ORIGINAL ARTICLE

Retrospective Study

Temozolomide and capecitabine regimen as first-line treatment in advanced gastroenteropancreatic neuroendocrine tumors at a Latin American reference center

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Abstract

BACKGROUND
Numerous studies have indicated that the temozolomide and capecitabine regimen (TEMCAP) exhibits a certain level of efficacy in treating advanced, well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NET). However, published data from Peru are limited. We hypothesize that this regimen could be a viable therapeutic option for advanced GEP-NET in the Peruvian population.

AIM
To evaluate overall survival (OS) in patients diagnosed with advanced GEP-NET treated with TEMCAP at the Instituto Nacional de Enfermedades Neoplásicas (INEN) in Lima-Perú.

METHODS
A retrospective review was conducted to identify patients with GEP-NEN treated with the TEMCAP regimen between 2011 and 2021 at the INEN. A total of thirty-eight patients were included in the final analysis: Thirty-five received TEMCAP as a first-line treatment, and three as a second-line treatment. The primary objective was to evaluate OS. The efficacy and safety of TEMCAP were assessed until the occurrence of unacceptable toxicity or disease progression. Survival outcomes were estimated using the Kaplan-Meier method.

RESULTS

The median age of the patients was 52 years (range 24-77 years), and 53.3% were female. The most common symptoms at diagnosis were abdominal pain in 31 patients (81.6%). Primary tumors included 12 in the rectum (31.6%), 11 in the pancreas (28.9%), 3 in the ileum (7.9%), 2 in the mesentery (5.3%), 2 in the small intestine (5.3%), 1 in the appendix (2.6%), 1 in the stomach (2.6%) and 6 cases of liver metastasis of unknown primary (15.8%). Five were neuroendocrine tumors (NET) G1 (13.2%), 33 were NET G2 (86.8%), five had Ki67 < 3% (13.2%), and 33 had Ki67 between 3% and 20% (86.8%). TEMCAP was administered to 35 (92.1%) patients as first-line treatment. OS at 12, 36, and 60 months was estimated in 80%, 66%, and 42%, respectively, with a median OS of 49 months.

CONCLUSION

TEMCAP therapy is a viable first-line option regarding efficacy and tolerability in areas where standard therapy is inaccessible.

Key Words: Well-differentiated; Gastroenteropancreatic neuroendocrine tumors; Capecitabine; Temozolomide; Retrospective study; Treatment; Chemotherapy

Core Tip: In this study, patients diagnosed with advanced gastroenteropancreatic neuroendocrine tumors who were treated with the temozolomide and capecitabine regimen exhibited a median overall survival of 49 months, with 42% surviving at 60 months. The regimen was well-tolerated, and most patients experienced stable disease. These findings suggest that this treatment could be viable in settings where standard therapies are unavailable or inaccessible, although further prospective studies are needed for confirmation.

INTRODUCTION

Neuroendocrine tumors (NEN) represent a diverse array of neoplasms arising from cells within the endocrine and nervous systems, and exhibit a broad spectrum of behaviors. While historically considered rare diseases, their prevalence has been increasing. In England, NEN are the 10th most prevalent cancer and the second most common gastrointestinal cancer, only preceded by colorectal cancer[1]. NEN have witnessed a notable surge over the past two decades; the age-adjusted incidence per 100000 persons increased from 4.90 in 2000 to 8.19 in 2018[2]. With regard to gastroenteropancreatic neuroendocrine tumors (GEP-NET) in the United States, the incidence is reported to be 3.56 cases per 100000 individuals[3].

The information published regarding NET in Latin American countries remains largely unreported, and clinical literature is highly scarce. An observational study in Argentina documented 532 NET cases, including 461 GEP-NET and 71 bronchial NET[4]. A NET registry from Brazil has compiled baseline data on the initial 1000 patients enrolled across 32 centers spanning all country regions. It categorized GEP-NET as the second most prevalent type, constituting 20.2% of cases, trailing only thoracic NEN[5]. In a retrospective review at the Instituto Nacional de Enfermedades Neoplásicas (INEN), 367 NEN were reported between 2010 and 2014. Gastroenteropancreatic NEN were the most prevalent, with 152 cases (44.84%), followed by thoracic NEN, with 75 cases (22.12%)[6].

The clinical practice guideline for medical management of GEP-NET at the INEN reported 650 cases of NEN between 2009 and 2018, with an average age of 55 years. The most frequent sites were the rectum (15%), lung (9.84%), stomach (8.3%), neuroendocrine Merkel cells (9.07%), and unknown primary (9.07%)[7]. According to the WHO classification for NEN, they are categorized into well-differentiated low-grade G1 (Ki67 < 3%), intermediate-grade well-differentiated G2 (Ki67 3%-20%), and high-grade well-differentiated G3 (Ki67 > 20%), based on the Ki67 proliferation index. G3 tumors are divided into well-differentiated high-grade or poorly differentiated high-grade neuroendocrine carcinomas (GEP-NEC) [8]. Of all NEN, approximately 80%-90% are well-differentiated[9]. GEP-NET can be classified according to their origin into two main groups: Pancreatic NET (pan-NET) and non-pan-NET. Furthermore, they can be classified based on hormone production in functioning and non-functioning tumors. Most GEP-NET are non-functioning; 20% of intestinal NET are functioning tumors, while pan-NET are functioning in 10%-30% of cases[9]. For non-functioning NET, early detection can be challenging unless the tumor has grown sufficiently large to cause symptoms.

Medical treatment options for advanced GEP-NET with antiproliferative effects include targeted drugs and systemic chemotherapy. Regarding somatostatin analogs (SSA), the CLARINET trial, which compared lanreotide to placebo,

estimated progression-free survival (PFS) rates at 24 months of 65.1% in the experimental arm and 33% in the placebo group[10]. These results were confirmed in the open-label extension study[11]. In the phase III PROMID trial, the median time to progression in the octreotide long-acting release (LAR) and placebo groups was 14.3 and 6 months, respectively [12]. However, the updated trial did not show a difference in OS[13]. Everolimus was shown to prolong PFS compared to placebo in previously treated GEP-NET patients[14,15]. Despite these findings, its efficacy in patients with GEP-NET associated with carcinoid syndrome remains unclear[16]. Sunitinib, a multitargeted tyrosine kinase inhibitor, demonstrated a median PFS of 11.4 months compared to 5.5 months in the placebo group in patients with advanced pan-NET. A 59% reduction in the risk of death was observed in favor of the experimental group[17]. More recently, the Netter 2 trial evaluated 177 Lu-dotatate as a first-line treatment in combination with octreotide LAR. It demonstrated a significant improvement in PFS in patients with newly diagnosed somatostatin receptor positive, G2 and G3, advanced GEP-NET compared to high-dose octreotide LAR alone[18].

Due to their high cost, these new agents are only available to some patients, especially in resource-limited countries. The restriction on access to first-line treatments at our institution creates an urgent need to investigate other effective alternatives. This study aims to assess the efficacy of the TEMCAP regimen as first-line therapy in patients with advanced GEP-NET in a Latin American population.

MATERIALS AND METHODS

Study population and data collection
A retrospective review was conducted to identify patients with GEP-NEN who were treated with the TEMCAP regimen at any point during their disease between 2011 and 2021. The registry data were provided by the Epidemiology and Statistics Department of the INEN. A total of forty-five GEP-NEN patients were identified, of which nine were excluded due to a diagnosis of NEC. Consequently, thirty-eight patients were included in the final analysis: Thirty-five received TEMCAP as a first-line treatment, and three received TEMCAP as a second-line treatment.

Inclusion criteria: Patients with a diagnosis of unresectable, metastatic, or recurrent GEP-NET; histologic grade 1 or 2; Ki67 index less than 20%.

Exclusion criteria: Patients with GEP-NEC, GEP-NET histologic grade 3, a Ki67 index greater than or equal to 20%, and incomplete medical records.

Primary and secondary objectives
The primary objective was to evaluate OS in the entire population. Secondary objectives included assessing PFS, evaluating OS and PFS in specific subgroups, including pan-NET and non-pan-NET; evaluating the objective response rate (ORR) and disease control rate (DCR), and assessing the regimen's toxicity by documenting treatment-related adverse effects.

Treatment and response criteria
The TEMCAP regimen consisted of capecitabine 750 mg/m² twice daily on days 1–14, followed by Temozolomide 200 mg/m² on days 10 to 14 in 28-day cycles until unacceptable toxicity or disease progression. The response was assessed by computed tomography (CT) according to RECIST 1.1 criteria. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events version 5.0 in all 38 patients.

Statistical analysis
A descriptive analysis was performed on qualitative variables using frequencies and percentages. Quantitative variables were summarized using measures of central tendency (mean, minimum, and maximum for normally distributed variables) and measures of dispersion (median, interquartile range, quartiles 1 and 3 for skewed distributions). OS was estimated from the start of chemotherapy to the date of death documentation or the last follow-up date. Patients who did not experience the event of interest were considered censored. PFS was estimated from the start of chemotherapy to the date of documented progression *via* CT following RECIST 1.1 criteria or the last follow-up date, with patients not experiencing the event also considered censored. Both OS and PFS estimates were calculated using the Kaplan-Meier method. Differences in survival according to study variables were evaluated using the log-rank test. A multivariate Cox proportional hazards model was fitted with variables showing significant differences in OS and PFS to assess their effect on the risk of death or progression, respectively. The proportional hazards assumption was tested in the adjusted model. A *P* value of < 0.05 was considered significant for differences in OS and PFS and for assessing the risk of death. All analyses were performed using R software.

RESULTS

Patient's characteristics
The median age was 52 years (24-77 years); 55.3% were females, and 44.7% were males. Lima was the most common region of origin (36.8%), followed by Huánuco (13.2%). The majority (92.1%) had an Eastern Cooperative Oncology Group

Table 1 Demographic and clinical features, *n* (%)	
Feature	***n* = 38**
Age at diagnosis (years)	
Median (min-max)	52 (24-77)
Sex	
Female	21 (55.3)
Male	17 (44.7)
Region of birth	
Lima	14 (36.8)
Huánuco	5 (13.2)
Ancash	3 (7.9)
Ica	3 (7.9)
Junín	3 (7.9)
Lambayeque	2 (5.3)
Ayacucho	2 (5.3)
Cajamarca	2 (5.3)
Amazonas	1 (2.6)
Cusco	1 (2.6)
Puno	1 (2.6)
Tacna	1 (2.6)
BMI, kg/m^2	
Median (IQR)	23.438 (20.65-26.279)
ECOG scale	
0	1 (2.6)
1	35 (92.1)
2	2 (5.3)
Symptoms	
Abdominal pain	31 (81.6)
Rectal bleeding	12 (31.6)
Weight loss	9 (23.7)
Diarrhea	5 (13.2)
Emesis	4 (10.5)
Flushing	2 (5.3)

IQR: Interquartile range; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group.

(ECOG) performance status of 1. The median body mass index (BMI) was 23.438 kg/m^2. The most common symptom was abdominal pain (81.6%), followed by rectal bleeding (31.6%), weight loss (23.7%), diarrhea (13.2%), emesis (10.5%), and flushing (5.3%). Demographic and clinical features are shown in Table 1. According to clinical staging, 15.8% were in stage III, 81.6% in stage IV, and one patient was in an unspecified stage. Two (5.3%) patients had unresectable tumors, 5 (13.2%) had recurrent disease, and 31 (81.6%) had metastatic disease at presentation. Among the 38 patients, the primary tumor locations were distributed as follows: Twelve (31.6%) were rectal tumors, eleven (28.9%) were pancreatic tumors (28.9%), three (7.9%) were ileum tumors, two (5.3%) were mesenteric tumors, two (5.3%) were small intestine tumors, one (2.6%) was an appendix tumor, one (2.6%) was a stomach tumor and six (15.8%) were liver metastases from an unknown primary.

Table 2 Systemic therapy, *n* (%)

Feature	*n* = 38
First-line treatment	
Temozolomide/capecitabine	35 (92.1)
CAPOX	1 (2.6)
Cisplatin/etoposide	1 (2.6)
Interferon alpha	1 (2.6)
First-line cycles	
Median (IQR)	9 (6-22.75)
Duration of first-line treatment, days	
Median (IQR)	331 (133.25-606)
Second-line treatment	
Yes	14 (36.8)
No	24 (63.2)
Second-line regimen, *n* = 14	
Capecitabine	4 (28.6)
CAPOX	3 (21.4)
TEMCAP	3 (21.4)
Cisplatin/etoposide	1 (7.1)
Dacarbazine (DTIC)	1 (7.1)
GEMOX	1 (7.1)
Temozolomide	1 (7.1)

IQR: Interquartile range; TEMCAP: Temozolomide and capecitabine regimen; CAPOX: capecitabine/oxaliplatin; GEMOX: gemcitabine/oxaliplatin.

Chemotherapy treatment

TEMCAP was administered to 35 patients (92.1%). The median number of chemotherapy cycles at first-line was nine. Fourteen patients (36.8%) received a second-line treatment. Among these patients, the most commonly used regimen was capecitabine in four patients (28.6%), followed by capecitabine/oxaliplatin and TEMCAP in three patients (21.4%) each, cisplatin/etoposide in one patient (7.1%), dacarbazine in one patient (7.1%), gemcitabine/oxaliplatin in one patient (7.1%), and temozolomide in one patient (7.1%). Characteristics of systemic therapy are shown in Table 2.

Efficacy

The responses of the 38 patients according to RECIST 1.1 were as follows: One (2.6%) patient had a complete response (CR), two (5.3%) had a partial response (PR), sixteen (42.1%) had stable disease (SD), fifteen (39.5%) had progressive disease (PD), and four (10.5%) were without RECIST evaluation. The ORR was 7.9%, and the DCR was 50%. Regarding the pan-NET subgroup, there was one CR, two PR, three SD, four PD, and one case without response evaluation; the ORR was 27.2%, and the DCR was 54.5%.

OS

With a median follow-up of 33.5 months (range 1–81 months), the estimated OS rates at 12, 36, and 60 months were 80%, 66%, and 42%, respectively, with a median OS of 49 months for the entire population (Figure 1A). The median OS in the pan-NET group was 64 months, compared to 44 months in the non-pan-NET group, with a *P*-value of 0.056, which was not statistically significant (Figure 1B).

PFS

Among the total population (*n* = 34; RECIST criteria not evaluated in 4 patients), 15 (44.1%) patients experienced PD, with a median follow-up time for PFS of 20 months (range 5-81 months). The estimated PFS at 12, 36, and 60 months was 84.2%, 49.9%, and 49.9%, respectively, with a median PFS of 34 months. In the pan-NET group, the median PFS was 78 months, compared to 27 months in the non-pan-NET group (Figure 1C).
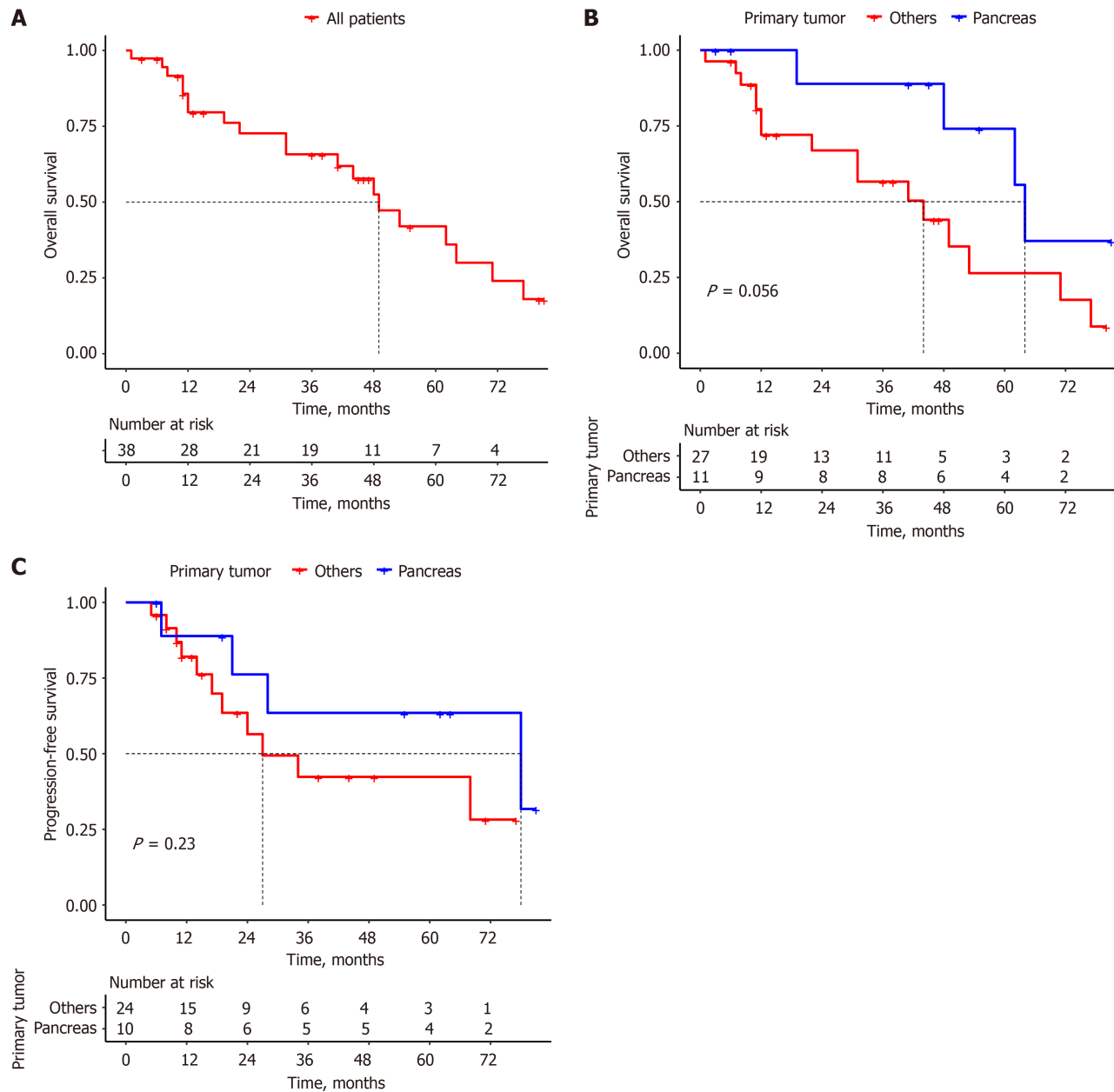
Figure 1 Overall survival. A: Overall survival (OS) in patients with gastroenteropancreatic neuroendocrine tumors; B: OS according to primary tumor; C: Progression-free survival based on primary tumor.

Safety profile

The most common adverse event of any grade was neutropenia, with 7 (18.4%) recorded events, followed by hand-foot syndrome with 6 (15.8%) events, and hypertransaminasemia and nausea with 5 (13.2%) events each. The total number of adverse events is shown in Table 3. Regarding adverse events grade 3 and 4, neutropenia occurred in three patients (7.9%), two (5.3%) experiencing grade 3 and one (2.6%) grade 4; Thrombocytopenia was observed in four patients (10.6%), two (5.3%) experiencing grade 3 and two (5.3%) grade 4; anemia was reported in two patients (5.3%), one (2.6%) experiencing grade 3 and one (2.6%) grade 4. Additionally, nausea of grade 3 was documented in one patient (2.6%).

DISCUSSION

We observed a median OS of 49 months in our study, similar to the findings of other studies that retrospectively evaluated OS with the TEMCAP regimen in GEP-NET[19-25].

Prospective data evaluating TEMCAP are scarce. The first prospective trial was phase II ECOG-ACRIN E2211, which compared TEMCAP *vs* temozolomide in advanced pan-NET. This trial met its primary endpoint with a PFS of 22.7 months in the TEMCAP arm *vs* 14.4 months in the temozolomide arm. Although the median OS was 4.9 months superior in the TEMCAP arm, it did not achieve statistical significance[26].

Table 3 Adverse events during chemotherapy by grade, *n* (%)

	Grade			
	1	2	3	4
Neutropenia	3 (7.9)	1 (2.6)	2 (5.3)	1 (2.6)
Hand-foot syndrome	5 (13.2)	1 (2.6)		
Hypertransaminasemia	3 (7.9)	2 (5.3)		
Nausea	4 (10.5)		1 (2.6)	
Peripheral neuropathy	4 (10.5)	1 (2.6)		
Vomiting	4 (10.5)	1 (2.6)		
Anemia	2 (5.3)		1 (2.6)	1 (2.6)
Asthenia	4 (10.5)			
Constipation	4 (10.5)			
Thrombocytopenia			2 (5.3)	2 (5.3)
Anorexia	3 (7.9)			
Diarrhea	2 (5.3)			
Sialorrhea	2 (5.3)			
Hyperbilirubinemia	1 (2.6)			

In our study, we observed an ORR of 7.9% with one (2.6%) CR and two (5.3%) PR; the DCR was 50%, including 16 patients (42.1%) with SD. Our DCR results are very similar to those in other retrospective studies. Crespo *et al*[22] evaluated TEMCAP in 65 patients with GEP-NET (70.8% had pan-NET) and the DCR was 47.7%, with two CR (3.1%), 29 PR (44.6%), and 27 (41.5%) SD. Fine *et al*[19] evaluated 18 patients with well-differentiated NET metastatic to the liver who had failed front-line therapy. The ORR was 61%, and the DCR was 83.2%. Abbasi *et al*[27] evaluated 21 patients (14 with pan-NET and 7 with carcinoid tumors) who failed treatment with SSA and platinum-based chemotherapy combined with etoposide and reported a DCR of 80%. The systematic review by Arrivi *et al*[25] evaluated 1,818 patients from 42 articles with advanced NEN of gastroenteropancreatic, lung, and unknown origin. The ORR was 77%, with a median OS ranging from 8 to 103 months. ORR and DCR appear more critical as surrogates of the PFS and OS for the TEMCAP regimen in GEP-NET.

Our results for pan-NET showed an ORR of 27.2% and a DCR of 54.5%, consistent with what has been described in the literature. Pan-NET have historically better chemotherapy responses than non-pan-NET. Our study also showed this trend, with OS in pan-NET being 20 months longer than non-pan-NET. The PSF for pan-NET in our series was 78 months compared to 27 months in non-pan-NET. Notably, of the 11 patients with pan-NET, 10 were evaluated according to RECIST 1.1, of which 4 showed disease progression; the remaining patients are still alive and continue to be followed up.

A meta-analysis revealed a lower ORR in non-pan-NET than in pan-NET patients; however, this difference was not statistically significant when high-risk bias studies were excluded[28]. In a cohort of 101 patients, which included 53 with pan-NEN and 44 with carcinoid tumors treated with temozolomide-based chemotherapy, an ORR of 34% was observed in pan-NEN compared to 2% in carcinoid tumors[29]. Patients with pan-NET who require clinically meaningful tumor shrinkage may benefit more from chemotherapeutic regimens.

Anemia, neutropenia, and thrombocytopenia were the most common grade 3-4 adverse events observed in our study, consistent with findings from other trials. Crespo *et al*[22] reported neutropenia in 7.7% of patients, while in the systematic review by Arrivi *et al*[25], the safety analysis of TEMCAP showed that 16.4% of the population experienced grade 3-4 toxicities, with hematological toxicities being the most common (27.2%). The prospective ECOG-ACRIN E2211 study reported grade 3-4 neutropenia in 13% of cases and thrombocytopenia in 10%[26]. Temozolomide-based regimens using a dose-dense schedule of 150 mg/m² daily every other week resulted in more hematological toxicities compared to the TEMCAP regimen. Grade 3-4 lymphopenia was reported in more than 50% of patients. Chan *et al*[30] reported grade 3 thrombocytopenia in 18% of patients. Opportunistic infectious complications were also reported during treatment with dose-dense temozolomide-based regimens[30,31]. This contrasts with our study, where no opportunistic infections were observed at a dose of 200 mg/m² for 5 days.

We must consider some limitations in our study inherent to all retrospective analyses, particularly the potential for selection bias. Additionally, the small sample size of 38 patients may have contributed to the lack of statistical significance in some outcomes. Despite these limitations, our data support the effectiveness of the TEMCAP regimen in patients with advanced GEP-NET.

CONCLUSION

This is the first retrospective study in Peru to evaluate the use of TEMCAP for advanced GEP-NET. The findings suggest that TEMCAP could be a viable first-line treatment in regions where standard therapies are not readily accessible, particularly for grade 2 tumors. A notable 42% OS rate at 60 months was observed. Prospective studies are needed to determine its value as a treatment option in this setting.

FOOTNOTES

Author contributions: Cruz-Diaz WE collected the data at the Instituto Nacional de Enfermedades Neoplásicas and wrote the initial manuscript; Paitan V and Haro-Varas J supervised the initial manuscript; Medina J reviewed the pathology slides, and Flores R reviewed the computed tomography and magnetic resonance imaging images; Mantilla R was responsible for conducting the statistical analysis, and Castro-Oliden V provided expert guidance and supervision throughout the study and critically reviewed the final manuscript; All authors read and approved the final manuscript.

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