	32/62	21/32	25/46	78/140
Line 3	8.71 (3.25, 24.20)	2.10 (1.51, 3.72)	7.36 (4.31, 20.75)	5.88 (3.25, 9.93)
Events/Subjects	19/41	17/20	21/30	57/91
Line 4	5.36 (1.91, --)	5.56 (1.68, 8.88)	13.64 (4.64, 46.75)	6.94 (3.98, 13.64)
Events/Subjects	8/22	9/12	8/15	25/49
Line 5	6.48 (0.49, 22.75)	3.48 (0.95, 10.49)	5.56 (2.14, --)	5.75 (2.96, 10.49)
Events/Subjects	6/12	4/6	8/12	18/30

PFS, progression-free survival.
Events/Subjects, total number of events/total number of subjects within the specified line of treatment.
All data are median (95% confidence intervals) in months.

STRENGTHS/LIMITATIONS

- 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
- Because of the retrospective nature of this analysis, there is a potential risk for misclassification or selection bias
- The proportion of mNETs whose tumor location was categorized as unknown/other may reflect variability among clinical practice in the community setting
- Follow-up duration was variable

CONCLUSIONS

- In this "real world" community oncology retrospective study, the most commonly used therapeutic class of drugs for treatment of patients with G1/G2 mNETs was somatostatin analogues; 20% of patients with G1/G2 tumors did not receive drug therapy during the observation time
- Patients with G1/G2 mNETs had a median OS similar to what has been reported in other US studies
- Those with intestinal tumors had longer OS rates than those with other/unknown tumors
- Among this patient group, median PFS was longest with first-line therapy and decreased with subsequent regimens

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