Impact of Progression on Resource Utilization in the Treatment of Advanced Neuroendocrine Tumors

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ABSTRACT

Background: Advanced neuroendocrine tumors (NET) are associated with high morbidity and mortality; however, literature on resource utilization upon disease progression is scarce. This study aims to compare resource use in advanced NET patients at diagnosis versus post-progression.

Methods: An online survey was administered to physicians across the US, UK, Germany, France, Brazil and Italy. The survey collected resource utilization during the baseline (time post-diagnosis but pre-progression), 1st, and 2nd progression periods. Progression was defined as measurable/radiographic evidence of tumor progression.

Results: 197 physicians participated, providing data on 394 patients. Average durations in baseline, 1st and 2nd progression were 12.8, 8.7 and 12 months, respectively. Advanced NET subtypes included gastrointestinal (GI) (45%), lung (24%), and pancreas (31%). Resource utilization consistently increased from baseline through progression.

Conclusions: It is important to characterize the burden posed by disease progression in advanced NET. Findings suggest that progression results in increased use of chemotherapy, PRRT, targeted therapies, and hospitalization rates.

BACKGROUND

- Neuroendocrine tumors (NET) are a group of diverse but related malignancies originating from neuroendocrine cells¹
- Patients are often diagnosed at a progressive stage of NET and, while in progression, typically undergo an extensive and exhaustive treatment regimen that may diminish their quality of life and impose substantial economic burden on the payers as well as the society¹
- Few studies have evaluated practice patterns and quantified resource utilization among NET patients, particularly after progression

OBJECTIVE

• To compare health care resource utilization in patients with advanced NET at diagnosis versus post-progression

METHODS

Study Design

- Data for health care resource utilization was collected through an in-depth online survey of physicians in the United States (US), United Kingdom (UK), France, Italy, Germany and Brazil from December 2010 to January 2011
- A survey invitation was sent to 4100 physicians with the objective to stop the study once approximately 180 responses were received, to meet the targeted sample distribution of: US, 50; UK, 30; Germany, 25; France, 25; Brazil, 25; and Italy 25
- Qualifying physicians were asked to abstract resource utilization data from charts of their recent patients with advanced gastrointestinal (GI), lung, or pancreatic NET
- Physicians were asked to provide information on at least 1 patient who had experienced tumor progression
- In addition, eligible physicians were required to have treated at least 3 patients with NET during the past year, to have experience of at least 3 years (but not greater than 30 years), and to allocate 50% of their time to direct patient care
- Inclusion criteria
- Patients diagnosed with well to moderately differentiated tumor histology
- Exclusion criteria
- Patients with poorly differentiated tumor histology
- Treatments administered (somatostatin analogs, chemotherapy, PRRT and other), surgical procedures, physician visits (survey physicians, other physicians), hospitalizations, laboratory tests and diagnostic scans were collected for each patient across all available follow-up time

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Patient Data Collection Period

- Data on resource utilization were collected during 3 distinct time periods (Figure 1)
- Chemotherapy use showed an upward trend from baseline to any progression event Baseline period (time post-diagnosis but pre-progression) (Table 1); however, data broken down by different disease states (i.e. baseline, first - First progression (period of time during which the patient is diagnosed with and treated progression and second progression) suggest that chemotherapy use may decline from for progressive NET) first progression to second progression among pancreatic NET patients (31.2% vs. 24.0%) but may actually increase among GI/lung NET patients (28.4% vs. 31.4%)
- Second progression (period of time during which the patient is diagnosed with and treated for a second disease progression following previous treatment for NET progression)
- Progression was defined as measurable tumor progression by radiographic evidence
- Resource use for this study is reported for "baseline period" and "any patient progression" where "any patient progression" includes both first progression and assumed second progression for all patients; therefore, any patient may be analyzed for up to 2 progressions

Figure 1. Advanced NET patient timeline.



• For patients who did not have a documented second progression, physicians were asked to consider a hypothetical second progression and to estimate resource utilization over a 1-year period following that progression. This method was applied due to the expectations that only a small sample of patients would have experienced an actual second progression (17.5% in this case) and those patients were likely to have had their follow-up period censored at different points

RESULTS

- 197 physicians responded to the survey by the end of January 2011 and provided data on 394 patients (precisely 2 patients per physician responder)
- Across all 6 countries, the majority of the respondents were medical oncologists (38%), followed by an equal proportion of gastroenterologists (25%) and endocrinologists (25%) (Figure 2)

Figure 2. Primary medical specialty of physician survey responders.



- The sample distribution of patients diagnosed with GI NET, lung NET and pancreatic NET as their primary tumor were 45%, 24% and 31%, respectively
- Overall, 229 (60.7%) patients with baseline data (n=377) experienced actual disease progression with a total of 295 progression events, including first and/or second progression

- Average duration of the baseline stage was 12.8 months and that of the first progression stage was 8.7 months
- More patients were hospitalized during progression than at baseline (**Table 1**)
- Somatostatin analog use trended lower overall from baseline to any progression (Table 1)
- It was also observed that the use of targeted therapy trended higher from baseline to any progression (Table 1)
- Patients were treated with PRRT during any progression nearly 3 times more frequently than during baseline (**Table 1**)
- The number of patients undergoing surgery, however, decreased during progression compared with baseline (**Table 1**)
- Proportions of resources used were found to vary by tumor type. Use of chemotherapy and PRRT was higher among GI/lung NET patients, whereas use of targeted therapy and surgery was higher among pancreatic NET patients (**Table 1**)
- However, resource utilization patterns from baseline to any progression event were observed to be consistent across different types of tumors (**Table 1**)

	Baseline, %			Any Progression, %		
	All NET (N=377)	GI/Lung (N=264)	Pancreas (N=113)	All NET (N=640)	GI/Lung (N=442)	Pancreas (N=198)
Chemotherapy*	21.8 (82)	23.9 (63)	16.8 (19)	29.2 (187)	30.3 (134)	26.8 (53)
PRRT	1.9 (7)	1.9 (5)	1.8 (2)	6.1 (39)	6.3 (28)	5.6 (11)
Somatostatin analogs	61.0 (230)	61.7 (163)	59.3 (67)	48.0 (307)	48.4 (214)	47.0 (93)
Routine Monitoring						
Ultrasound	52.5 (198)	50.0 (132)	58.4 (66)	40.2 (257)	39.1 (173)	42.4 (84)
CT scans (conventional or helical)	84.9 (320)	86.4 (228)	81.4 (92)	81.6 (522)	82.8 (366)	78.8 (156)
Other imaging [#]	49.6 (187)	48.1 (127)	53.1 (60)	34.4 (220)	33.5 (148)	36.4 (72)
Biomarkers	69.0 (260)	68.2 (180)	70.8 (80)	55.2 (353)	54.1 (239)	57.6 (114)
Laboratory tests	56.2 (212)	52.6 (139)	64.6 (73)	46.9 (300)	43.4 (192)	54.6 (108)
Visits (surveyed physicians)	97.1 (366)	96.6 (255)	98.2 (111)	96.3 (616)	95.7 (423)	97.5 (193)
Hospitalizations	37.1 (140)	36.0 (95)	39.8 (45)	43.9 (281)	43.0 (190)	46.0 (91)
Surgery	28.7 (108)	26.5 (70)	33.6 (38)	23.9 (153)	23.1 (102)	25.8 (51)
Targeted therapies [†]	1.3 (5)	1.1 (3)	1.8 (2)	3.9 (25)	2.9 (13)	6.1 (12)

Table 1. Resource Utilization: Baseline Versus Any Progression

*Chemotherapy included 5-fluorouracil, actinomycin-D, capecitabine, carboplatin, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, etopo side, gemcitabine, irinotecan, mitotane, oxalipaltin, streptozocin, temzolomide and vincristine. *Other imaging included PET, SRS, mIBG, MRI, and chest X-ray.

[†] Targeted therapy includes everolimus, sunitinib, imatinib and bevacizumab.

DISCUSSION

- An upward trend was observed in the utilization of chemotherapy, PRRT (mostly ex-US³), targeted therapy and patients undergoing hospitalization from baseline to any progression
- However, study results suggest that rates of chemotherapy use may decline from first to second progression among pancreatic NET patients, perhaps due to their limited treatment efficacy for these patients

- Although use of targeted therapy appeared to increase during progression compared with baseline, point estimates of usage rates remained lower than the use of chemotherapy during progression, likely due to lack of targeted therapies being approved at the time of this study
- Targeted therapy use was also projected to increase in second progression versus first progression
- A decrease in surgeries observed with progression may be attributed to the fact that in an advanced stage, metastasis is observed and the tumor is often deemed nonresectable
- Tests (e.g. imaging scans and laboratory tests) were performed at a higher rate at baseline, likely due to their use during the initial stages of diagnosis

LIMITATIONS

- By accepting the survey invitation, physicians self-selected themselves to participate in the survey; therefore, the study results are vulnerable to selection bias
- Additionally, the screening criteria of physicians and inclusion/exclusion criteria of patients might have excluded certain physicians and patients who would be part of the real-world NET population (e.g. patients treated by physicians with less than 2 years of experience), thereby affecting generalizability of the study results
- A total of 17 patients included in the study were deemed to have already entered into their first disease progression upon diagnosis of NET; therefore, information was not available for these patients at baseline. This could have resulted in underestimating resource use post-progression, as the data for baseline and progression may be incomplete
- Resource use data for patients in second progression were collected over a hypothetical scenario of 12 months and, hence, the reported results may not reflect actual resource utilization in second progression
- Targeted therapy use was not included as an explicit option in the survey and was assessed using an "other treatment" category for all nonspecified therapies, which might have underestimated actual targeted therapy
- Statistical comparisons were not conducted for this study; thus, results should only be interpreted as trends in resource use and practice patterns

CONCLUSIONS

- Recent recommendations propose that progression-free survival should be the primary endpoint in clinical trials in NET.² It is therefore important to characterize the impact of progression in the real world
- This study suggests that progression may result in increased use of chemotherapy, targeted therapy and PRRT as well as increased rates of hospitalization, and it confirms the overall high level use of resource utilization as disease progresses
- Targeted therapy use was reported to be relatively low, likely due to the limited awareness of the phase III data; however, its use is expected to increase in the future
- Resource utilization was found to follow a consistent pattern across NET tumor types as the disease progresses, suggesting that progression has a greater impact on resource utilization than tumor type

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