Graphical Analysis of Treatment Patterns among Patients with Pancreatic Neuroendocrine Tumors Newly Treated with Cytotoxic Chemotherapy or Targeted Therapy

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BACKGROUND

- Based on a study using SEER data from 1973 to 2004, the estimated prevalence of all neuroendocrine tumors (NET) in the US was over 100,000 cases in 2004.[1]
- Pancreatic neuroendocrine tumors (PNET), when progressive, may be treated with somatostatin analogues (SSAs), targeted therapy, and cytotoxic chemotherapy.
  - Everolimus and sunitinib, both targeted therapies, were approved for PNET in 2011.
- Treatment sequences for PNET vary considerably across providers and are not well described in real-world clinical practice settings.

Objective

- Using longitudinal commercial claims data, identify and evaluate real world treatment patterns of PNET patients newly treated with everolimus, sunitinib, or cytotoxic and other PNET therapies.

METHODS

Study Design

- Retrospective cohort study using combined data from two large HIPAA-compliant commercial claims databases.

Inclusion criteria:

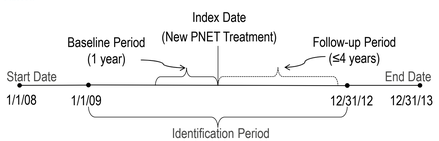
- ≥1 medical claim with a diagnosis of PNET (ICD-9-CM 157.4) in any diagnosis field during the identification (ID) period of 1/1/2009 – 12/31/2012; AND
- Receipt of either everolimus, sunitinib, OR cytotoxic chemotherapy and other PNET therapy[a] during the ID period.
- Date of first PNET treatment claim in the ID period was defined as the index date.

Exclusion criteria:

- Receipt of any pharmacologic treatment (everolimus, sunitinib, or cytotoxic and other therapy) for PNET during the 1-year pre-index (baseline) period (prior SSA use was allowed); OR
- Not continuously enrolled during the baseline period.

- We followed all patients from the index date until the end of enrollment or study end (12/31/2013). Median follow-up time = 448 days.

Figure 1: Study Time Frame



Study Measures

- Demographic variables: age, gender, and geographic region.
- Index treatment was categorized as everolimus, sunitinib, or cytotoxic and other PNET therapy.
- Everolimus, sunitinib, or cytotoxic and other PNET therapies that were identified on the index date were defined as the index treatment.
- PNET treatment duration and sequence were examined for the index and subsequent treatments.
  - Duration was defined as the number of days supplied from the first treatment fill/administration to either the last observed claim for the same treatment category plus its days supply (ignoring gaps of ≤90 days; injectable medications were assumed to have a 28-day supply), or a change to another treatment category, or disenrollment, or study end.

Statistical Analysis

- Descriptive statistics, including means, medians, standard deviations, and percentages, were reported as appropriate for the study measures and stratified by everolimus, sunitinib, and cytotoxic and other PNET therapy groups.
- PNET index treatment was evaluated with a novel graphical technique (GRAPHx) that plots treatment patterns using individual patient records, allowing for visual evaluation of different patterns. Each treatment was represented by a different color.
- All data transformations and statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC).

[a] Other PNET therapy includes bevacizumab.

RESULTS

- The final study population was 585 PNET patients newly treated with either everolimus, sunitinib, or cytotoxic and other PNET therapy **(Table 1)**.
  - 15.9% (n=93) of patients received everolimus, 11.5% (n=67) received sunitinib, and 72.6% (n=425) received cytotoxic and other therapies.
  - We found no instances in which patients used multiple index treatment types (e.g., everolimus and cytotoxic chemotherapy) on the index date.
  - Mean age was 55.4 years (SD=9.9), 43% were female, and all geographic regions were represented, with no statistically significant between-group differences.
- Temozolomide, capecitabine, 5-FU, and oxaliplation (in combinations together or alone) made up 81% (344/425) of cytotoxic and other therapy regimens **(Table 2)**.
- Switching from cytotoxic and other PNET therapy to everolimus or sunitinib, or vice versa, was seen in 21.9% (n=128) of patients **(Figure 2)**.
  - 71 patients treated with cytotoxic and other PNET therapy went on to everolimus or sunitinib (54.9% to everolimus, 45.1% to sunitinib).
  - 40.6% of everolimus users and 52.0% of sunitinib users switched to cytotoxic and other therapies; the remainder of each from one targeted agent to the other.

Table 1: Patient Demographics Stratified by Index Treatment

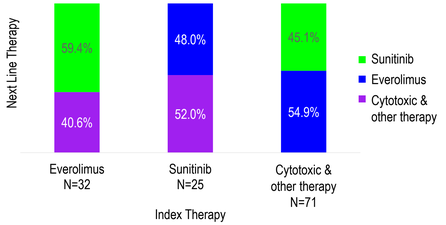
	Index Treatment				
	Everolimus N=93	Sunitinib N=67	Cytotoxic & other therapy N=425	All Newly Treated PNET Patients N=585	p-value
Age, mean (SD)	56.0 (9.0)	54.9 (10.0)	55.3 (10.1)	55.4 (9.9)	0.742
Female, no. (%)	47 (50.5)	25 (37.3)	181 (42.6)	253 (43.2)	0.218
Region, no. (%)					0.618
Northeast	14 (15.1)	9 (13.4)	82 (19.3)	105 (17.9)	
Midwest	31 (33.3)	24 (35.8)	114 (26.8)	169 (28.9)	
South	34 (36.6)	23 (34.3)	165 (38.8)	222 (37.9)	
West	14 (15.1)	11 (16.4)	64 (15.1)	89 (15.2)	

Table 2: Type of Cytotoxic & Other PNET Therapies at Index[a]

No.	Therapeutic Regimen	Frequency	Percent
1	Temozolomide / Capecitabine	83	19.53
2	Fluorouracil / Oxaliplatin	77	18.12
3	Capecitabine	73	17.18
4	Fluorouracil	52	12.24
5	Temozolomide	36	8.47
6	Oxaliplatin	23	5.41
7	Doxorubicin	17	4.00
8	Streptozocin / Doxorubicin / Fluorouracil	16	3.76
9	Streptozocin / Doxorubicin	8	1.88
10	Streptozocin / Fluorouracil	8	1.88
11	Capecitabine / Oxaliplatin	6	1.41
12	Dacarbazine	4	0.94
13	Streptozocin	3	0.71
14	Doxorubicin / Fluorouracil	2	0.47
15	Fluorouracil / Oxaliplatin / Bevacizumab	2	0.47
16	Temozolomide / Thalidomide	2	0.47
17	Capecitabine / Bevacizumab	1	0.24
18	Streptozocin / Doxorubicin / Capecitabine	1	0.24
19	Temozolomide / Bevacizumab	1	0.24
20	Thalidomide	1	0.24

[a] Cytotoxic & other PNET therapy cohort includes 9 patients who received bevacizumab monotherapy.

Figure 2: Next Line Treatment Among Patients Who Switched Therapy



- Everolimus and sunitinib initiators remained on treatment for a mean of 282.3 days and 236.3 days, respectively, vs. 173.0 days for initiators of cytotoxic and other therapies **(Figure 3)**.
  - In a subset of 338 patients who were continuously enrolled during the study period, 113 (33.4%) used an SSA within one year prior to initiating everolimus, sunitinib, or cytotoxic and other therapies and 81 (24.0%) continued SSA use after initiation (results not shown).

Figure 3: Length of Use of Index Treatment

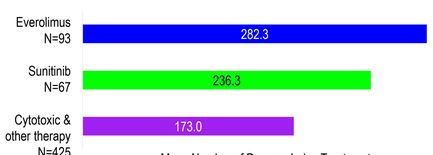
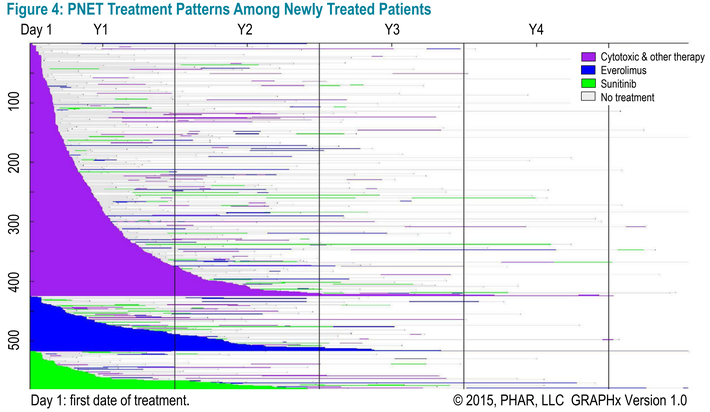


Figure 4: PNET Treatment Patterns Among Newly Treated Patients



- **Figure 4** shows a graphical representation of index treatment initiation, duration of use, and switching to subsequent therapy among individual patients. As described above, the majority of patients initiated treatment with therapies other than everolimus and sunitinib, followed by initiators of everolimus and then initiators of sunitinib. In addition, switching occurred frequently for all treatment groups.

LIMITATIONS

- This study examined use of everolimus, sunitinib, and cytotoxic and other PNET therapies. SSA use prior to or during the aforementioned therapies was not assessed. Therefore, readers should be aware of the caveats when interpreting the results.
- Sensitivity and specificity of our claims-based algorithm for identifying PNET patients has not been validated.
- Patients included in this study were those with commercial insurance plans captured in the two claims databases. Results may not be representative of patients with other types of insurance or who are uninsured.

CONCLUSION

- Treatment was shown to follow multiple patterns for PNET patients newly treated with everolimus, sunitinib, or cytotoxic and other therapy, with some patients receiving everolimus or sunitinib first and others receiving alternative therapies.
- Real world treatments for PNET patients follow no clear treatment pattern from the initial to subsequent treatment.
- Among patients we studied, cytotoxic and PNET therapies other than everolimus or sunitinib are used first more commonly, but generally for a shorter duration than everolimus or sunitinib regimens that are initiated first.
  - This difference in treatment duration may reflect a more favorable tolerability profile in everolimus and sunitinib, better disease control, differences in administration schedules, or confounding, as we were unable to control for clinical differences between groups.
- Future research, which might include medical chart studies, may be used to evaluate the clinical outcomes associated with these observed treatment sequences.

References

[1] Yao et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. Journal of Clinical Oncology. 2008 Jun 20;26(18):3063-72.

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