Treatment Patterns and Burden of Illness in Patients Initiating Targeted Therapy or Chemotherapy for Pancreatic Neuroendocrine Tumors

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Objective: The aim of this study was to characterize treatment patterns and burden of pancreatic neuroendocrine tumors (PNET).

Methods: Using 2 claims databases, we identified patients with PNET initiating targeted therapy (everolimus, sunitinib) or chemotherapy from 2009 to 2012. The first targeted/cytotoxic therapy was considered index treatment. Treatment patterns were graphically evaluated from index treatment initiation until enrollment or study end, whichever occurred first. Disease burden was examined by index group for first follow-up year.

Results: In treatment pattern analyses (582 newly treated patients with PNET), 72.2% received chemotherapy index treatment, 16.2% everolimus, and 11.7% received sunitinib. Median index treatment duration was 242, 146, and 126 days for everolimus, sunitinib, and cytotoxics ($P < 0.01$). Sunitinib initiators switched most often followed by everolimus and cytotoxic initiators. In disease burden analyses, 338 patients met inclusion criteria, with mean age of 54.5 (standard deviation, 9.9) years, 45.6% were female, and there were no significant between-group differences. Targeted therapy initiators had more prior somatostatin analog use versus cytotoxics (53.4% vs 25.1%, $P < 0.001$); 72.5% had comorbidities after treatment initiation; 42.9% had 1 or more inpatient hospitalization; and 47.9% had 1 or more emergency department visit.

Conclusions: Pancreatic neuroendocrine tumor treatment patterns varied; cytotoxics were more often used as early therapy than targeted agents, but for less time. Patients had high health care utilization, irrespective of treatment, potentially from burdensome symptoms and comorbidities.

Key Words: chemotherapy, comorbidities, somatostatin analog, targeted agents, treatment persistence

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Gastrointestinal and pancreatic neuroendocrine tumors (GEP-NET) are rare neoplasms that are derived from neuroendocrine cells. These slow-growing tumors store and secrete peptides and neuroamines, which may cause characteristic hormonal syndromes.[1–3] Pancreatic neuroendocrine tumors originate in the islets of Langerhans. The incidence of diagnosed NET has increased significantly in the United States over the decades from 1.09 cases per 100,000 individuals in 1973 to 5.25 cases per 100,000 individuals in 2004[4] and to 6.98 per 100,000 in 2012.[5] More specifically, the estimated incidence of PNET is less than 1 per 100,000 individuals, yet constitutes up to 10% of pancreatic tumors.[6–8]

The clinical management of PNET may include the use of somatostatin analogs (SSAs), targeted therapy, or chemotherapy at various stages or indications of disease.[9] Somatostatin analogs are often considered the first-line therapy for NET.[10,11] In patients with PNET, SSAs, which are well tolerated, may be particularly helpful in controlling symptoms of hormone secretion if present.[9] Among patients with advanced PNET, SSAs may also be used for tumor control, with a potentially long-lasting effect.[8,9] Although no chemotherapy has received US Food and Drug Administration approval for progressive PNET, it remains a National Comprehensive Cancer Network (NCCN) recommended treatment option.[9,11] In addition, in 2011, the US Food and Drug Administration approved 2 targeted therapies, also for progressive PNET: everolimus (Afinitor, Novartis, East Hanover, NJ), an inhibitor of the mammalian target of rapamycin, and sunitinib (Sutent; Pfizer, New York, NY), an oral tyrosine kinase inhibitor of the vascular endothelial growth factor receptor. Findings from 2 clinical trials that were published in 2011 endorsed everolimus and sunitinib as acceptable therapies for advanced PNET.[12,13]

Recent studies have reported on the clinical,[3,14,15] economic,[14,15] and quality-of-life burden[15,16] of patients with NET; however, real-world data on such burden solely for patients with PNET are limited.[3,14] In addition, although it is well known that SSAs may be used in the early treatment of PNET,[10,11] subsequent treatment patterns among patients with PNET who initiated chemotherapy or targeted therapy are not fully understood. This study, using 2 US commercial claims databases, aimed to characterize treatment patterns and burden of illness among patients with PNET who initiated targeted therapy or chemotherapy.

MATERIAL AND METHODS

This was a retrospective cohort study using combined Truven Health MarketScan and IMS PharMetrics administrative claims databases to analyze treatment patterns, comorbidities, and health care utilization among patients diagnosed with PNET and initiating treatment with everolimus, sunitinib, or chemotherapy. MarketScan and PharMetrics are both large administrative claims databases that are Health Insurance Portability and Accountability Act (HIPAA)-compliant and contain deidentified claims from patients with employer-sponsored health insurance in the United States. These databases contain information on enrollment and benefits, limited patient, provider, and hospital demographics, inpatient and outpatient services and costs, and outpatient pharmacy data. The data include the following information reported on administrative claims: diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] diagnosis codes) and procedures (Current Procedural

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Terminology 4 [CPT-4] and *ICD-9-CM* procedure codes) in the outpatient and inpatient settings and prescription medications (National Drug Codes) filled through outpatient pharmacies.

The study population comprised patients of any age diagnosed as having PNET (*ICD-9-CM* code 157.4) who then initiated treatment with a targeted agent (i.e., everolimus or sunitinib) or chemotherapy, both of which occurring during the identification period of January 1, 2009, to December 31, 2012. For each patient, the date of the first targeted therapy or chemotherapy claim in the identification period was defined as the index date. The initial treatment was thus considered index treatment if patients had no prior therapy with chemotherapy or targeted agents for PNET in the 1 year preceding the index date (baseline period) (e.g., prior use of SSAs was allowed). Chemotherapy included any of 8 agents reported as being used in this setting (temozolomide, streptozotocin, doxorubicin, fluorouracil, capecitabine, dacarbazine, oxaliplatin, or thalidomide).[9,13,17–22] To account for possible duplicate patients, if 2 patients had the same age, sex, geographic region, index treatment, and index date, 1 patient was randomly removed.

A portion of the study focused on treatment patterns. In the treatment pattern analysis, we identified patients with PNET who were continuously enrolled during the baseline period and then followed them until the end of enrollment or study end (December 31, 2013). Pancreatic neuroendocrine tumor treatment duration and sequence were examined for the index and all subsequent treatments received during the follow-up period (ie, not restricted to the first post-index year) using claims data following the index date. 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 up to 90 days; injectable medications were assumed to have a 28-day supply), or a change to another treatment category, or disenrollment, or study end. Discontinuation of treatment was defined as a therapy gap of more than 90 days. Treatment changes between therapy classes (e.g., everolimus to a cytotoxic) or between targeted therapies (e.g., everolimus to sunitinib), but not between chemotherapies, were considered switches.

Treatments were then evaluated with a graphical evaluation tool that plots treatment use over time using individual patient records and allowing visual identification of different patterns. Each color represented a different type of therapy (everolimus, sunitinib, or chemotherapy), with each row representing 1 patient. Treatment changes can be observed by shifts in color along a single row. Results were described by index therapy and within therapies.

The other portion of the analysis assessed disease burden. In the disease burden analysis, we focused on a subset of patients who had continuous enrollment during the baseline period and the first year of follow-up. Baseline measures included age, sex, region, Charlson Comorbidity Index, number of chronic conditions, and use of SSAs. We examined health care utilization (inpatient hospitalizations, emergency department [ED] visits, and office visits) and several comorbidities that are potentially related to PNET treatment using claims from the 1-year follow-up period. The comorbidities were selected from the following categories that were derived from a review of prescribing information for common PNET treatments[23–26]: blood, cardiac, gastrointestinal, infections (defined as infections of urinary tract and upper respiratory tract, pneumonia, bronchitis, nasopharyngitis, cystitis, sinusitis, and sepsis), kidney and urinary tract, lung, neurologic, pain, and skin.[27] Only newly reported comorbidities after the index date were considered. Patients with preexisting comorbidities, with claims in the preindex period, were excluded. All clinical conditions were identified using their respective *ICD-9-CM* codes, so the severity of these conditions could not be determined.

Descriptive statistics, including means, medians, standard deviation (SD), and percentages, were reported for all study measures, and stratified by comparison group. For bivariate comparisons between 2 treatment groups, χ^2 and *t*-tests were used for categorical and continuous variables, respectively.

RESULTS

A total of 582 patients with PNET initiating targeted therapy or chemotherapy were included in the treatment pattern analysis. Of those, 338 were continuously enrolled for 1 year after the index date and were therefore included in the disease burden analysis.

In the treatment pattern analysis, 72.2% (n = 420) of patients received chemotherapy as index treatment, whereas the remaining patients received targeted therapy (16.2% everolimus and 11.7% sunitinib). Eight chemotherapeutic agents were used, although temozolomide, capecitabine, fluorouracil, and oxaliplatin alone or in combination comprised 83.6% (351/420) of regimens. Median duration of the index treatment was 242 days with everolimus, 146 days with sunitinib, and 126 days for chemotherapy

TABLE 1. Treatment Pattern Analysis: Treatment Patterns Among 582 Patients With PNET Initiating Targeted Therapy or Chemotherapy

	All Newly Treated Patients With PNET (N = 582)				
	Targeted Therapy (n = 162)				
	Everolimus (n = 94)	Sunitinib (n = 68)	Chemotherapy (n = 420)	*P* (Everolimus vs Cytotoxic Chemo)	*P* (Sunitinib vs Cytotoxic Chemo)
Days on index treatment,* median	242	146	126	<0.001	0.007
Index treatment was censored (end of enrollment or study end before treatment stop), n (%)	24 (25.5)	10 (14.7)	33 (7.9)		
Ever switch to subsequent treatment in follow-up,†‡ n (%)	31 (33.0)	25 (36.8)	70 (16.7)		

*Median values account for censoring; treatment discontinuation defined as gap of more than 90 days; *P* values generated using log-rank test.

†Patients have variable follow-up time.

‡Switch among the 3 treatment categories: chemotherapy, everolimus, or sunitinib.

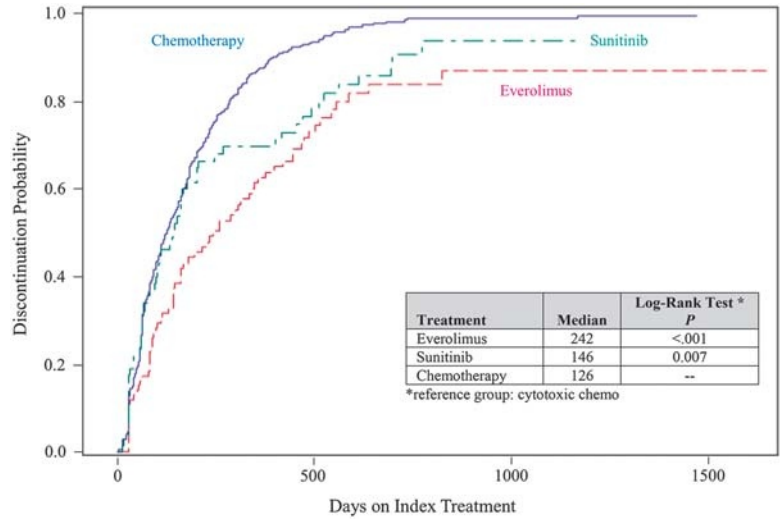

FIGURE 1. Treatment pattern analysis: duration of index treatment among 582 patients with PNET initiating targeted therapy or chemotherapy. Median duration of the index treatment was 242 days with everolimus, 146 days with sunitinib, and 126 days for chemotherapy therapy ($P < 0.001$ and $P = 0.007$).

therapy ($P < 0.001$ and $P = 0.007$; Table 1 and Fig. 1). A numerically higher percentage of patients who initiated sunitinib switched to a different treatment (36.8%) compared with patients whose index treatment was everolimus (33.0%; Table 1).

In the graphical analysis of treatment patterns, chemotherapy represented the largest index treatment group, but treatment generally did not last as long as it did with targeted therapies (Fig. 2). A few patients remained on therapy for prolonged periods, with treatment lasting more than 3 years in several cases. This can be observed in the greater number of colored rows after initial therapy was discontinued in the bottom sections (targeted) compared with the top (chemotherapy) (Fig. 2). The choice of subsequent treatment varied by and within each group (Fig. 2).

In the disease burden analysis, the average age was 54.5 (SD, 9.9) years (range, 10–82 years), and 45.6% of patients were female (Table 2). Most patients were from the South (38.5%), followed by 29.9% from the Midwest, 18.3% from the Northeast, and 13.3% from the West regions of the United States. Between-group differences for age, sex, and region were not statistically significant. The mean Charlson Comorbidity Index was higher among patients receiving targeted therapy compared with chemotherapy (10.6 vs 9.9, respectively; $P = 0.010$), although the mean number of chronic conditions was approximately 5 for both groups ($P = 0.370$). Prior use of SSAs was more prevalent among patients whose index treatment was targeted therapy compared with chemotherapy (53.4% vs 25.1%, respectively; $P < 0.001$), with the vast majority of SSAs used being octreotide (not shown).

Overall, 72.5% of all patients with PNET had claims for comorbidities occurring after beginning new treatment, and most symptoms occurred in similar proportions in both groups (Table 3). A group difference was observed for the presence of infections, which occurred more often among patients on targeted treatment (40.8%) compared with those on chemotherapy (26.8%, $P = 0.011$), although several other comorbidities were more common among patients taking chemotherapy versus targeted therapy: nausea and vomiting (33.2% vs 18.4%, $P = 0.006$), thrombocytopenia (13.6% vs 4.9%, $P = 0.018$), neutropenia (8.1% vs 1.0%, $P = 0.010$), and venous thrombosis (13.6% vs 3.9%, $P = 0.007$). Inpatient and outpatient health service encounters were common among patients with PNET, irrespective of treatment type. Nearly 43% of all patients had at least 1 inpatient hospitalization, and 47.9% had at least 1 ED visit during the first year of follow-up (Table 4). Patients had a mean of 25.5 (SD, 25.0) visits during this same period.

DISCUSSION

Understanding treatment patterns and burden of illness for PNET is essential to determining the most effective, efficient, and comprehensive way to diagnose, treat, manage, and care for those affected by this growing disease. There appears considerable variation in pattern of pharmacotherapeutic treatment for PNET. Although more patients initiate chemotherapy than targeted therapy, a wide variety of treatment sequences were observed. This is consistent with national evidence-based guidelines, which recommend everolimus, sunitinib, or chemotherapy without giving a clear hierarchy.[7,8] We identified 1 prior pilot study that reported first-line pharmacotherapy, and in that study, treatment included chemotherapy in 8 patients and targeted therapy in 7.[28] Decision making about the initiation and selection of treatment is dependent on numerous clinical pathological factors, including tumor grade, growth pattern, symptoms, performance status, and organ function. Modifications of treatment dose and schedule are appropriate, depending on the circumstance.[8–11] This may explain why no clear pattern of pharmacotherapeutic treatment for PNET exists.

Patients with PNET treated with targeted therapy as the index PNET treatment remain on this initial treatment for a longer duration than those treated with chemotherapy, possibly because of better tolerability or outcomes, although switching occurs often in both directions. Had we defined changes between chemotherapies as switches, the difference in duration of use between targeted and cytotoxic agents might have been greater. In clinical trials, targeted therapy is generally associated with fewer adverse effects and better survival than chemotherapy.[12,13] One clinical trial was terminated early because the risk of serious adverse events, disease progression, and death was higher in patients treated with placebo compared with those treated with sunitinib.[13] A recent meta-analysis of everolimus clinical trials reported a 67% incidence of stomatitis, 9% of which were grade 3/4.[29] The 6% stomatitis rate we observed

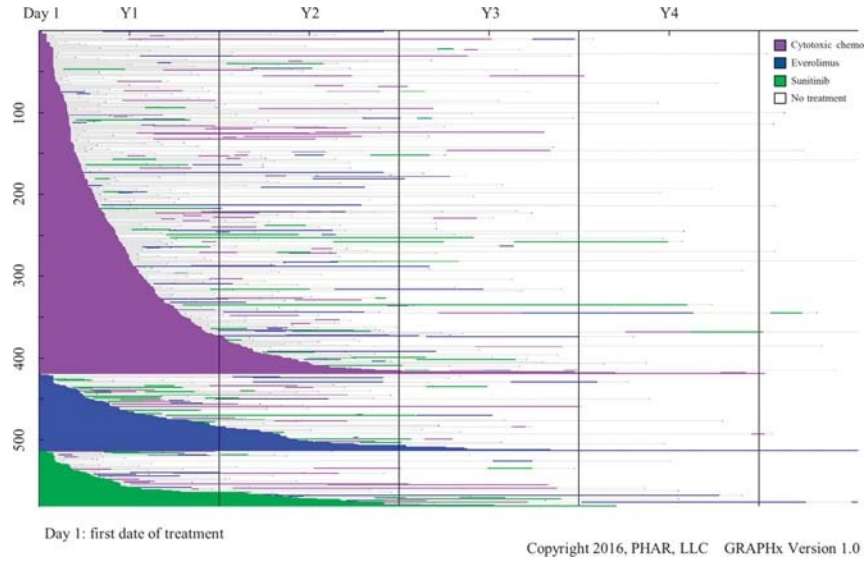

FIGURE 2. Treatment pattern analysis: treatment patterns among 582 newly treated patients with PNET. In the graphical analysis, each color represents a different type of therapy, with each row representing 1 patient. Treatment changes can be observed by shifts in color along a single row. Results are aggregated by index therapy, and within therapies, by length of continuous treatment. Gray regions represent patients enrolled but not using any of the drugs of interest, and black dots represent disenrollment.

with targeted therapy may reflect the fact that conditions not leading to additional treatment are less likely to be coded in claims.[30] That is, less severe cases of stomatitis (or other conditions) that did not trigger a new prescription may not have been coded and thus would not have been identified in our study. Patients treated with targeted therapy had increased progression-free survival compared with those treated with placebo.[12,13] We could not compare adverse effects or efficacy in this study.

In addition, our graphical analysis revealed that a substantial number of enrolled patients did not receive treatment, which is consistent with literature on the undertreatment of significant medical conditions in general and cancer specifically.[14,31–33] A 2009 study of more than 3000 patients with pancreatic cancer diagnosed from 1994 to 2003 found 42% of patients had no treatment of any kind.[31] A similarly sized study found a third of patients with colorectal cancer liver metastasis were untreated.[32] Cancer patients may decline treatment because they assume their quality of life will suffer, even if their length of life is extended, or because they prefer nontraditional therapies, or because they cannot tolerate treatment adverse effects. The American Society of Clinical Oncology encourages patients and their doctors to openly discuss the point at which further cancer treatment should be stopped.[33] We found no literature to provide a direct comparison with our findings. A prior study of treatment patterns in neuroendocrine tumors did not specifically address PNET, nor did it identify particular pharmacotherapies used.[14]

Our analysis of the burden of illness for PNET reveals that such patients consume substantial resources regardless of treatment type. Patients with PNET using targeted therapy or chemotherapy visit the ED or are hospitalized at high rates and, on average, have frequent physician office visits. These findings are consistent with studies showing an increased use of resources, such as physician visits, hospitalizations, and chemotherapy, as the PNET disease progresses. The need for diagnostics—including imaging, ultrasound, biomarker, and laboratory tests—in order

TABLE 2. Disease Burden Analysis: Baseline Characteristics Among 338 Newly Treated Patients With PNET

	Index Treatment			
	Targeted Therapy (n = 103)	**Chemotherapy (n = 235)**	**All (n = 338)**	***P****
Age, mean (SD), y	54.5 (9.3)	54.5 (10.1)	54.5 (9.9)	0.996
Sex, female, n (%)	48 (46.6)	106 (45.1)	154 (45.6)	0.799
Region, n (%)				
Northeast	15 (14.6)	47 (20.0)	62 (18.3)	0.500
Midwest	35 (34.0)	66 (28.1)	101 (29.9)	
South	41 (39.8)	89 (37.9)	130 (38.5)	
West	12 (11.7)	33 (14.0)	45 (13.3)	
Comorbidity index, mean (SD)	10.6 (2.2)	9.9 (3.1)	10.1 (2.9)	**0.010**
Chronic conditions, mean (SD)	4.9 (1.7)	5.1 (2.1)	5.1 (2.0)	0.370
SSA use, n (%)	55 (53.4)	59 (25.1)	114 (33.7)	**<0.001**

*Values in bold indicates statistical significance ($P < 0.05$).

TABLE 3. Disease Burden Analysis: Newly Reported Comorbidity* During the First-Year Postindex Date

	Index Treatment			
	Targeted Therapy (n = 103)	Chemotherapy (n = 235)	All Newly Treated Patients With PNET (n = 338)	*P*†
Presence of selected comorbidity following new treatment, n (%)	73 (70.9)	172 (73.2)	245 (72.5)	0.661
Infections‡	42 (40.8)	63 (26.8)	105 (31.1)	**0.011**
Nausea/vomiting	19 (18.4)	78 (33.2)	97 (28.7)	**0.006**
Anemia	26 (25.2)	70 (29.8)	96 (28.4)	0.394
Selected lung conditions§‖	14 (13.6)	39 (16.6)	53 (15.7)	0.485
Thrombocytopenia	5 (4.9)	32 (13.6)	37 (10.9)	**0.018**
Hypertension§	12 (11.7)	19 (8.1)	31 (9.2)	0.269
Neutropenia	1 (1.0)	19 (8.1)	20 (5.9)	**0.010**¶
Acute renal failure	5 (4.9)	14 (6.0)	19 (5.6)	0.685
Rash	6 (5.8)	8 (3.4)	14 (4.1)	0.304
Stomatitis or mucositis	6 (5.8)	6 (2.6)	12 (3.6)	0.135
Congestive heart failure§	0 (0.0)	6 (2.6)	6 (1.8)	0.183¶
Febrile neutropenia	0 (0.0)	5 (2.1)	5 (1.5)	0.328§
Cardiomyopathy§	2 (1.9)	2 (0.9)	4 (1.2)	0.588¶
Myocardial infarctions§	2 (1.9)	2 (0.9)	4 (1.2)	0.588¶
Neuropathy	0 (0.0)	2 (0.9)	2 (0.6)	0.999§
Gastrointestinal perforation	0 (0.0)	2 (0.9)	2 (0.6)	0.999§
Stroke§	1 (1.0)	1 (0.4)	2 (0.6)	0.517¶
Hemorrhage	0 (0.0)	1 (0.4)	1 (0.3)	0.999¶
Venous thrombosis	4 (3.9)	32 (13.6)	36 (10.7)	**0.007**¶
Arterial thromboembolism	0 (0.0)	1 (0.4)	1 (0.3)	0.999¶

*Values in bold indicates statistical significance ($P < 0.05$).

†*P* values in bold are significant.

‡Includes infections of the urinary tract and upper respiratory tract, pneumonia, bronchitis, nasopharyngitis, cystitis, sinusitis, and sepsis.

§Only newly reported comorbidities after the index date were considered. Patients with preexisting comorbidities, with claims in the preindex period, were excluded.

‖Includes noninfectious pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

¶Fisher's exact test.

to appropriately treat, manage, and continuously follow up and monitor PNET and its disease and treatment-related conditions may account for the increase in resource utilization.

This study has several limitations. First, the sensitivity and specificity of our claims-based algorithm for identifying patients with PNET have not been validated; however, we used a standard approach of requiring initial and confirmatory *ICD-9-CM* diagnoses to identify patients with PNET, and our resulting sample showed similar age, treatment, and utilization characteristics as those reported previously.[34–37] Second, the sample size of patients

TABLE 4. Disease Burden Analysis: Health Care Utilization During the First Year Postindex date

	Index Treatment			
	Targeted Therapy (n = 103)	Chemotherapy (n = 235)	All Newly Treated Patients With PNET (n = 338)	*P*
No. of inpatient hospitalizations, n (%)				0.463
0	63 (61.2)	130 (55.3)	193 (57.1)	
1	23 (22.3)	53 (22.6)	76 (22.5)	
2+	17 (16.5)	52 (22.1)	69 (20.4)	
No. of ED visits, n (%)				0.374
0	51 (49.5)	125 (53.2)	176 (52.1)	
1	22 (21.4)	58 (24.7)	80 (23.7)	
2+	30 (29.1)	52 (22.1)	82 (24.3)	
No. of office visits, mean (SD)	23.3 (18.1)	26.5 (27.4)	25.5 (25.0)	0.215

receiving targeted therapy is small and is a combination of patients receiving everolimus and those receiving sunitinib; thus, we did not conduct adjusted analyses, making our findings descriptive only. Third, patients included in this study were those with commercial insurance plans captured in the 2 analyzed claims databases. Results may not be representative of patients with other types of insurance, Medicare, or those uninsured. Fourth, administrative claims data lack information about disease severity; as a result, we could not assess and adjust for severity of illness when making comparisons among treatment groups. Fifth, although PNET treatment patterns and burden of illness for patients treated with targeted therapy and those treated with chemotherapy were explored, the study included only patients with PNET. As a result, utilization of resources by patients with PNET could not be compared with those without PNET. Future studies using non-PNET control subjects are warranted. We reported use of SSAs among patients who began chemotherapy or targeted therapy; however, patients may also initially be treated with SSA alone, and these patients would not have been included in our study. Future studies should include these patients, particularly because the potential impact of SSAs on tumor burden, rather than symptoms alone, has been increasingly discussed.[38] Finally, patients in this study were identified in years 2009 to 2012 and treated in the years from 2009 to 2013, and practices may have changed since that time. In particular, everolimus and sunitinib were approved for the treatment of PNET in 2011, halfway through our study period; however, both were marketed for other indications before 2011, and evidence of their efficacy in PNET was published in abstract form more than a year before their approval.[39]

CONCLUSIONS

Real-world treatments for PNET followed varied patterns with respect to use of the index and all subsequent agents. Cytotoxics are used more commonly as early therapy than targeted agents, but generally for a shorter duration than targeted therapies. This difference in treatment duration may reflect a more favorable tolerability profile in targeted therapies, better disease control, or confounding, as we were unable to control for clinical differences between groups. One potential use of our findings is as a benchmark to which future studies of this rare condition can be compared in order to track changes in treatment over time.

Pancreatic neuroendocrine tumor carries a high burden of illness among all patients, irrespective of treatment type. A large proportion of patients with PNET are hospitalized or go to the ED in a given year. More than two-thirds of newly treated patients experienced a comorbidity, potentially related to treatment. Increased resource use may result from disease symptoms and/or comorbid conditions.

To our knowledge, this is the first claims study in the United States to provide these assessments of burden focused on newly treated patients with PNET alone. Further research, ideally using data that better reflect currently approved therapies, is needed to better understand this burden. Such research should include assessments of costs associated with the health care resource use, as well as costs associated with decreased quality of life and worse functional status.

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