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Temozolomide Alone or Combined with Capecitabine for the Treatment of Metastatic Neuroendocrine Neoplasia: A "Real-World" Data Analysis

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Keywords
Neuroendocrine tumors · Neuroendocrine carcinoma · Neuroendocrine neoplasia · Temozolomide · Capecitabine and temozolomide · Peptide receptor radionuclide therapy

Abstract

Background: Neuroendocrine neoplasias (NENs) are a rare group of tumors with different prognosis and response to therapy. Their heterogeneity is dependent on the site of origin, morphology, and Ki67. Temozolomide (TEM) appears to be active in metastatic NENs (mNENs) but there is limited evidence about its efficacy in gastrointestinal NENs. We analyzed "real-world" data on the use of TEM alone or in association with capecitabine (CAPTEM) in patients with mNENs. ***Patients and Methods:*** One hundred consecutive patients with advanced NENs treated with TEM or CAPTEM between 2009 and 2019 were included. A pretreatment tumor growth rate (TGR_0) was calculated. Overall survival (OS), progression-free survival (PFS), tolerance, objective response rate (ORR), and disease control rate (DCR) were analyzed. A propensity score analysis and inverse probability of treatment weights for Cox regression models were used. ***Results:*** TEM-based therapy was administered to 95 patients (26.3% CAPTEM and 83.7% TEM) with a median age of 59 years (range 26–85) years. ECOG performance status was 0–2. Carcinoid syndrome was reported in 12 (12.6%) patients. Twenty (21.1%) patients with grade (G) 3 neuroendocrine carcinoma (NEC) and 9 (9.4%) with G3 neuroendocrine tumors (NETs) were included in the analysis. Median PFS of the entire group was 10.4 months (95% confidence interval [CI]: 6.0–11.5). In multivariate analysis, a higher risk of progression was observed for NEC G3 patients (hazard ratio [HR] 2.70, 95% CI: 1.25–5.84) and for a TGR ≥19.55 (HR: 2.53, 95% CI: 1.45–4.40). Median OS was 23.4 months (95% CI: 17.0–29.0) and was similar in both treatment groups (23.9 vs. 20.5 months for TEM and CAPTEM, respectively, $p = 0.585$). In multivariate analysis, TGR ≥19.55 was associated with a higher risk of death (HR: 2.18, 95% CI: 1.16–4.11) than TGR <19.55, as was NEC G3 (HR: 2.42, 95% CI: 1.04–5.59) with respect to NETs. No differences in terms of mPFS or mOS were seen in relation to the primary site of disease. In the 86 patients evaluable for response, ORR was 44.1% and the DCR was 70.9%. Mild adverse events (grade I–II) included anemia, neutropenia, and headache. Rare cases of G 3 neutropenia and thrombocytopenia were recorded. ***Conclusions:*** TEM-based regimens are associated

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with a high DCR and a relatively tolerable toxicity profile in NENs of pancreatic, intestinal, and lung origin. Further investigation of these specific NETs is warranted in prospective clinical trials.

Introduction

Rationale

Neuroendocrine neoplasias (NENs) are rare tumors arising from cells of the diffuse neuroendocrine system commonly located in the gastrointestinal (GI) tract and the lungs. Despite their low incidence, prevalence is high and has substantially increased over the last 2 decades [1, 2]. Given the lack of screening programs, NENs are often only diagnosed when the disease has spread to other organs. Prognosis varies substantially on the basis of site of origin, differentiation, and proliferation index (Ki67) [3]. Consequently, the pathological and clinical classification is based on these factors [4, 5]. In particular, NENs of the gastroenteropancreatic tract are subdivided into grade (G)1, G2, and G3 neuroendocrine tumors (NETs) and G3 neuroendocrine carcinomas (NECs) on the basis of Ki67 and morphology [6, 7].

Lung NENs are categorized according to mitosis and necrosis into typical and atypical carcinoids and poorly differentiated small-cell and large-cell NECs [8]. Recently, a new entity called supra-carcinoid was hypothesized for lung NENs with an intermediate clinical behavior between carcinoids and large-/small-cell NECs [9]. Several treatments for NETs have been validated or investigated in prospective clinical trials, including somatostatin analogs (SSAs), peptide receptor radionuclide therapy (PRRT), multi-kinase inhibitors such as sunitinib, axitinib, lenvatinib, and pazopanib, and the mammalian target of rapamycin inhibitor, everolimus [10–13].

Platinum-based chemotherapy regimens remain the cornerstone of treatment for poorly differentiated NECs [14, 15]. Temozolomide (TEM), a second-generation alkylating agent that works by methylating DNA and triggering cell death by apoptosis, is widely used to treat glioblastoma [16]. Its activity is not cell-cycle specific and can also be used in low-proliferating tumors [17].

TEM has been investigated as monotherapy or in combination with other compounds (capecitabine, bevacizumab, thalidomide, and everolimus) in NETs, obtaining a significant tumor response in pancreatic and thoracic NENs. The drug has also shown some activity in G3 NENs, but GI NETs appear to be less chemoresponsive [18, 19].

The TEM combination with capecitabine (CAPTEM) is a widely used regimen supported by good in vitro results. 5-fluorouracil depletes the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT) and has been shown to potentiate the effect of TEM. However, the role of MGMT in NENs remains unclear [20]. In some retrospective series, CAPTEM was associated with significant objective response rate (ORR) in both chemotherapy-naive and heavily pretreated patients with pancreatic NENs (pNENs) and non-gastroenteropancreatic NENs. However, efficacy is still much debated for GI NENs [21].

To date, clinical trials of TEM in NEN patients have focused mainly on pNENs and lung NENs (ClinicalTrials.gov Identifier: NCT02698410; NCT01824875). Chatzellis et al. [22] conducted a retrospective analysis of CAPTEM in 79 patients with primary pNENs (30, 38%) or GI NENs (15, 19%). Median progression-free survival (PFS) and overall survival (OS) was 10.1 and 102.9 months, respectively. In multivariable analysis, Chatzellis et al. [22] found that a pancreatic or lung primary tumor site was an independent prognostic factor for PFS (p = 0.002) and OS (p = 0.028). Furthermore, De Mestier et al. [23] compared CAPTEM with 5-fluorouracil-dacarbazine in 247 NEN patients, reporting a similar PFS in the 2 groups 13.9 vs. 18.3 months, p = 0.86. The majority of patients receiving CAPTEM had primary pNENs (82.3%) and only 27 had non-pNENs [23], supporting the idea that pNENs tend to be more chemosensitive than non-pNENs [24, 25]. Thomas et al. [26] reported a PFS of 13 months and OS of 38 months in NEN patients undergoing CAPTEM, regardless of tumor site or grade. ORR and disease control rate (DCR) were 21 and 70%, respectively. However, the study also included patients without metastases and one-third of the patients were treated with a systemic treatment other than SSAs [26].

In an evolving therapeutic scenario such as that of NETs, more information is needed on treatment strategies and on the impact of TEM side effects on subsequent or previous therapies. The aim of the present work was to report the results of a "real-world" experience of TEM-based chemotherapy in patients with NENs.

Patients and Methods

One-hundred consecutive patients with locally advanced, unresectable, or metastatic NENs who had received at least 1 cycle of TEM-based chemotherapy from January 2009 to December 2019 were retrospectively selected. A biopsy-proven diagnosis of NEN

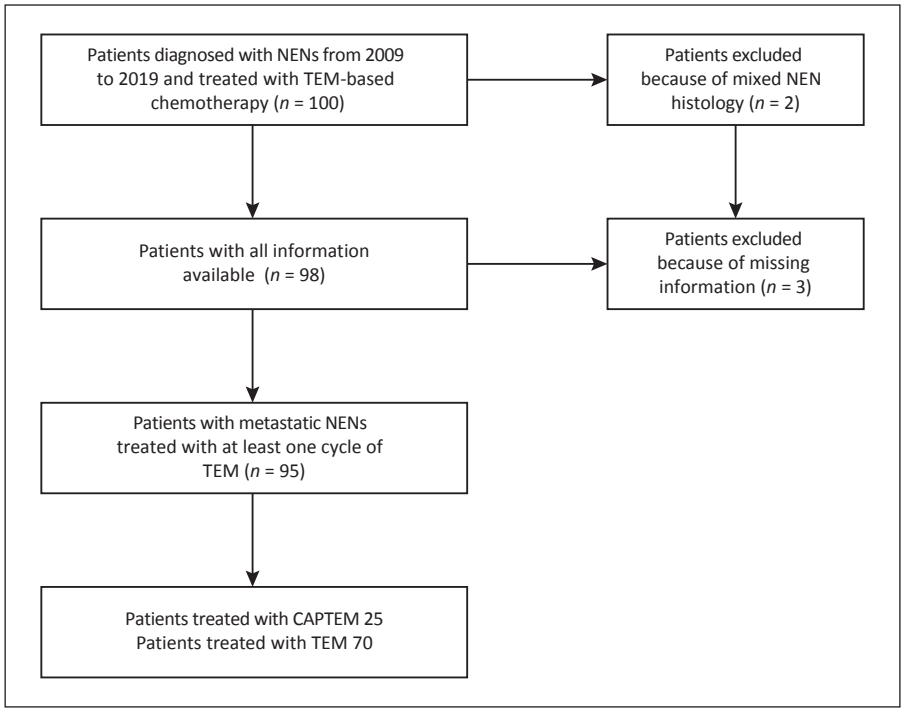

Fig. 1. Flow diagram of patients identified and included in the final analysis. NEN, neuroendocrine neoplasia; TEM, temozolomide; CAPTEM, capecitabine and temozolomide.

with measurable disease in either computed tomography (CT) or magnetic resonance imaging was the inclusion criterion. Patients were required to have progressive disease at radiological follow-up based on RECIST (Response Evaluation Criteria in Solid Tumors) criteria applied by a dedicated radiologist [27]. Ninety-five patients were considered eligible for the study (Fig. 1).

The decision to initiate TEM-based therapy was made by a multidisciplinary and interdisciplinary specialized tumor board of our institute, which is a member of the European Union Reference Network for Rare Cancers Neuroendocrine Tumor Group (EURACAN G4 NET). PRRT was available before the approval of lutetium Lu-177 dotatate for use in controlled phase II clinical trials. Patient and tumor characteristics (histology, grading, and secretory status), history of prior treatments and functional imaging properties acquired from ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET/CT), and somatostatin receptor imaging (Ga^{68} DOTATOC/DOTATATE PET/CT) were retrospectively collected. Histopathological diagnosis was performed by a dedicated pathologist on the basis of existing guidelines and updated according to 2017 and 2019 WHO classifications [6, 7]. Data were collected on tumor morphology (well vs. poorly differentiated) and Ki67 proliferation index to evaluate their prognostic impact. MGMT assessment was not routinely performed. All patients underwent dihydropyrimidine dehydrogenase analysis before starting CAPTEM.

The main side effects were graded according to National Cancer Institute Common Toxicity Criteria (version 5.0) [28]. TEM alone was administered over 5 days every 28 days. The CAPTEM regimen consisted of oral administration of capecitabine (750 mg/m^2) twice daily from days 1–14 and TEM once daily from days 10–14, every 28 days. In both regimens, TEM was started at a dose of 150 mg/m^2 for the first cycle and increased to 200 mg/m^2 for the following cycles [29, 30]. Ondansetron prophylaxis was administered 30 min before TEM.

All patients underwent a contrast-enhanced thoraco-abdomino-pelvic CT scan and/or abdominal MRI a maximum of 6 weeks before the start of chemotherapy. A clinical and biological evaluation, as well as a CT scan and/or MRI were performed at our institute every 3 months. If a scan had been performed elsewhere, the imaging was revised by an expert radiologist from the NEN multidisciplinary board.

Patients with no information on radiological assessment were not included in the response analysis. An alternative scenario was considered to taking account of these patients. All patients were included in the survival analysis, and those still undergoing TEM but not in progression entered the analysis with a PFS equal to the duration of treatment.

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS (project identification code: #L1P33). A waiver of informed consent was received from the Institutional Review Board. STROBE guidelines were used to guarantee the quality of data reporting.

Calculation of Tumor Growth Rate

Tumor growth rate (TGR) was calculated for all patients and expressed as the percentage change in tumor size over 1 month (%/m) using a previously published formula:

$$TGR = 100 \times (\exp[TG] - 1)$$
$$TG = (3\log[D2/D1])/\text{time (months)}$$

where TG = tumor growth, D1 = tumor size at date 1, D2 = tumor size at date 2, and time (months) = (date 2 – date 1 + 1)/30.44. Tu-

mor size was determined using the sum of the longest diameters of target lesions only [31, 32]. Pretreatment TGR_0 was calculated for each patient by comparing the baseline scan (before starting TEM-based therapy) with the previous scan.

Statistical Analysis

In this retrospective study, descriptive statistics were used to summarize demographic and clinical patient characteristics: continuous variables are reported as median (range), while categorical variables are reported as frequencies and percentages. OS was calculated as the time from start of TEM-based treatment to date of death or last follow-up visit. PFS was calculated as the time from start of TEM-based treatment to date of progressive disease or last follow-up visit. Survival curves for OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Median OS and PFS were reported with 95% confidence intervals (CIs). Univariate and multivariate Cox regression models were carried out to identify independent factors for OS and PFS, and hazard ratios (HRs) are reported with 95% CIs.

Propensity score analysis was used to balance covariates for patients treated with TEM-alone and CAPTEM in the nonrandomized setting of the study. A logistic regression model including baseline variables was used to generate a propensity score and inverse probability of treatment weights was used to weight the Cox regression models. Receiver operating characteristic curve analysis was used to determine potential TGR cutoff values in relation to disease progression within 12 months. Areas under the curve were plotted, 95% CIs were constructed, and sensitivity and specificity values were calculated. For overall response analysis, to taking account of all patients included in the study, an estimate value for response was calculated. This value was derived from multiple imputation models which included the distribution of observed data for some relevant prognostic factors such as stage of disease, line of therapy, and presence of metastasis. All p values were 2-sided and $p < 0.05$ was considered statistically significant. Power calculation was performed using pwr package in R software (version 3.6.3). Considering 20% as response under null hypothesis, 44% as observed response rate, 0.05 as significant level, and 86 as sample size, a power of 96% was found. Statistical analyses were carried out with STATA/MP 15.0 for Windows (StataCorp LP, College Station, TX, USA).

Results

Patient and Tumor Characteristics

Table 1 presents the main demographics and tumor characteristics of the 95 patients (male $n = 55$ [57.9%] and female = 40 [42.1%]) included in the study. Median age was 59 (range 26–85) years. Performance status was between 0 and 2 for all patients. Overall, the majority of patients had G2 NETs ($n = 53$, 55.8%). Twenty (21.1%) had G3 NECs and 9 (9.4%) had G3 NETs. Of note, one-third of the patients had tumors of GI origin and 25 (28.7%) of lung origin. There were also cases of other tumors: renal (2 patients), laryngeal (2), gallbladder (1), urinary bladder neuroendocrine (1), and unknown origin (2). Around half of the patients (49.5%) had >2 sites of metastasis. Carcinoid syndrome was reported in 12 (12.6%) patients, 5 (5.2%) had adrenocorticotropic hormone-producing tumors and 3 (3.1%) insulin-producing disease. All pa-

Table 1. Main characteristics of patients undergoing TEM-based chemotherapy

	N (%)
Gender	
Male	55 (57.9)
Female	40 (42.1)
Median age at treatment, years (range)	59 (26–85)
Site of primary disease	
Lung	25 (28.7)
Pancreas	23 (26.5)
GI tract	29 (33.3)
Other	10 (11.5)
Unknown	8
Classification	
NET G1	13 (13.7)
NET G2	53 (55.8)
NET G3	9 (9.4)
NEC G3	20 (21.1)
Morphology	
Well-differentiated	69 (72.6)
Poorly differentiated	26 (27.4)
Syndromic disease	21 (22.1)
ACTH-producing	5 (25.0)
Carcinoid	13 (62.0)
Insulin-producing	3 (15.0)
PET/CT (^{18}FDG)	
Negative	23 (24.7)
Positive	70 (75.3)
Unknown	2
PET/CT (^{68}gallium)	
Negative	22 (23.4)
Positive	72 (76.6)
Unknown	1
Previous surgery	
No	49 (51.6)
Yes	46 (48.4)
Site of metastasis	
Liver	79 (83.2)
Lung	35 (36.8)
Brain	6 (6.3)
Lymph node	55 (57.8)
Bone	47 (49.5)
Others	8 (8.4)

NET, neuroendocrine tumor; G, grade; ACTH, adrenocorticotropic hormone; PET/CT, positron emission tomography/computed tomography; GI, gastrointestinal; NEC, neuroendocrine carcinoma; ^{18}FDG, ^{18}fluoro-2-deoxy-D-glucose; TEM, temozolomide.

Table 2. Main characteristics of previous treatments and TEM-based chemotherapy

	N (%)
Previous treatment	
PRRT	59 (62.1)
Chemotherapy	62 (65.2)
Liver embolization	9 (9.5)
Targeted therapy	44 (46.3)
Median TRG pre-TEM (range)	14.2 (3.7–80)
TEM treatment	
TEM	69 (73.4)
CAPTEM	25 (26.6)
Unknown	1
SSA with TEM-based chemotherapy	65 (69.8)
Octreotide	32 (49.2)
Lanreotide	33 (50.8)
Line of TEM-based treatment	
I-line	7 (7.4)
II-Line	30 (31.6)
III-Line	36 (37.9)
IV-Line	18 (18.9)
Further line	4 (4.2)

SSA, somatostatin analog; PRRT, peptide receptor radionuclide therapy; TRG, tumor growth rate; TEM, temozolomide; CAPTEM, capecitabine and temozolomide.

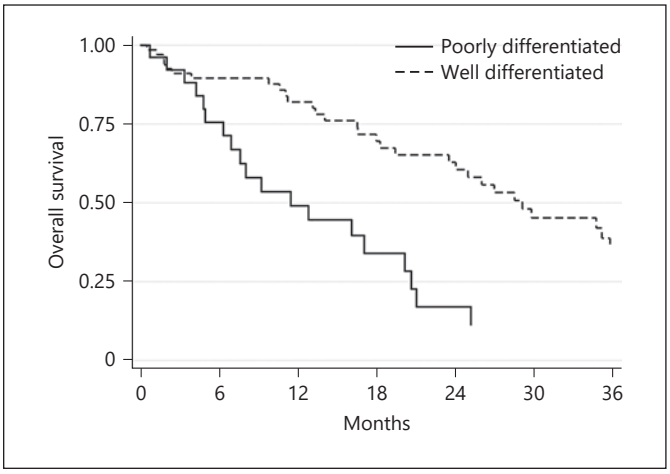

Fig. 2. Kaplan-Meier curve for OS by morphology (poorly vs. well-differentiated). OS, overall survival.

tients were actively progressing at the start of treatment, with a median TGR of 14.2 (range 3.7–80.0). ^{18}FDG-PET/CT and ^{68}Ga-PET/CT were positive in 70 (75.3%) and 72 (76.6%) patients, respectively.

Sixty-nine (73.4%) patients underwent TEM monotherapy and 25 (26.6%) CAPTEM. Of the 94 patients included in the final analysis, 65 (69.8%) received SSAs (32 [49.2%] octreotide and 33 [50.8%] lanreotide) in association with TEM. One patient was not evaluable for time-to-event analysis, and in 8 cases there were no data available for response analysis. The majority of patients (n = 91, 95.8%) had received at least 1 prior line of systemic treatment, with a median of at least 2 prior systemic treatments (range 0–6). Prior therapies included SSAs (n = 65, 68.4%), everolimus or sunitinib (n = 23, 24.2%), cytotoxic chemotherapy (n = 48, 50.5%), and PRRT (n = 51, 53.7%). Fewer than half of the patients (43.8%) had undergone baseline surgical resection, and 9 (8.4%) had received locoregional treatment for liver metastases (Table 2).

Outcomes

The overall response rate (ORR) of the 86 evaluable patients was 44.1%, with a DCR of 70.9%. Considering all patients (n = 95) receiving at least 1 treatment cycle, ORR and DCR were 40.0 and 67.3%, respectively. Twenty-five (29.1%) patients showed disease progression. Receiver operating characteristic curve analysis for TGR in relation to 12-month PFS showed an area under the curve of 0.61 and a TGR cutoff point was identified TGR = 19.55 (sensitivity 0.40 and specificity 0.88).

Median follow-up was 33.7 months (range 0.7–69.9). Median PFS and OS were 10.4 months (95% CI: 6.0–11.5) and 23.4 months (95% CI: 17.0–29.0), respectively. Patients with well-differentiated tumor morphology had a median OS based on raw data of 29.0 months (95% CI 23.4–36.4) compared to 11.4 (95% CI 6.2–20.0) months for those with poorly differentiated disease ($p < 0.001$) (Fig. 2; Table 3). Patient outcome reflected WHO 2017–2019 classification subgroups. Interestingly, the NET G3 patients appeared to benefit greatly from TEM-based treatment. No differences in OS and PFS were seen between the CAPTEM and TEM-alone groups (Fig. 3a, b). Median OS of the 68 evaluable TEM patients was 23.9 (16.0–35.0) months compared to 20.5 (12.7–28.4) months for the 25 patients treated with CAPTEM (p = 0.585).

A propensity score was calculated using gender, age, morphology, syndromic or non-syndromic disease, prior surgery, Ki67 value, time of diagnosis, treatment line of TEM administered, and stage at diagnosis as baseline covariates. OS analysis in the weighted dataset (Table 4) obtained results similar to raw data findings: different treatments and different sites of primary disease did not influence OS patterns. Conversely, poorer prognosis for patients with NEC G3 was confirmed in both univariate

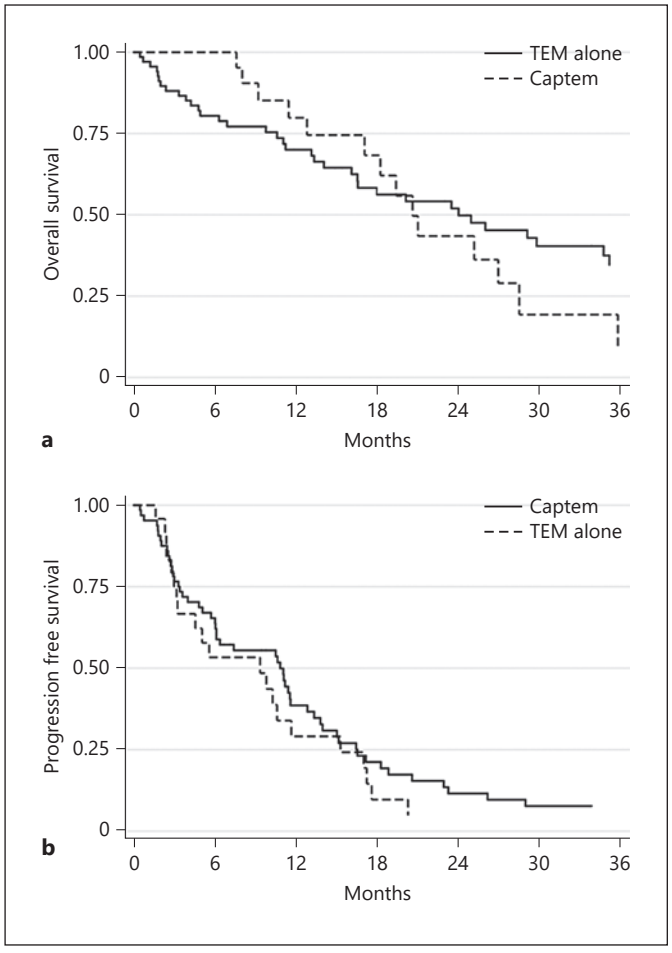

Fig. 3. Kaplan-Meier curve for OS (**a**) and PFS (**b**) by treatment TEM-alone versus CAPTEM. OS, overall survival; PFS, progression-free survival; TEM, temozolomide; CAPTEM, capecitabine and temozolomide.

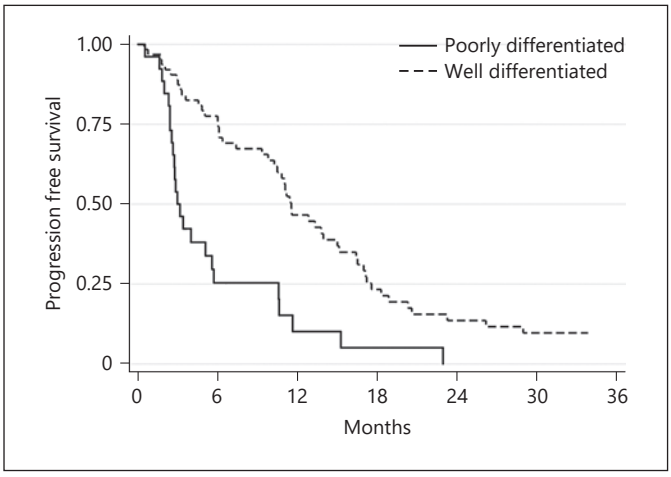

Fig. 4. Kaplan-Meier curve for PFS by morphology (poorly vs. well-differentiated). PFS, progression-free survival.

and multivariate Cox regression models (HR: 2.42, 95% CI: 1.04–5.59). Patients with TGR_0 ≥19.55 had a shorter OS (HR: 2.18, 95% CI: 1.16–4.11) than those with TGR <19.55. Morphology did not confirm its prognostic role in multivariate analysis due to collinearity with WHO classification (Table 4).

The results of PFS analysis based on raw data are shown in Table 5. No differences were observed for treatment or site of primary disease. The NEC G3 subgroup showed a poorer PFS (median PFS 2.7 months, 95% CI: 2.3–3.9), as did patients with poorly differentiated morphology (median PFS 2.9 months [95% CI: 2.5–5.5] compared to 11.5 months [95% CI: 10.2–14.9] for well-differentiated one) (Fig. 4) and the subgroup with TGR ≥19.55 (median PFS 3.2 months [95% CI: 2.6–5.5] compared to patients with TGR <19.55 [median PFS 11.5 months, 95% CI: 9.3–15.0]). Data on multivariate analysis confirmed a worse PFS for patients with NEC G3 (HR: 2.70, 95% CI: 1.25–5.84) and for those with TGR ≥19.55 (HR: 2.53, 95% CI: 1.45–4.40). Well-differentiated morphology had a protective, albeit not significant, effect due to collinearity (HR: 0.62, 95% CI: 0.36–1.07) (Table 6). Outcome subgroup analysis is reported in see online suppl. File 1; for all online suppl. material, see www.karger.com/doi/10.1159/000513218.

Side Effects

Safety outcomes of TEM-based chemotherapy are shown in Table 7. Hematological G 1–2 adverse events were as follows: anemia 13/95 (13.7%), thrombocytopenia 8/95 (8.4%), and neutropenia 23/95 (24.2%). There were no cases of neutropenic fever. Grade 3 neutropenia and nausea/vomiting was observed in 4 (4.5%) and 2 (2.1%) patients, respectively. Mild nausea and vomiting were registered in 21 (22.1%) cases. Eleven (11.6%) patients reported G 1 headaches. A G1 increase in Cr levels and G2 hypertransaminasemia were observed in 5.2 and 1% of the patients, respectively. Other low-incidence side effects were muscle pain, fever, and diarrhea. None of the patients died due to or experienced long-term, irreversible toxicity. There were no cases of discontinued treatment because of drug-induced toxicity, and all patients continued treatment until maximum response, progression (clinical or radiographic), or conclusion of investigator-defined duration of therapy.

Table 3. OS analysis of raw data of the entire population

Variables	Patients, *n**	Events, *n*	Median OS (95% CI)	*p* value (log-rank test)
Total	94	55	23.4 (17.0–29.0)	–
Treatment				
TEM	68	41	23.9 (16.0–35.0)	0.585
CAPTEM	25	14	20.5 (12.7–28.4)	
Site of primary disease				
Lung	25	17	29.0 (13.2–35.7)	0.789
Pancreas	23	10	20.5 (12.7-NE)	
GI tract	28	16	23.4 (13.0–44.5)	
Others	10	7	17.9 (4.7-NE)	
NET/NEC				
NET G1	13	6	29.7 (14.0-NE)	<0.001
NET G2	52	27	24.9 (17.0–34.6)	
NET G3	9	4	35.7 (1.2-NE)	
NEC G3	20	18	7.9 (4.7–12.7)	
Morphology				
Well differentiated	68	21	29.0 (23.4–36.4)	<0.001
Poorly differentiated	26	34	11.4 (6.2–20.0)	
TGR				
<19.55	64	35	28.4 (20.9–35.7)	0.006
≥19.55	28	18	10.5 (7.5–16.0)	

OS, overall survival; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; TGR, tumor growth rate; TEM, temozolomide; CAPTEM, capecitabine and temozolomide; GI, gastrointestinal. * Patients, *n* varies on the basis of missing values of single covariates.

Discussion

The present study describes a real-world experience of TEM-based chemotherapy in patients with NENs of various proliferation rates and primary sites treated in an Italian tertiary cancer center. In recent years, several studies have reported on the use of TEM-based chemotherapy in advanced NENs, focusing mainly on the CAPTEM combination [18, 20,22–26, 29, 30, 33–41]. Of note, TEM-based regimens appear to be more active in pancreatic and lung NETs than in GI NETs [22, 23].

We obtained a DCR of 70.9% from the use of TEM-based chemotherapy. Furthermore, patients had a median PFS of 10.4 months and a median OS of 23.4 months. Of note, our case series comprised a number of heavy pretreated patients with a median of 2 previous systemic therapeutic lines and with highly progressive disease, as indicated by the TGR_0. Furthermore, this benefit was obtained regardless of the site of origin of the primary tumor, especially in GI NENs.

It is known that tumor response is dependent on the natural history of the disease. Gomez-Roca et al. [42] underlined that pretreatment TGR evaluation can negatively impact the assessment of treatment efficacy. In particular, slow-growing tumors may increase the risk of hypothesizing that an inactive treatment is efficient and, conversely, appraising a therapy as active in tumors with a high pretreatment TGR may lead to the early stopping of the drug development process [42]. Interestingly, in some studies on the use of SSAs in NETs, a TGR cutoff of 4% appeared to have a prognostic value [43].

In our study, patients had a higher TGR than that normally used to evaluate the efficacy of cytostatic drugs. This trend has not been reported in the literature may explain why GI NEN patients had a significantly better PFS after TEM-based chemotherapy, even after adjusting for tumor differentiation and Ki67 proliferation rate. GI NETs are relatively slow-growing tumors initially but may acquire more aggressive features during the course

Table 4. OS analysis on weighted dataset

Variables	Univariate HR from Cox regression model (95% CI)	*p* value	Multivariate HR from Cox regression model (95% CI)	*p* value
Treatment				
TEM	1.00	–		
CAPTEM	0.91 (0.47–1.76)	0.790		
Site of primary disease				
Lung	1.00	–		
Pancreas	0.65 (0.26–1.61)	0.356		
GI tract	0.73 (0.34–1.56)	0.433		
Others	1.82 (0.81–4.08)	0.141		
NET/NEC				
NET G1/G2/G3	1.00	–	1.00	0.039
NEC G3	2.47 (1.37–4.42)	0.002	2.42 (1.04–5.59)	
Morphology				
Poorly differentiated	1.00	–	1,000	0.226
Well differentiated	0.26 (0.14–0.48)	<0.001	0.58 (0.25–1.38)	
TGR				
<19.55	1.00	–	1.00	0.015
≥19.55	2.56 (1.27–5.15)	0.008	2.18 (1.16–4.11)	

OS, overall survival; TEM, temozolomide; CAPTEM, capecitabine and temozolomide; HR, hazard ratio; CI, confidence interval; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; G, grade; GI, gastrointestinal; TGR, tumor growth rate.

Table 5. PFS analysis of raw data

Variables	Patients, *n**	Events, *n*	Median PFS (95% CI)	*p* value (log-rank test)
Total	89	74	10.4 (6.0–11.5)	–
Treatment				
TEM	64	53	10.7 (6.0–12.7)	0.405
CAPTEM	24	21	9.3 (3.1–11.6)	
Site of primary disease				
Lung	25	22	12.7 (9.3–15.0)	0.208
Pancreas	22	14	11.0 (9.3–15.0)	
GI tract	26	22	10.4 (5.9–16.4)	
Others	9	9	–	
NET/NEC				
NET G1	11	9	11.0 (6.0–18.2)	<0.001
NET G2	50	41	11.3 (6.0–13.2)	
NET G3	8	5	–	
NEC G3	20	19	2.7 (2.3–3.9)	
Morphology				
Well differentiated	63	50	11.5 (10.2–14.9)	<0.001
Poorly differentiated	26	24	2.9 (2.5–5.5)	
TGR				
<19.55	61	48	11.5 (9.3–15.0)	<0.001
≥19.55	26	24	3.2 (2.6–5.5)	

TEM, temozolomide; CAPTEM, capecitabine and temozolomide; PFS, progression-free survival; CI, confidence interval; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; GI, gastrointestinal; TGR, tumor growth rate; G, grade. * Patients, *n* varies on the basis of missing values of single covariates.

Table 6. PFS analysis of weighted dataset

Variables	Univariate HR from Cox regression model (95% CI)	*p* value	Multivariate HR from Cox regression model (95% CI)
Treatment			
TEM	1.00	–	
CAPTEM	0.87 (0.50–1.54)	0.655	–
Site of primary disease			
Lung	1.00	–	
Pancreas	0.63 (0.27–1.44)	0.278	–
GI tract	0.93 (0.51–1.72)	0.838	–
Others	2.30 (1.01–5.28)	0.049	–
NET/NEC			
NET G1/G2/G3	1.00	–	1.00
NEC G3	1.48 (0.77–2.83)	0.231	2.70 (1.25–5.84)
Morphology			
Poorly differentiated	1.00	–	1.00
Well-differentiated	0.28 (0.15–0.52)	<0.001	0.62 (0.36–1.07)
TGR			
<19.55	1.00	–	1.00
≥19.55	3.12 (1.75–5.56)	<0.001	2.53 (1.45–4.40)

HR, hazard ratio; CI, confidence interval; GI, gastrointestinal; TEM, temozolomide; CAPTEM, capecitabine and temozolomide; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; TGR, tumor growth rate; PFS, progression-free survival; G, grade.

Table 7. Main side effects of TEM-based chemotherapy

Toxicity	All grade, *n* (%)	G1, *n* (%)	G2, *n* (%)	G3, *n* (%)	G4, *n* (%)
Anemia	13 (13.7)	9 (69.2)	4 (30.8)	–	–
Neutropenia	27 (28.4)	10 (37.1)	13 (48.1)	4 (14.8)	–
Thrombocytopenia	8 (8.4)	6 (75.0)	1 (12.5)	1 (12.5)	
Headache	11 (11.6)	11 (100.0)	–	–	–
Hand and foot syndrome	2 (2.1)	1 (50.0)	1 (50.0)	–	–
Nausea/vomiting	23 (24.2)	17 (73.9)	4 (17.4)	2 (8.7)	
Muscle pain	1 (1.0)	1 (100.0)	–	–	–
Fever	1 (1.0)	1 (100.0)	–	–	–
Diarrhea	1 (1.0)	1 (100)	–	–	–
Increased Cr	5 (5.2)	5 (100.0)	–	–	–
Hypertransaminasemia	1 (1.0)	–	1 (100.0)	–	–
Increased alkaline phosphatase	1 (1.0)	–	2 (100.0)	–	–
Fatigue	12 (12.6)	10 (83.3)	2 (16.7)	–	–

G, grade; TEM, temozolomide.

of the disease due to treatments received and may become more responsive to chemotherapy. Further studies are needed in this area.

Chatzellis et al. [22] reported that CAPTEM was rarely associated with serious toxicities and had low discontinuation rates, even in patients who were on treatment for >1 year. Similarly, our cohort experienced a fairly low rate (25%) of adverse effects (G 1–2 toxicity), confirming the good tolerability of TEM-based chemotherapy, even in highly pretreated NEN patients. None of our patients discontinued treatment.

Of note, our case series was composed of patients previously treated with PRRT, and to the best of our knowledge, there are very few other studies on the use of this radionuclide therapy before TEM-based chemotherapy. Our findings are important because they underline the safety and efficacy of a myelotoxic treatment such as TEM after PRRT, but also because they describe a real-world NEN population before the approval of lutetium Lu-177 dotatate, for NETs, especially those of GI origin [44]. Furthermore, the benefit seen in patients with G3 NETs, even though there were few patients with this specific disease, warrants further clinical research. The role of the CAPTEM regimen in NECs also needs to be better clarified. An Italian multicenter prospective clinical trial is ongoing to investigate the activity and safety of CAPTEM in both of these patients, G3 NETs and NECs, and will hopefully better clarify the role of this regimen in the therapeutic strategy of NETs [45].

An evaluation of TEM-based therapy in a larger population of non-pNENs is currently lacking in the literature. The present study of NEN, the largest of its kind to include patients with non-pNENs, helps to further our understanding of these tumors by describing the use of TEM-based therapy in a progressive metastatic NEN setting.

Limitations

The limitations of the present study include its retrospective, monocenter nature, and the heterogeneity of the patients enrolled. Another issue is that MGMT, which has been hypothesized as a predictor of response to TEM in NENs, was not routinely evaluated. Nevertheless, the median PFS and OS observed were encouraging, especially the latter. The response rate of 44% and DCR of 70.4% were also relatively high, indicating that this regimen could be used to reduce the tumor burden and palliate symptoms.

Conclusion

Although the present study does not answer the question as to whether CAPTEM is more effective than TEM-alone in NENs, it suggests that the combination treatment, whilst not prolonging PFS, may nevertheless obtain a higher ORR. Tolerance to CAPTEM was similar to that of TEM. Hence, CAPTEM may be preferable when tumor shrinkage is the main therapeutic objective, especially in a neoadjuvant setting when surgery is an option or in cases of symptomatic disease and/or high tumor bulk. Conversely, TEM-alone may be sufficient in patients with impaired performance status or extrahepatic metastases.

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Statement of Ethics

All procedures in this study were performed in accordance with the ethical standards of the IRST IRCCS Ethics Committee (project identification code: #L1P33) and the 1964 Helsinki Declaration and later amendments. All the subjects gave written informed consent. The Institution Review Board has approved the study protocol

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

A.B. and T.I. conceived the idea and designed the study. G.M., V.F., G.D.M., and S.C. were responsible for data acquisition. C.S., C.C., and A.D.V. researched the literature on the topic. N.R. and L.M. analyzed and interpreted the clinical results. F.F. performed the statistical analyses. A.B., T.I., C.L., and F.F. drafted the manuscript. G.M., V.F., G.D.M., S.C., C.C., C.S., A.D.V., N.R., and L.M. critically reviewed the manuscript, providing important feedback. All authors approved the final version for submission.

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