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Treatment Outcomes of Well-Differentiated High-Grade Neuroendocrine Tumors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine carcinoma • Neuroendocrine neoplasm • Neuroendocrine tumor • High-grade • Peptide receptor radionuclide therapy • CAPTEM

Abstract

Introduction. Recent classification of neuroendocrine neoplasms has defined well-differentiated high-grade neuroendocrine tumors (NET G3) as a distinct entity from poorly differentiated neuroendocrine carcinoma. The optimal treatment for NET G3 has not been well-described. This study aimed to evaluate metastatic NET G3 response to different treatment regimens.

Materials and Methods. This was a retrospective study of patients with NET G3 within the Mayo Clinic database. Patients' demographics along with treatment characteristics, responses, and survival were assessed. Primary endpoints were progression-free survival (PFS) and overall survival. Secondary endpoints were objective response rate (ORR) and disease control rate (DCR).

Results. Treatment data was available in 30 patients with median age of 59.5 years at diagnosis. The primary tumor was mostly pancreatic (73.3%). Ki-67 index was ≥55% in 26.7% of cases. Treatments included capecitabine + temozolomide (CAPTEM) (n = 20), lutetium 177 DOTATATE (PRRT; n = 10), Platinum-etoposide (EP; n = 8), FOLFOX (n = 7), and everolimus (n = 2). CAPTEM exhibited ORR 35%, DCR 65%, and median PFS 9.4 months (95% confidence interval, 2.96–16.07). Both EP and FOLFOX showed similar radiographic response rates with ORR 25.0% and 28.6%; however, median PFS durations were quite distinct at 2.94 and 13.04 months, respectively. PRRT had ORR of 20%, DCR of 70%, and median PFS of 9.13 months.

Conclusion. Among patients with NET G3, CAPTEM was the most commonly used treatment with clinically meaningful efficacy and disease control. FOLFOX or PRRT are other potentially active treatment options. EP has some activity in NET G3, but responses appear to be short-lived. Prospective studies evaluating different treatments effects in patients with NET G3 are needed to determine an optimal treatment strategy. ***The Oncologist*** 2021;26:383–388

Implications for Practice: High-grade well-differentiated neuroendocrine tumors (NET G3) are considered a different entity from low-grade NET and neuroendocrine carcinoma in terms of prognosis and management. The oral combination of capecitabine and temozolomide is considered a good option in the management of metastatic NET G3 and may be preferred. FOLFOX is another systemic option with reasonable efficacy. Similar to other well-differentiated neuroendocrine tumors, peptide receptor radionuclide therapy seems to have some efficacy in these tumors.

Introduction

In recent years, gastroenteropancreatic (GEP) grade 3 neuroendocrine neoplasms (NEN G3) have increasingly become recognized as a clinical entity [1–3]. The World Health Organization (WHO) 2017 and, later, 2019 classifications for neuroendocrine neoplasms (NENs) introduced a new category of neuroendocrine tumor, high-grade well-differentiated neuroendocrine tumors (NET G3) as separate from neuroendocrine carcinoma (NEC) [4, 5] NET G3 is considered distinct from NEC in that

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Table 1. Baseline characteristics

Characteristics	Entire NET G3 cohort (*n* = 71)	NET G3 with treatment data (*n* = 30)
Sex, *n* (%)		
F	33 (46.5)	9 (30)
M	38 (53.5)	21 (70)
Age at diagnosis		
Median	63	59.5
Range	16–84	30–77
Primary tumor location, *n* (%)		
Pancreas	41 (57.7)	22 (73.3)
Small bowel	12 (16.9)	5 (16.7)
Unknown	5 (7)	1 (3.3)
GI NOS	4 (5.6)	0
Colon	3 (4.2)	1 (3.3)
Stomach	2 (2.8)	1 (3.3)
Liver	1 (1.4)	0
Esophagus	1 (1.4)	0
Mesentery NOS	1 (1.4)	0
Lung	1 (1.4)	0
Number of metastatic sites, *n* (%)		
> 1	36 (50.7)	17 (56.7)
1	29 (40.8)	12 (40.0)
0	6 (8.5)	1 (3.3)
Surgery of primary tumor? *n* (%)		
Yes	23 (32.4)	12 (40)
No	48 (67.6)	18 (60)
Ki-67		
Median	30.1	30.55
Range	20.4–90	21–84
Ki-67 above or equal to 55, *n* (%)		
Yes	12 (16.9)	8 (26.7)
No	59 (83.1)	22 (73.3)
Synaptophysin+, *n* (%)		
Yes	66 (100)	28 (100)
N-miss	5	2
Chromogranin+, *n* (%)		
Yes	59 (90.8)	26 (96.3)
Weakly positive	3 (4.6)	1 (3.7)
No	3 (4.6)	0
N-miss	6	3
Positive FDG-PET, *n* (%)		
Yes	9 (75)	3 (60)
No	3 (25)	2 (40)
N-miss	59	25
Positive SRI, *n* (%)		
Yes	44 (91.7)	26 (96.3)
No	4 (8.3)	1 (3.7)
N-miss	23	3
Sites of metastases, *n* (%)		
Liver	61 (85.9)	28 (93.3)
Lymph node	17 (23.9)	8 (26.7)
Bone	11 (15.5)	7 (23.3)
Lung	7 (9.9)	3 (10)
Peritoneum	6 (8.5)	4 (13.3)
Mesentery	4 (5.6)	2 (6.7)
Adrenal	2 (2.8)	2 (6.7)
Brain	2 (2.8)	2 (6.7)
Spleen	2 (2.8)	0
Omentum	1 (1.4)	0
Breast	1 (1.4)	0

Summary of baseline characteristics among the entire NET G3 cohort.

Abbreviations: F, female; FDG-PET, flurodeoxyglucose-positron emission tomography; M, male; N-miss, data not available; NET G3, well-differentiated high-grade neuroendocrine tumor; NOS, not otherwise specified; SRI, somatostatin receptor imaging; SRS, somatostatin receptor scintigraphy.

morphologically it appears well-differentiated on histology despite sharing an elevated proliferative activity such as Ki-67 index >20% and mitotic rate >20/10 high-power field [4].

NET G3 compose approximately 18% of NEN G3 [1, 2] and are mostly (46%–65%) of pancreatic origin [1, 2, 6]. This new classification and identification of NET G3 as an entity has prognostic and therapeutic implications [3]. One retrospective study found a significantly higher median overall survival (mOS) in NET G3 than in NEC, with 98.7 versus 17 months ($p < .001$) [2]. Another study revealed mOS of 41 months in NET G3 versus 17.0 months in NEC [3]. In addition to survival differences, treatment responses also differ between NET G3 and NEC. Following the NORDIC study, which established platinum-etoposide (EP) as the standard of care first-line treatment for NEC [7], subsequent retrospective studies have shown reduced response rate and progression-free survival after EP therapy in NET G3 compared with NEC [2, 3].

Currently, most of the treatment regimens used for NET G3 are either extrapolated from both NEC and NET grade (G) 1–2 treatments or are based on small retrospective studies. In addition to EP, the other treatment options include somatostatin analogs (SSAs), capecitabine and temozolomide (CAPTEM), sunitinib, everolimus, immunotherapy, and peptide receptor radionuclide therapy (PRRT) [6, 8, 9]. In this retrospective analysis, we aim to evaluate the clinical outcomes of patients with NET G3 treated with different cytotoxic regimens at Mayo Clinic. SSA use in NET G3 is discussed in a separate retrospective Mayo Clinic study [10].

Table 2. Survival among patients with well-differentiated high-grade neuroendocrine tumors stratified by Ki-67

Outcomes	Ki-67 ≥55% (*n* = 12)	Ki-67 >20%–54% (*n* = 59)	Total (*n* = 71)
Median follow-up, mo			9.20 (0.46–47.80)
OS from diagnosis, mo			
Events	4	19	23
Median survival (95% CI)	NR (0.394–NR)	42.09 (15.64–NR)	42.09 (15.64–NR)

Abbreviations: CI, confidence interval; mo, months; OS, overall survival; NR, not reached.

Table 3. Treatment response and survival in NET G3

Outcomes	CAPTEM (*n* = 20)	PRRT (*n* = 10)	EP (*n* = 8)	FOLFOX (*n* = 7)	Everolimus (*n* = 2)
Line of therapy, *n* (%)					
First	10 (50.0)	1 (10)	4 (50.0)	2 (28.6)	0 (0.0)
Second	10 (50.0)	1 (10)	3 (37.5)	2 (28.6)	1 (50.0)
Third or higher	0 (0.0)	8 (80)	1 (12.5)	3 (42.9)	1 (50.0)
Best response, *n* (%)					
PR	7 (35.0)	2 (20.0)	2 (25.0)	2 (28.6)	0 (0.0)
SD	6 (30.0)	5 (50.0)	2 (25.0)	2 (28.6)	1 (50.0)
PD	7 (35.0)	3 (30.0)	4 (50.0)	3 (42.9)	1 (50.0)
DCR	13 (65.0)	7 (70.0)	4 (50.0)	4 (57.1)	1 (50.0)
ORR	7 (35.0)	2 (20.0)	2 (25.0)	2 (28.6)	0 (0.0)
PFS, months (95% CI)	9.40 (2.96–16.07)	9.13 (3.42-NR)	2.94 (1.31–6.37)	13.04 (0.89-NR)	1.23 (0-NR)
OS, months (95% CI)	41.23 (17.48-NR)	NR (7.29-NR)	39.56 (2.10-NR)	NR (8.28-NR)	NR (NR-NR)
Median follow-up (*n* = 30), mo	18.91 (1.64–47.80)	18.91 (1.64–47.80)	18.91 (1.64–47.80)	18.91 (1.64–47.80)	18.91 (1.64–47.80)

Abbreviations: CAPTEM, capecitabine and temozolomide; CI, confidence interval; DCR, disease control rate; EP, Platinum-etoposide; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; NET G3, well-differentiated high-grade neuroendocrine tumor; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide radionuclide receptor therapy; SD, stable disease.

Materials and Methods

This is a retrospective study that was approved by the Mayo Clinic Institutional Review Board. Patients with NET G3 were identified within the Mayo Clinic database (Arizona, Florida, and Minnesota) between 1992 and 2019. Patients with NET G3 were selected based on pathology reports indicating well-differentiated morphology and Ki-67 >20%. All tissue biopsies were reviewed by Mayo pathologists. Electronic medical records were reviewed, and information from patient demographics, pathology reports, tumor characteristics, imaging, and received treatments were extracted. Demographics included patient age, gender, and date of diagnosis. Tumor characteristics include site of primary NET, number and sites of metastases, Ki-67 index, and somatostatin receptor imaging (SRI) positivity. Treatment response and survival data were assessed retrospectively by reviewing imaging scans and using the RECIST version 1.1 criteria [11].

The primary endpoints were PFS (defined as time from date of treatment initiation to date of progression or death) and overall survival (OS; defined as time from date of treatment initiation to the date of death). Patients were censored if there was no progression or if they were lost to follow-up. Secondary endpoints include objective response rate (ORR), defined as partial or complete response, and disease control rate (DCR), defined as ORR + stable disease.

Descriptive statistics such as median and range were used to describe age and Ki-67. Frequency was used to describe gender distribution, primary and metastatic sites, immunochemistry positivity, and treatment response. The 95% confidence interval (CI) for median survival times was calculated using the log-log method.

Results

Baseline Characteristics

A total of 71 patients (male: *n* = 38, female: *n* = 33) with NET G3 were identified with a median age of 63 years (range, 16–84) at time of diagnosis (Table 1). The most common primary tumor was the pancreas (57.7%), followed by small bowel (16.9%). The liver was the most common site of metastasis (85.9%). Median Ki-67 was 30.1% (range, 20.4%–90%). A total of 91.7% of patients were SRI positive compared with 75% fluorodeoxyglucose–positron emission tomography (FDG-PET) positive among those who received corresponding imaging (Table 1). Median OS from time of diagnosis was 42.09 months (95% CI, 15.64–not reached [NR]; Table 2).

Treatment Response

Systemic treatment data was available in 30 patients (male: *n* = 21, female: *n* = 9), with median age of 59.5 years (range,

Table 4. CAPTEM stratified by Ki-67: Treatment response and survival data

Outcomes	Ki-67 ≥ 55% (*n* = 6)	Ki-67 20–54% (*n* = 14)
Best response, *n* (%)		
PR	4 (66.7)	3 (21.4)
SD	0 (0.0)	6 (42.9)
PD	2(33.3)	5 (35.7)
DCR	4 (66.7)	9 (64.3)
ORR	4 (66.7)	5 (35.7)
PFS, months (95% CI)	17.18 (0.53–NR)	7.70 (2.17–11.99)
OS, months (95% CI)	NR (0.99–NR)	41.23 (13.80–NR)

Abbreviations: CI, confidence interval; DCR, disease control rate; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 5. CAPTEM stratified by treatment line: Treatment response and survival data

Outcomes	First-Line (*n* = 10)	Second Line (*n* = 10)
Best response		
PR	5 (50.0)	2 (20.0)
SD	3 (30.0)	3 (30.0)
PD	2 (20.0)	5 (50.0)
DCR	8 (80.0)	5 (50.0)
ORR	5 (50.0)	2 (20.0)
PFS (mo) (95% CI)	10.35 (1.45–17.18)	4.44 (0.53–NR)
OS (mo) (95% CI)	41.23 (4.30–NR)	NR (0.99–NR)

Abbreviations: CI, confidence interval; DCR, disease control rate; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

30–77) at time of diagnosis (Table 1). Median follow-up was 18.91 months (1.64–47.80; Table 3). Treatment regimens included CAPTEM (*n* = 20), lutetium Lu 177 DOTATATE (PRRT; *n* = 10), EP (*n* = 8), folinic acid/fluorouracil/oxaliplatin (FOLFOX; *n* = 7), and everolimus (*n* = 2; Table 3). CAPTEM was the most commonly used regimen (10 first line and 10 second line), with ORR of 35%, DCR of 65%, and median of PFS 9.40 months. We further stratified CAPTEM-treated patients by treatment line (first vs. second) and by Ki-67 (Ki-67 ≥55 vs. Ki-67 20–54) as demonstrated in Tables 4 and 5. ORR was 50% versus 20%, DCR was 80% versus 50%, and PFS was 10.35 versus 4.44 months for those who received CAPTEM first and second line, respectively.

PRRT was the next-most commonly used treatment (*n* = 10), with ORR of 20%, DCR of 70%, and median PFS of 9.13 months (95% CI, 3.42–NR). EP was used in eight patients (4 in first-line and 4 in second-line or higher), with ORR of 25.0%, DCR of 50.0%, and median PFS of 2.94 months (95% CI 1.31–6.37). Similarly, FOLFOX was used in seven patients (2 first-line, 2 second-line, and 3 in later lines), with ORR of 28.6%, DCR of 57.1%, and PFS of 13.04 months (95% CI, 0.887–NR). Table 3 summarizes the treatment data and responses rates for the various therapies used.

Discussion

In this retrospective study of patients with NET G3, we found that NET G3 tumors mostly originate from the pancreas with a variable Ki 67 that is mostly <55%. In addition, most of these tumors have positive SRI and can have avidity on FDG-PET. These findings are consistent with other studies examining NET G3 [1–3, 6].

In our cohort, CAPTEM was the most commonly used systemic treatment with the highest observed response rate (ORR of 35%) and second-longest PFS (9.4 months). In contrast, the ORR was 28.6%, 25.0%, and 20.0% for FOLFOX, EP, and PRRT, respectively, with FOLFOX having the longest median PFS of 13.04 months. Similar findings were reported in a recent multicenter study from Germany [12].

CAPTEM has been traditionally used in advanced pancreatic G1/G2 NET retrospective studies, and a recent randomized phase II study showed documented activity in this disease [13–17]. A recent meta-analysis examined the use of CAPTEM in advanced NEN (G1–3), finding that median PFS (mPFS) ranged from 3.4 to 6 months in G3 NEN [18]. Additionally, DCR was 56.91% (95% CI, 36.44–77.39; p = .10) among G3 NEN–exclusive studies [18]. Both DCR and mPFS among our patient cohort who received CAPTEM are higher than what was found in the meta-analysis, likely because of including studies that did not comment on morphological differentiation or incorporate the recent WHO classification for G3 NEN (NET G3 vs. NEC).

Other retrospective studies evaluating patients with NET G3 showed similar CAPTEM efficacy. For example, two multicenter retrospective studies were recently reported. A study of 56 patients with NET G3 showed an ORR of 52%, time to treatment failure of 5.8 months, and mOS of 30.1 months [19]. Another study from China examined 17 patients with NET G3 who received CAPTEM, with ORR of 11.8%, DCR of 81.3%, and mPFS of 8.4 months (95% CI, 8.3–8.6 months) [20]. In a retrospective analysis of 11 metastatic cases of NET G3 treated with CAPTEM, patients who received CAPTEM first-line compared with those who received prior systemic treatment had a higher OS (29 vs. 20 months, p = .49) and PFS (17 vs. 8 months, p = .3) [21]. Similarly, a recent multicenter retrospective study of 21 patients with NET G3 who received temozolomide-based therapy (mostly CAPTEM) in a first-line setting showed ORR of 28.6%, DCR of 66.7%, and mPFS of 12.0 months [12].

Among our patients with NET G3, we found that those who received CAPTEM first-line had mPFS 10.35 months (95% CI, 1.45–17.18) compared with mPFS 4.44 months (0.53–NR) in those who received CAPTEM second line (Table 5). Treatment response was also higher among those who received CAPTEM first-line compared with second line, with ORR 50% versus 20% and DCR 80% versus 50%. The ORR and DCR among patients who received CAPTEM first-line were higher in our study compared with the findings in Apostolidis et al.'s study [12], which may be due to their inclusion of patients who received temozolomide monotherapy and our small sample size. Nevertheless, the data suggest that there is possibly an improved treatment response and survival advantage for patients with NET G3 who receive CAPTEM first-line over second line, similar to

the findings in Sahu et al.'s study [21]. CAPTEM was recently shown to be very safe in a large retrospective study of 426 patients, and severe myelotoxicity is rare, but severe thrombocytopenia and neutropenia was more commonly seen among women than men [22]. No cases of myelodysplastic syndrome were seen in patients receiving CAPTEM, with the exception of three patients who also had received PRRT [22]. Moreover, there were no cases of opportunistic *Pneumocystis jirovecii* infections among the patients treated, and therefore, prophylactic antibiotic therapy is not indicated unless patients are concurrently treated with other immunosuppressive agents such as corticosteroids.

PRRT has been previously found to yield an OS benefit over high-dose long-acting octreotide with ORR 18% in patients with metastatic well-differentiated NET of midgut primary (Ki-67 <20%) in the NETTER-1 trial [23]. For patients with NET G3, PRRT has not been investigated in a prospective manner, but trials are underway (NCT03972488). However, as these tumors are SRI positive (approximately 91.7% in our cohort), PRRT is considered a potential option [24]. This has been shown in retrospective series [25, 26], with ORR reaching 42% in a recent multicenter retrospective study of 114 patients and median PFS of 19 months [26]. Our NET G3 patient cohort had 10 (33%) patients who received PRRT, with ORR of 20%, DCR of 70%, and median PFS of 9.13 months (95% CI, 3.42–NR). These differences might be explained by the fact that most of our PRRT patients were heavily pretreated (80% third-line or more) and the small sample size.

In our patient cohort, seven patients received EP, with ORR of 25.0%, DCR of 50.0%, PFS of 2.94 months (95% CI, 1.31–NR), and mOS of 39.56 (95% CI, 2.10–NR). Platinum-based therapy has been traditionally used and recommended as first-line therapy in patients with NEC following the NORDIC NEC study [7, 8, 27]. However, Heetfeld et al. reported lower DCR (33% vs. 68%; $p = .03$) and PFS (2.4 vs. 5.9 months; $p = .049$) in NET G3 compared with NEC, respectively, showing that platinum-based therapy may not be as efficacious in NET G3 [2]. Additionally, this may be in concordance with the findings in the NORDIC NEC study, in which tumors with Ki-67 < 55% (differentiation unspecified) were less responsive to platinum-based therapy than tumors with Ki-67 ≥ 55% (15% vs. 42%, $p < .001$) [7]. Another study found 0% response rate among NET G3 compared with 31% in NEC among patients with GEP and thoracic NEN who received cisplatin-based chemotherapy ($p = .31$) [3]. This is in line with a Japanese multicenter study of platinum-based therapy in pancreatic NEN G3, in which response rate was 0% in NET G3 compared with 55.9% in NEC ($p < .001$) [28]. However, in a recent Chinese retrospective study of G3 GEP NEN, there was no significant difference in PFS of NET G3 versus NEC (2.6 months vs. 3.6 months, $p = .318$), and the RR was 30% and 25%, respectively [20]. Similarly, a recent multicenter retrospective analysis evaluated patients with NET G3 who received EP in a first-line setting ($n = 34$), finding ORR of 35.3%, DCR of 67.6%, and mPFS of 5.2 months [12]. In our study, the response rate and mPFS are comparable to observed ORR and survival in the more recent retrospective studies of EP in NET G3. This could suggest that although EP may display treatment effect, its duration of efficacy may be limited in NET G3. However, the small sample size limits our interpretation of the data.

In our cohort, seven patients were treated with FOLFOX, with an ORR of 28.6%, DCR of 57.1%, and mPFS of 13.04 months (95% CI, 0.89–NR). Median OS was not reached. FOLFOX has previously been found to have treatment response in retrospective studies of metastatic NET G1, G2, and NEC G3 [29, 30]. A multicenter retrospective analysis evaluated 36 patients with NET G3 who received FOLFOX in the first-line setting, finding ORR of 52.8%, DCR of 80.6%, and mPFS of 6.0 months [12]. Our response rates were lower than the above study, but mPFS was higher. These discrepancies are likely because of limited sample size and only two patients had received FOLFOX as first-line therapy.

Other treatment regimens have been used in NET G3, including sunitinib, immune checkpoint inhibitors, and SSAs [10, 31, 32]. In a separate Mayo Clinic study, treatment response and survival were assessed in patients with NET G3 who received SSA ($n = 14$), finding ORR of 14.3%, DCR of 64.3%, and mPFS of 4.4 months (95% CI, 2.9–24) [10].

Conclusion

Among patients with NET G3 treated at Mayo Clinic, CAPTEM was found to be the most commonly used treatment with reasonable efficacy and disease control. Although EP was initially considered not to show activity in NET G3, our study did show treatment response. EP could be considered early on in patients with clinically aggressive NET G3, especially if there are concerns about a poorly differentiated component. FOLFOX was shown to be an acceptable therapy option with the longest PFS in our analysis. Given the observed efficacy of CAPTEM and favorable safety profile, it may be preferred over other regimens in the first-line setting. Further prospective studies evaluating different treatments effects in patients with NET G3 are needed to determine an optimal treatment strategy.

Author Contributions

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Disclosures

Jason Starr: Natera, Ipsen, Pfizer (C/A), Natera, Merus, Molecular Templates, Macrogenics, Rafael Pharmaceuticals, Incyte, Vedanta, Aprea (RF), Pfizer (OI); **Thorvardur R. Halfdanarson:** Ipsen, Lexicon, AAA, Curium (C/A), ThermoFisher Scientific, Ipsen (RF). The other authors indicated no financial relationships.

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