Efficacy and safety of capecitabine-temozolomide (CAPTEM) regimen in patients with neuroendocrine neoplasms – experience from NETwerk, a Belgian ENETS Center of Excellence

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Abstract

Neuroendocrine neoplasms (NEN) are rare tumors originating from neuroendocrine cells, commonly found in the gastrointestinal tract and the pulmonary tract. Metastatic well-differentiated neuroendocrine tumors (NET) grade 3 present unique challenges, as they are positioned between the more indolent NET grade 1-2 and the aggressive neuroendocrine carcinomas (NEC). Due to the scarcity of data regarding the optimal systemic treatment for metastatic NET grade 3 and aggressive NET grade 2 subtypes, guidelines remain inconclusive.

This retrospective study analyzed data from the NETwerk database, encompassing patients treated with the capecitabine-temozolomide (CAPTEM) regimen between June 2016 and January 2024. The cohort included patients with NET grades 1-3 and NEC. The study focused on assessing the efficacy and safety of CAPTEM. In total, data from 36 patients was analyzed.

The median progression-free survival (mPFS) was 13 months, and median overall survival (mOS) was 17 months. Overall response rate (ORR) was 25.8%, and the disease control rate (DCR) was 67.7%. NET grade 2 patients had the highest mPFS, while NET grade 3 exhibited the most favorable mOS. Subgroup analysis showed that panNEN had superior mPFS and mOS compared to other primary tumor sites, with significant differences in mOS based on NEN type. Safety analysis in 20 patients indicated good tolerance and safety.

CAPTEM is an efficient and safe regimen for metastatic NEN, with promising outcomes in NET grade 2-3 patients. The promising findings pave the way for further exploration into various aspects of CAPTEM, to better define its position in the therapeutic landscape of NEN. (Acta gastroenterol belg., **2025**, 88, **119-127**).

Keywords: Neuroendocrine tumors, CAPTEM, efficacy, safety.

Introduction

Neuroendocrine neoplasms (NEN) are rare neoplasms originating from neuroendocrine cells, which can originate from multiple organ systems (1). Most frequently, they arise from the gastrointestinal (termed gastroenteropancreatic (GEP) NEN), followed by the pulmonary tract (termed lung NEN) (1, 2). According to the WHO 2019 classification (3), GEP NEN can be subdivided into well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC). NET can be further subdivided based on the Ki-67 index into NET grade 1 (Ki-67-index <3%, mitotic index (m.i.) <2/10 high-power field (HPF)²/10 HPF), NET grade 2 (Ki-67-index 3-20%, m.i. 2-10 HPF²/10 HPF), and NET grade 3 (Ki-67-index >20%, m.i. >20 HPF²/10 HPF). Finally, NEC have a Ki-67-index >20% with m.i. >20 HPF²/10 HPF. For lung NEN, the WHO 2019 classification is as follows: typical carcinoid (m.i. <2 HPF²/10 HPF), atypical carcinoid (m.i. 2-10 HPF²/10 HPF or presence of necrosis), and NEC (m.i. >10 HPF²/10 HPF, and can be further subdivided into small-cell NEC (SC-NEC) and large-cell NEC (LC-NEC)).

Globally, the incidence of NEN is rising (4, 5), largely due to improved diagnostic strategies and imaging modalities. Moreover, they have a high prevalence (4, 5), given the more favorable survival profile compared to other solid malignancies (6, 7). Among NEN, lung NEN have the highest incidence (1.6 per 100000), followed by small intestinal NEN (siNEN) (1.2 per 100000) and pancreatic NEN (panNEN) (0.8 per 100000) (7). NEN are often asymptomatic in early stages, causing up to 40% of NEN being diagnosed at advanced/metastatic stages (especially non-functional NEN) (8). This results in worse outcomes and higher morbidity, as compared to early-stage diagnoses or incidental findings. Upon suspicion of a NEN, the diagnosis often consists of cross-sectional imaging (computed tomography (CT) or magnetic resonance imaging (MRI)), nuclear imaging (e.g. 68-Ga-DOTANOC PET, 18-FDG PET, etc.), endoscopic evaluation, or a combination thereof. Thereafter, histopathological confirmation is obtained through a biopsy. In case of clinical suspicion of a functional NEN, specific biomarkers like chromogranin A (CgA)

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are often tested too, but frequently lack accuracy (9).

The choice for treatment depends on multiple factors, including functional status (9), tumor grade, tumor stage, NEN subtype, etc. In case of localized disease (non-metastatic), locoregional treatment options like endoscopic resection, surgery, liver-directed therapy, etc. are often applied. However, in case of metastatic disease systemic therapy is needed. Well-differentiated metastatic NET grade 1-2 are typically treated with long-acting somatostatin analogues (SSA) in first-line (10), and targeted therapy (e.g. everolimus (11) and sunitinib (12)) or peptide receptor radionucleotide therapy (PRRT) (13) in subsequent lines. On the contrary, given the aggressive disease course and worse prognosis associated with NEC, the preferred treatment option often consists of cytotoxic chemotherapy in form of a platinum-based regimen (cisplatinum or carboplatinum) in combination with a topoisomerase II inhibitor (etoposide) (14). However, the characteristics of metastatic well-differentiated NET grade 3 fall on a spectrum between the more indolent nature of NET grade 1-2 and the more aggressive behavior of NEC in terms of disease course and aggressiveness. Data on the ideal systemic treatment option in metastatic setting for these NET grade 3 and for subtypes of NET grade 2 with a more aggressive disease course and/or bulky disease, remains scarce (15, 16), leading to inconclusive guidelines (1, 17).

Given the more aggressive characteristics of these subtypes (grade 3 and aggressive grade 2 NET), treatment with cytotoxic chemotherapy regimens has been tested, and has shown promise in clinical practice. Moreover, most data is available for panNET, as they are considered the most chemo-sensitive among GEP NET (18), resulting in scarcity of data for other GEP NET subtypes. Initially, in analogy to NEC, treatment with a platinum-based regimen (cisplatinum or carboplatinum) in combination with a topoisomerase II inhibitor (etoposide) was applied to GEP NET, however data for the NORDIC NEC study demonstrated the limited efficacy of this regimen in tumors with Ki-67 index <55% (14). Immunotherapy has also not shown any meaningful benefit (19). On the contrary, chemotherapy regimens including alkylating agents (temozolomide, streptozocin (STZ), dacarbazine) as single agents or in combination with antimetabolites such as 5-fluorouracil (5-FU) or capecitabine have shown promise in GEP NET (16, 20). Other examples like combination of STZ, 5-FU and an anthracycline (doxorubicin), have also been applied into clinical practice. Despite the fact that they show promising efficacy, the toxicity profile is often not favorable (21). Finally, the fact that STZ is not reimbursed for NET in Belgium and needs to be imported from abroad, has impeded its application in clinical practice for patients in Belgium.

In recent years, the combination of an oral alkylating agent, temozolomide (TEM), in combination with an antimetabolite, capecitabine (CAP), which is an oral prodrug for 5-FU, known as capecitabine-temozolomide (CAPTEM), has emerged and has shown promise in terms of both antitumoral activity and tolerance profile (20) in these subtypes of aggressive metastatic (GEP) NET grade 2 with/without bulky disease and (GEP) NET grade 3 in general. The dose of the regimen can vary per center, but the patients in this study received the full dose consisting of capecitabine 750 mg/m2 twice daily during day 1-14 and temozolomide 100 mg/m2 twice daily during day 10-14 in a 28 day cycle. However, data for this regimen mainly originates from retrospective studies (20), with only one prospective clinical trial (22) conducted to date, which reported overall mOS of 58.7m, mPFS of 22.7m, and ORR of 39.7% for the CAPTEM combination in patients with panNET grade 1-2. This has led to doubt and lack of consensus regarding its benefit in NEN, and subsequently its clinical application has been heterogeneous.

To further explore the evidence related to the use of CAPTEM in NEN, especially in aggressive metastatic (GEP) NET grade 1-2 with/without bulky disease, (GEP) NET grade 3, and lungNEN, we aim to study real-world data on the efficacy and safety of the CAPTEM regimen in a cohort of NEN patients from NETwerk, a Belgian ENETS Center of Excellence (CoE). Moreover, the results of this study could strengthen the existing evidence supporting the use of CAPTEM in the management of NEN, ultimately enhancing clinical decision-making and patient outcomes.

Methods

Database

An in-depth analysis of a cohort of NEN patients treated in NETwerk was conducted in this retrospective study. NETwerk is an ENETS Center of Excellence (CoE) and an EURACAN European Reference Network (ERN), which is a collaboration between eight hospitals in the Antwerp region. It consists of the following hospitals: AZ Klina, AZ Monica, VITAZ, AZ Rivierenland, AZ Voorkempen, ZAS Ziekenhuizen, and Antwerp University Hospital, and maintains its own NETwerk database (Oncobase). In this study, data present in the database from June 2016 till January 2024 of all patients with NET grade 1-3 or NEC, treated with CAPTEM was extracted and analyzed. The extracted clinicopathological and treatment data was used to conduct analyses. The study was conducted in accordance with the Declaration of Helsinki, good clinical practice (ICH GCP), the EU General Data Protection Regulation 2016/679 (GDPR), and relevant Belgian laws, including the Belgian Privacy Act of 30 July 2018.

Efficacy

Efficacy was assessed through overall survival (OS) and progression-free survival (PFS). OS is defined as

the time from the start of CAPTEM treatment until death of any cause or until the day of last follow-up. PFS is defined as the time from the start of CAPTEM treatment until disease progression or patient death or until the day of last follow-up for the patients who were still alive and did not show signs of progression at that point. Radiological response rates were assessed using imaging reports and clinical information from patients' records.

Safety

To explore the safety and toxicity profile of CAPTEM the occurrence of treatment-emergent adverse events (TEAEs) were captured and were retrospectively graded per Common Terminology Criteria for Adverse Events (CTCAE) v5.0. These are defined as any adverse event with an onset date on or after the first dose of CAPTEM, or any adverse event that worsened after the first dose CAPTEM.

Statistical analyses

Descriptive statistics, such as mean with standard deviations, median with interquartile range, or percentages for categorical data, were used. Associations of categorical variables were assessed using Chi-square or Fisher's exact tests, t-tests for normally distributed continuous variables, and Spearman correlation for non-normally distributed continuous variables. Survival analysis was conducted using Kaplan-Meier curves, log-rank tests, and Cox proportional hazard models. In case of missing data due to absence of follow-up data, right censoring was applied. Patients with right censoring are marked with crosses on the Kaplan-Meier curves. After the point of censoring, these patients were no longer be counted as individuals at risk when calculating survival probabilities. If no last date of follow-up was available, the patients were excluded from the survival analysis. Data analysis was performed using R version 4.2.2, utilizing the "survival" and "survminer" packages. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient demographics

A total of 36 patients met the eligibility criteria and were included for analyses. From these 36 patients, 23 (69.7%) were male and 13 (30.3%) were female, with mean ages of 62 (range: 36-84) and 65 years (range: 50-80) respectively. Within this cohort, patients with NET grade 2 were the most prevalent (n=14, 38.9%), followed by NET grade 3 (n=10, 27.8%), NEC (n=8, 22.2%), and NET grade 1 (n=4, 11.1%). The primary tumor was located in the pancreas (n=22, 61.1%), followed by the gastrointestinal tract (excl. pancreas) (n=9, 25%), lung (n=4, 11.1%), and thymus (n=1, 2.8%). Moreover, most patients had metastatic disease (n=35, 97.2%), with mainly liver metastases (n=30, 85.7%), followed by lymph node metastases (n=13, 85.7%), peritoneal metastases (n=9, 25.7%), but also in other locations (see Table 1). Finally, 8 (22.2%) patients were treatment-naïve when starting treatment with CAPTEM, and 28 (77.8%) patients had received minimum one form of prior treatment, including SSA, targeted therapy with everolimus or sunitinib, chemotherapy, and more (see Table 1).

Efficacy

When analyzing treatment response rates, 5 patients receiving <2 cycles of CAPTEM (e.g. short therapy of <1m due to intolerance) were excluded. Subsequently, response rate analyses were conducted on the per protocol treated population of the remaining 31 patients who received >2 cycles of CAPTEM. In these 31 patients, complete remission (CR) was observed in 1 (3.2%) patient, partial response (PR) in 7 (22.6%) patients, stable disease (SD) in 10 (32.3%) patients, progressive disease (PD) in 7 (22.6%) patients, and no response data was available for 11 (35.5%) patients (as the scans were conducted in external hospitals outside the NETwerk consortium). This results in disease control rate (DCR) of 67.7% and ORR of 25.8%. Response rates after stratification based on tumor location can be found in Table 2.

When observing the overall, intention-to-treat, cohort, the mPFS was 13m (95% CI, 6m-NA). Moreover, when comparing survival rates while stratifying for the primary tumor location, the mPFS was 19m (95% CI, 6m-NA) for pancreatic NEN, 13m (95% CI, 3m-NA) for gastrointestinal tract NEN, and 8.5m (95% CI, 4m-NA) for lung NEN. These differences were not statistically significant (p=0.89) (Figure 1). When comparing survival rates while stratifying for NEN types based on the WHO 2019 classification, mPFS was not reached for NET grade 1, and was 19m (95% CI, 9m-NA) for NET grade 26m (95% CI, 4m-NA) for NET grade 3, and 4m (95% CI, 2m-NA) for NEC. These differences were also not statistically significant (p=0.35) (Figure 2). Finally, when comparing survival rates while stratifying for the line of treatment during which CAPTEM was administered, mPFS of 6m (95% CI, 4m-NA) was found for CAPTEM in first-line compared to 13m (95% CI, 9m-NA) for CAPTEM in subsequent lines of treatment (p=0.54).

In terms of OS, mOS for the overall cohort was 17m (95% CI, 13m-NA). Even though there is a numeric

Table 1. — **Patient demographics.**

Sex (%)	Male	23/36 (69.7%)
	Female	13/36 (30.3%)
Mean age (range)	Male	62 (36-84)
	Female	65 (50-80)
NEN type (%)	NET grade 1	4/36 (11.1%)
	NET grade 2	14/36 (38.9%)
	NET grade 3	10/36 (27.8%)
	NEC	8/36 (22.2%)
Ki-67 index (%)	0-2%	3/36 (8.3%)
	2-20%	15/36 (41.7%)
	20-55%	13/36 (36.1%)
	>55%	3/36 (8.3%)
	Unknown	2/36 (5.6%)
Location primary tumor	Pancreas	22/36 (61.1%)
	Gastro-intestinal tract (excl. pancreas)	9/36 (25%)
	Lung	4/36 (11.1%)
	Thymus	1/36 (2.8%)
Metastases	Yes	35/36 (97.2%)
	No	1/36 (2.8%)
Location metastases	Liver	30/35 (85.7%)
	Lymph node	13/35 (37.1%)
	Peritoneum	9/35 (25.7%)
	Bone	9/35 (25.7%)
	Lung	8/35 (22.9%)
	Other (incl. brain, muscle)	4/35 (11.4%)
Previous lines of treatment	None	8/36 (22.2%)
	SSA	17/36 (47.2%)
	Carboplatin/cisplatin-etoposide	7/36 (19.4%)
	FOLFOX	5/36 (13.9%)
	Other chemotherapy	4/36 (11.1%)
	PRRT	3/36 (8.3%)
	Everolimus	9/36 (25%)
	Sunitinib	2/36 (5.6%)
	Resection primary tumor	9/36 (25%)
	Liver-directed therapy (e.g. SIRT)	3/36 (8.3%)

Table 2. — **Response rates (RR).**

Response rates (RR)	CR	PR	SD	PD	NR*	ORR	DCR
overall cohort	1/31	7/31	13/31	7/31	3/31	25.8%	67.7%
panNEN	1/19	5/19	6/19	5/19	2/19	31.6%	63.2%
GI-NEN (excl. pancreas)	0/7	2/7	3/7	1/7	1/7	28.6%	71.4%
lung NEN	0/4	0/4	3/4	1/4	0/4	0%	75%
thymus NET	0/1	0/1	1/1	0/1	0/1	0%	100%
* patients receiving <2 cycles of CAPTEM (e.g. short therapy of <1m due to intolerance) are excluded from RR-analyses.							
CR (complete response); PR (partial response); SD (stable disease); PD (progressive disease); NR (not reported); ORR (overall response rates); DCR (disease control rates).							

difference in the mOS of males compared to females, 22m (95% CI, 13m-NA) versus 15m (95% CI, 4m-NA)) respectively, this difference was not statistically significant (p=0.60). Upon stratification based on tumor location, the mOS was 22m (95% CI, 13m-NA) for pancreatic NEN, followed by 18m (95% CI, 16m-NA) for lung NEN, 10m (95% CI, 4m-NA) for gastrointestinal tract (excl. pancreas) NEN, again not statistically significant (p=0.60) (Figure 3). When stratifying based on NEN type, the best mOS of 31m (95% CI, 13m-NA) was seen for NET grade 3, followed by 18m for NET grade 1 (95% CI, 9m-NA), 17m (95% CI, 13m-NA) for NET grade 2, and 4m (95% CI, 2m-NA) for NEC (p=0.40) (Figure 4). Finally, when comparing survival rates while stratifying for the line of treatment during which CAPTEM was administered, mOS of 13m (95%

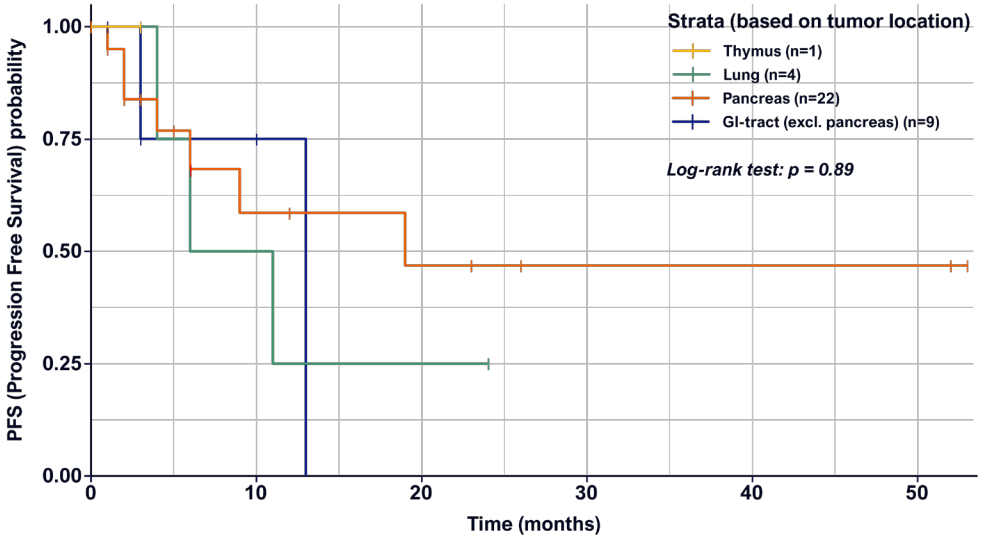
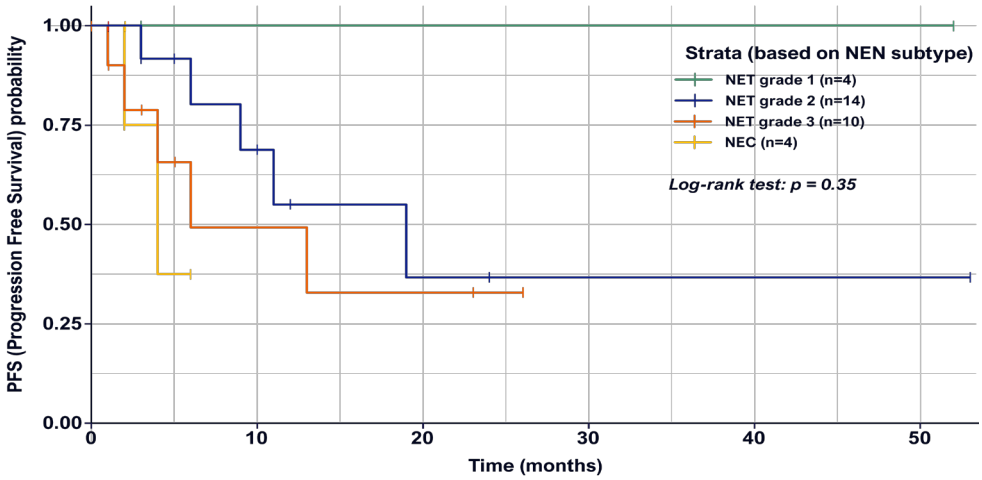


Figure 1.



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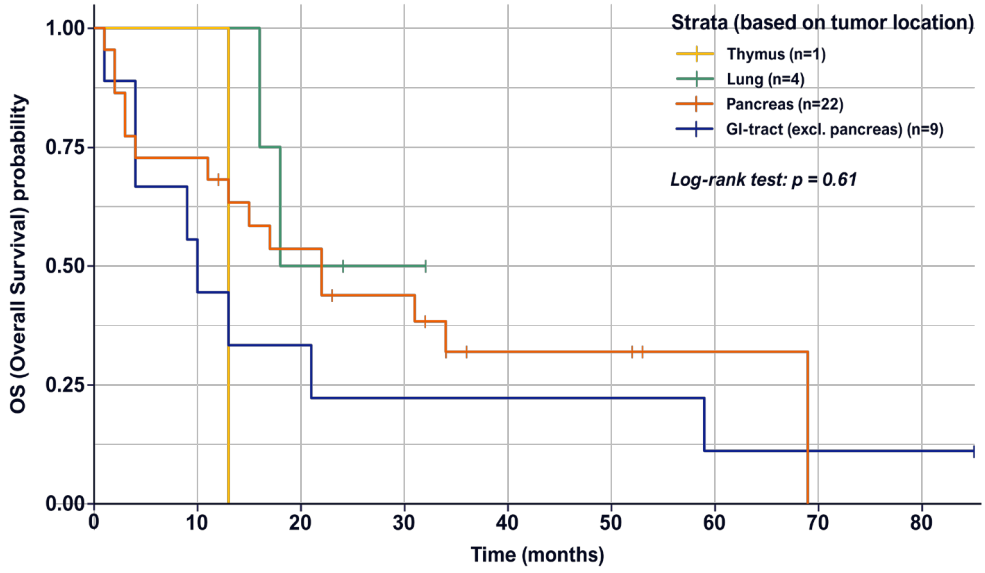

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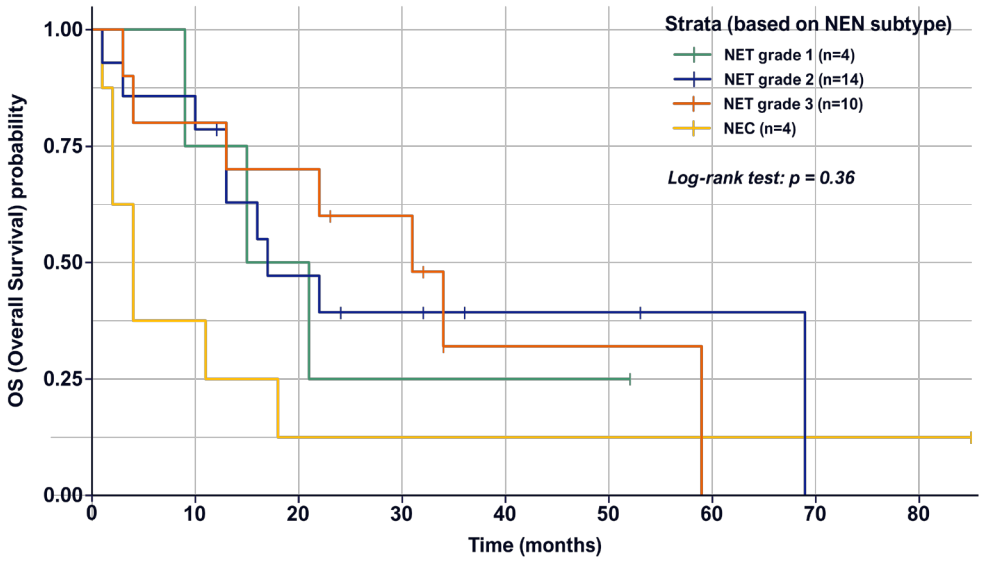

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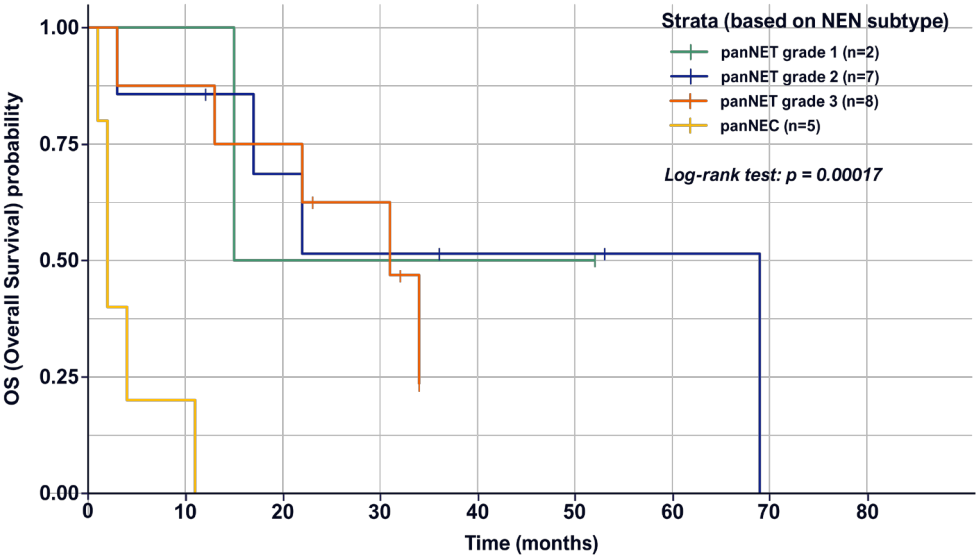

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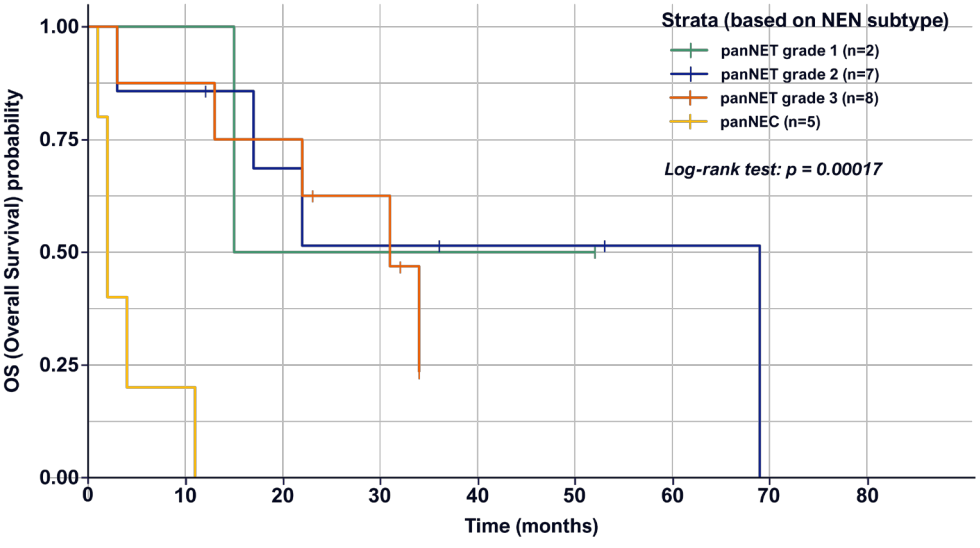

Figure 6.

Table 3. — **Adverse events as per CTCAE v5.0**

	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	4/20 (20%)	2/20 (10%)	0	1/20 (5%)
Anemia	11/20 (55%)	4/20 (20%)	4/20 (20%)	0
Neutropenia	4/20 (20%)	0	0	0
Nausea	4/20 (20%)	5/20 (25%)	4/20 (20%)	0
Hand-foot syndrome (palmar-plantar erythrodysesthesia)	4/20 (20%)	0	0	0
Fatigue	10/20 (50%)	5/20 (25%)	1/20 (5%)	0
Diarrhea	5/20 (25%)	0	2/20 (10%)	0

CI, 3m-NA) was observed for CAPTEM in first-line compared to 22m (95% CI, 13m-NA) for CAPTEM in subsequent lines of treatment (p=0.46).

Further analysis of the subgroup of panNEN (n=24) revealed the following findings. When comparing mOS rates while stratifying for NEN types based on the WHO 2019 classification, the best mOS was found for NET grade 2 (69m, 95% CI, 22m-NA), followed by NET grade 3 (17m, 95% CI, 9m-NA), NET grade 1 (15m, 95% CI, 15m-NA), and NEC (2m, 95% CI, 2m-NA) (Figure 5). For mPFS similar trends were observed, although not statistically significant (p=0.48), where mPFS was 19m (95% CI, 9m-NA) for NET grade 2, followed by 6m (95% CI, 2m-NA) for NET grade 3, and 2m (95% CI, 2m-NA) for NEC, with mPFS not reached for NET grade 1 (Figure 6).

Tolerance and safety

From the overall cohort of 36 patients, treatment in 5 patients was stopped <1m due to either clinical progression or suboptimal WHO ECOG performance status. From the remaining 31 patients, in-depth tolerance data could be obtained from 20 patients, as outlined in Table 3.

Discussion

In this retrospective study, we report the results related to CAPTEM efficacy and safety within a Belgian cohort of 36 patients. Overall, mPFS was 13m and mOS was 17m, with an ORR of 25.8% and DCR of 67.7%. NET grade 2 exhibited the highest mPFS, while NET grade 3 had the most favorable mOS. Subgroup analyses revealed that mPFS and mOS rates were highest in panNEN when compared to NEN of other primary tumor locations. In depth analysis of the panNEN group revealed interesting findings like statistically significant differences in mOS rates upon stratification based on NEN type based on the WHO 2019 classification. Finally, safety and tolerance analysis in 20 patients revealed good general tolerance and safety.

When looking into more detail for lung NEN, the mPFS ranges from 9.4m (23) to 13m (24) and the mOS ranges from 30.4m (23) to 68m (24) for similar cohorts of patients with typical and atypical carcinoids. This is in contrast to our findings, where the mPFS of 8.5m and especially the mOS of 18m for 4 patients with atypical carcinoid (n=3) and SC-NEC (n=1) were lower, although due to the limited sample size the significance of these findings needs to be interpreted cautiously. Nevertheless, these survival rates reported in literature for typical and atypical carcinoids of the lung indicate that the use of CAPTEM is a viable therapeutic option after failure of previous lines of systemic treatment like SSA, targeted therapy, and PRRT.

When looking into more detail to panNEN, within our cohort the mPFS was 19m for all patients with panNEN, and the mOS was 22m. In heterogenous cohorts of well-differentiated panNET of grade 1-3 mPFS ranging from 17m (25) up to 20.6m (26) have been reported in literature, which is in line with the mPFS of our cohort. However, higher mOS rates, ranging from 21.4m (26) up to 62m (27), have been reported in literature for similar cohorts of patients with panNEN treated with CAPTEM. This narrow gap between mPFS and mOS within our cohort could potentially be explained by the lack of good next-line treatment options after progression under CAPTEM in an already pretreated cohort. Another possible explanation could be that the disease obtains a more aggressive biology while becoming resistant to CAPTEM and subsequently results in a rapid decline of the patients after progression.

Interestingly, our results showed statistically significant difference in mOS (p=0.0017) and numeric difference mPFS rates upon stratification of panNEN based on NEN type with mPFS and mOS rates of respectively 19m and 69m for panNET grade 2, and 6m and 31m for panNET grade 3. This is also in contrast with data from a large cohort of 300 patients (25) reported in literature with mPFS and mOS rates of respectively 14.5m and 67.4m for panNET grade 2, and 24.6m and 76.2m for panNET grade 3. The findings in the literature seem to align better with the tumor biology, where the more aggressive panNET grade 3 often respond better to chemotherapy like CAPTEM than the lower grade panNET. The findings within our cohort where the panNET grade 2 seem to do better under CAPTEM than the panNET grade 3 tumors, could potentially be due to more pretreated conditions at baseline for the panNET grade 3 patients, or a worse baseline performance status.

Several systemic treatment options exist for metastatic panNET of grade 1-2, where a first-line mPFS of 38.5m was reached with SSA (CLARINET trial (10)). For second-line treatment, mPFS rates of 8.0m in panNET grade 1-2 for double dose SSA (CLARINET FORTE trial (28)), 11m in panNET grade 1-2 for everolimus (RADIANT-3 trial (11)), 11m for panNET 1-2 for sunitinib (12), and 8.4m for PRRT with 177-Lu-DOTATATE (NETTER-1 trial (13)) were found. In comparison to these numbers, the reported survival rates for CAPTEM in low-intermediate grade NET look promising, especially for panNET grade 2. Moreover, as the study cohort included patients who were pretreated with SSA, targeted therapy, PRRT, primary surgery, or a combination thereof, CAPTEM seems a potent next-line treatment option after failure of the previous lines of treatment.

In contrast to the metastatic GEP NET grade 1-2, there is a lack of prospective data on therapeutic options in case of aggressive GEP NET grade 2 with/without bulky disease and GEP NET grade 3 in general. As these tumors present with a more aggressive disease course treatment with chemotherapy is often initiated to obtain disease control. Unlike in NEC, the combination of cisplatin/carboplatin with etoposide is not effective in well-differentiated NET grade 3 (14-16). On the contrary, treatment regimens including combinations of STZ with 5-FU (with/without doxorubicin) (21, 29, 30), STZ with 5-FU and cisplatin (31), or FOLFOX + bevacizumab (32) have been proposed and have shown efficacy. For example, the combination of STZ and 5-FU has resulted in mOS up to 54.8m (21), mPFS up to 23m (21), and ORR ranging from 28.0% (21) up to 42.7% (33). However, the toxicity profile for this regimen was not favorable, as treatment discontinuations of up to 21.6% patients due to toxicity (mainly kidney toxicity) have been reported (21). For STZ with 5-FU and doxorubicin, outcomes like mOS of 63m, mPFS of 20m, and ORR 41% in 246 panNET patients were obtained. However, toxicity was not favorable with 32% of patients requiring dose-reductions due to toxicity (30). Finally for FOLFOX + bevacizumab (32) mOS rates 25.6m and ORR of 42.9% was achieved, however again with notable toxicity (e.g. grade 3-4 peripheral neurotoxicity in 44% of patients).

In contrast to these regimens, CAPTEM has emerged as a promising option in terms of efficacy and tolerance, as demonstrated in our cohort and in the literature above, especially for panNET grade 2-3. Another benefit of CAPTEM is that it is administered orally as compared to other regimens which are given intravenously, resulting in better and more patient friendly application. However, more (prospective) studies are needed in order to gain more insight into factors like time-to-response, efficacy compared to emerging chemotherapy regimens like FOLFIRINOX, efficacy in extra-pancreatic GEP NET like siNET, optimal sequence of chemotherapeutic regimens, etc. Additionally, with the recent parallel emergence of PRRT, there is a chance that chemotherapy-based regimens could be replaced by PRRT altogether. For instance, the NETTER-2 (34) study demonstrated a mPFS of 22.8m with objective response rates of 43% in the PRRT-arm for first-line treatment in GEP NET grade 2-3. Despite this, we hypothesize that there could be a place for CAPTEM-based treatment for aggressive GEP NET grade 2 with/without bulky disease and GEP NET grade 3 (especially panNET), in scenarios after progression upon first-line PRRT, or in absence of somatostatin-receptor (SSTR) positivity or mismatch of SSTR-positive lesions with 18-FDG-PET positive lesions, or in settings where reduction of tumor bulk needs to be obtained, as in these setting PRRT may not be the optimal treatment solution.

Finally in terms of safety and toxicity, this study found good general tolerance and safety, with mainly myelotoxicity (thrombocytopenia, neutropenia, and anemia), fatigue, nausea, and other toxicities like diarrhea and hand-foot syndrome (palmar-plantar erythrodysesthesia). These safety and toxicity profiles are in line with data reported by Al-Toubah et al. (27) and Unal et al. (35). However, these data need to be interpreted with caution, as for example aggravating of myelotoxicity may occur in case of previous lines of treatment with chemotherapy, PRRT or targeted therapy. Therefore, the risk for toxicity due to CAPTEM needs to be assessed carefully on a patient to patient basis, considering their medical history and previous treatments.

The main limitations of this study were that it was conducted on a retrospective and heterogeneous cohort, with limited sample sizes and uneven distribution per tumor location or NEN subtype. Another limitation was the missing data, due to which some analyses lacked statistical power.

Despite these limitations, this study shows promising survival rates for panNET grade 2-3 tumors, further strengthening the argument for using CAPTEM in these patients, either as a first-line or subsequent line of treatment. This also paves way for exploration of difference in survival rates with sequential treatment with different modalities to find the most optimal sequence of treatment for these patients. Finally, further exploration is needed into aspects that include but are not limited to: time-to-response of CAPTEM compared to other existing treatment options, efficacy compared to emerging chemotherapy regimens like FOLFIRINOX, optimal sequence of chemotherapeutic regimens, and its place alongside PRRT (30).

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