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Chemotherapy for Well-Differentiated Pancreatic Neuroendocrine Tumours with a Ki-67 Index ≥10%: Is There a More Effective Antitumour Regimen? A Retrospective Multicentre Study of the French Group of Endocrine Tumours (GTE)

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Keywords

Chemotherapy · Differentiation · Gastroenteropancreatic endocrine tumours · Proliferation · Ki-67 index

Abstract

Background: The best chemotherapy regimen for well-differentiated pancreatic neuroendocrine tumours (pNETs) with a Ki-67 index ≥10% is still debated. We evaluated the antitumour efficacy of various first-line chemotherapy regimens (streptozocin based, platinum based, or dacarbazine/temozolomide based) in this situation. ***Methods:*** In this retrospective multicentre study of the French Group of Endocrine Tumours (GTE), we recruited consecutive patients with advanced well-differentiated pNETs and a Ki-67 index ≥10% receiving chemotherapy between 2000 and 2012. The primary endpoint was progression-free survival (PFS) according to RECIST. ***Results:*** Seventy-four patients (42 men, median age 55.5 years) were enrolled from 10 centres. Fifty-one patients (69%) had grade 2 NET and 61 (82%) were stage IV. Median overall survival was 36.3 months. Forty-four patients (59%) received streptozocin-based, 18 (24%) platinum-based, and 12 (16%) dacarbazine/temozolomide-based chemotherapy regimens. These 3 groups were similar regarding

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age, functioning tumours, grade, the number of metastatic sites, and surgery for primary tumours, but not regarding surgery for metastases and time since diagnosis. Grade 3 NET (HR 2.15, 95% CI: 1.18–3.92, $p = 0.012$) and age above 55 years (HR 1.84, 95% CI: 1.06–3.18, $p = 0.030$) were associated with shorter median PFS in the multivariate analyses. Compared to streptozocin-based chemotherapy, no difference was found in terms of PFS for the platinum-based or for the dacarbazine/temozolomide-based chemotherapy regimen: median PFS was 7.2, 7.5, and 7.2 months, respectively ($p = 0.51$). ***Conclusions:*** Patients with intermediate or highly proliferative well-differentiated pNETs may benefit from 1 of the 3 chemotherapy regimens. Increased age and grade 3 were associated with shorter median PFS. Randomised studies searching for response predictors and the best efficacy-tolerance ratio are required to personalise the strategy.

Introduction

Neuroendocrine neoplasms (NENs) are rare neoplasms, with an annual incidence of 5 per 100,000 [1, 2]. NENs are classified as poorly differentiated neuroendocrine carcinomas (NECs) or well-differentiated neuroendocrine tumours (NETs) based on their morphology and proliferative index, which form the basis for the WHO 2010 classification [3]. Patients with NEC have a poorer prognosis than those with NET [1, 4–7]. As part of NETs, the annual incidence of pancreatic NETs (pNETs) is estimated to be 0.30–0.60 per 100,000 [1, 7, 8], and up to 60–80% of patients present with distant metastases or locally advanced tumours [1, 5, 9–12]. However, the outcomes of these patients are very heterogeneous. Indeed, 5-year overall survival (OS) rates of more than 75% or less than 30% have been reported for stage IV patients [9–11, 13–16]; grade and tumour burden are considered to be the 2 most important prognostic factors for substratifying these patients' prognostic outcomes [5, 9, 10, 12].

In advanced pNETs, multiple lines of treatment are now approved, including lanreotide-, everolimus-, sunitinib-, and streptozocin-(STZ) based chemotherapy [17–20]. Current guidelines recommend STZ-based chemotherapy for aggressive pNETs as defined by a high grade (G2, Ki-67 index >10%), a high tumour burden, and progressive and/or symptomatic disease. In contrast, European guidelines use this cut-off of 10% (G1 or low G2) to determine whether a patient is eligible for curative surgery, for hepatic transplantation, and/or for somatostatin analogue therapy [21–25]. In addition, alternatives to STZ-based chemotherapy are also cited, including temozolomide- or platinum-based chemotherapy regimens [22, 26]. Indeed, renewed interest in the capecitabine-temozolomide regimen has emerged as a potential competitor of historical STZ-based chemotherapy [27]. Moreover, platinum-based chemotherapy – such as cisplatin- and oxaliplatin-based chemotherapy regimens, which are currently recommended mainly for patients with poorly differentiated NECs [28] – has been reported to evoke partial responses in pNET patients including subgroups of patients with a high proliferative index [29–32]. Taken together, these results warrant clarification regarding the putative role of each of these regimens in a precisely defined aggressive pNET population of patients, and also identification of response predictors. Indeed, the Ki-67 proliferative index has been recognised as a major prognostic parameter, even if its role as putative response predictor has yet to be confirmed [33].

The aim of this study was to evaluate the antitumour efficacy of STZ-based, platinum-based, and dacarbazine/temozolomide-based chemotherapy regimens as first-line chemotherapy for patients with aggressive advanced pNETs as defined by a Ki-67 index ≥10%, with progression-free survival (PFS) as the primary endpoint. A retrospective multicentre study was designed within the French Group of Endocrine Tumours (GTE) to answer this question.

Subjects and Methods

Patients

All the consecutive patients who received first-line cytotoxic chemotherapy for advanced pNET in one of the centres of the GTE between 2000 and 2012 were considered for inclusion. The patients were retrospectively identified from a national registry or from hospital charts. The inclusion criteria were: (1) locally advanced or metastatic unresectable pNET; (2) a reviewed diagnosis of well-differentiated morphology as confirmed by the French pathological network (TENpath); (3) a Ki-67 index ≥10%; (4) first-line STZ-based, platinum-etoposide-based, or dacarbazine/temozolomide-based cytotoxic chemotherapy; and (5) sporadic cases. The exclusion criteria were: (1) non-chemotherapy first-line treatment, including targeted therapy or hepatic artery embolisation; (2) absence of RECIST 1.0 [34]-evaluable imaging; and (3) presence of an inherited syndrome. Patients treated with somatostatin analogues prior to or during first-line chemotherapy were eligible. To ensure consistency, determination of eligibility and data collection were undertaken by a single investigator (G.R.) on site, with the main focus on the quality control of pathological reporting, thereby ensuring that well-conducted morphological differentiations were clearly notified and also that RECIST evaluations were adequately performed.

The following parameters were recorded from all patients at the time of chemotherapy initiation: gender, age, main presenting symptoms (including the presence of a functioning syndrome), Ki-67 index, tumour grade, stage and number of metastatic sites, and presence of hepatic or extrahepatic metastases. All treatments received before, during, and after the first-line cytotoxic chemotherapy were recorded. The date of death or last follow-up was also recorded.

The pathological characteristics of each tumour were evaluated in one of the expert centres participating in the TENpath network [35]. The differentiation was systematically described by the pathologist of each expert centre. The Ki-67 proliferative index is expressed as a percentage based on the count of Ki-67-positive cells in 500–2,000 tumour cells in areas with the highest immunostaining using the MIB1 antibody. Grading was performed on the primary tumour in 18 cases (25%), on the metastasis in 32 cases (44%), or in both in 23 cases (31%) (in the case of the last, the highest Ki-67 index was used in this study). All the pathological criteria were verified for each included patient at the time of the review of all files on site by the same investigator (G.R.). The Ki-67 index results were subclassified into 2 subgroups: ≤20% (grade 2) or >20% (grade 3) according to the 2010 WHO classification as well as recent proposals [36–38].

First-Line Cytotoxic Chemotherapy

The treatment for each patient was chosen by local multidisciplinary committees of the GTE according to treatment guidelines and patient status. The following information was collected on each patient: the type of chemotherapy regimen, the total duration of first-line chemotherapy, and the dose. First-line chemotherapy was substratified into 3 subgroups: STZ-based chemotherapy (STZ-BC group), platinum-based chemotherapy (P-BC group), and dacarbazine- or temozolomide-based chemotherapy (D/T-BC group). Dosage was classified as follows: (1) full dose, if the patient received the whole dose as planned during the full course of first-line treatment, or (2) reduced dose.

Tumour Response Evaluation of First-Line Chemotherapy

Imaging follow-up was performed every 2 or 3 months with thoracic and abdominal CT scans and/or abdominal MRI. Response to chemotherapy was classified into complete response, partial response, stable disease, or progressive disease according to the RECIST 1.0 [34] criteria based on local radiological reviews. Complete and partial responses were jointly considered as objective responses (ORs). The date of progression was also recorded.

Endpoints

The primary endpoint was PFS, calculated from the date of the first-line cytotoxic chemotherapy to the date of progression or of death from any cause. Progression-free survivors at the date of last follow-up were censored. Patients receiving another treatment prior to progression (such as surgery or hepatic artery embolisation) were also censored at the time of the last evaluation before starting the second treatment. The secondary endpoint was the first-line chemotherapy response rate.

Statistical Analysis

The main patient characteristics were assessed for the whole cohort and then compared between the 3 chemotherapy-defined groups. Median OS, calculated from the onset of first-line chemotherapy until death of any cause, was described and the main prognostic factors for OS were searched in our population.

Median PFS and response rates were evaluated for the whole cohort and then compared between the 3 chemotherapy-defined groups. Finally, PFS was assessed according to the chemotherapy regimen, adjusted for the main potential prognostic factors, as identified in our population and from the literature.

Qualitative variables are presented as numbers (percentages); they were compared between groups using the Fisher exact test due to the small sample size. Quantitative variables are presented as medians [ranges] and compared with the Mann-Whitney-Wilcoxon or the Kruskal-Wallis test according to the number of groups compared. PFS and OS and their 95% CIs were estimated using the Kaplan-Meier method and compared between groups using log-rank tests. Cox regression was used in our multivariate survival analyses. All statistical analyses were performed using R software version 3.1.1.

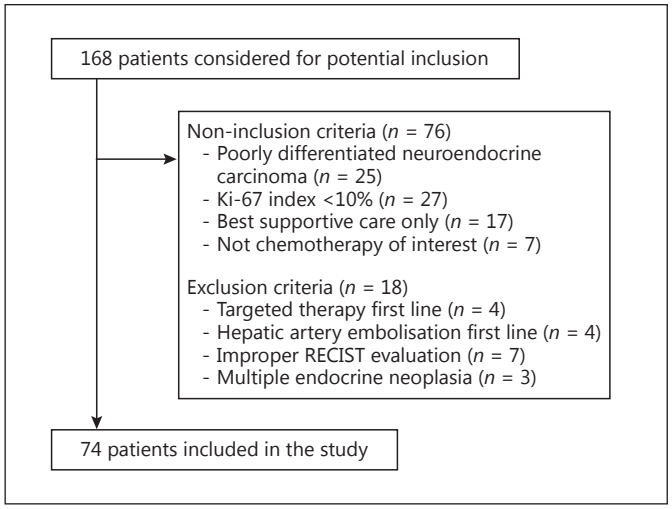

Fig. 1. Flow chart of the patients included.

Results

Patient Characteristics

Ten centres participated in the study, and 168 files were initially considered. The following exclusion criteria were met: poorly differentiated NEC (n = 25); pNET with a Ki-67 index <10% (n = 27); receiving only supportive care due to deterioration in global health status (n = 17); and receiving chemotherapy different from the 3 regimens under investigation (n = 7). Furthermore, 18 patients met other exclusion criteria, as detailed in Figure 1. Finally, the 74 remaining patients were included in this study (Fig. 1).

Table 1. Characteristics of the study population according to the regimen received as first-line chemotherapy

Characteristics	All patients (n = 74)	STZ-BC group (n = 44)	P-BC group (n = 18)	D/T-BC group (n = 12)	p value
Male gender	42 (57%)	27 (61%)	6 (33%)	9 (75%)	0.055
Age, years	55.5 [33.6–78.7]	55.4 [35.3–77.0]	55.1 [33.6–78.7]	59.9 [37.0–75.3]	0.73[a]
Main presenting symptom (n = 71 eligible for analysis)					
Functioning tumours	7 (10%)	5 (11%)	1 (6%)	1 (8%)	0.68
Abdominal pain	20 (28%)	11 (25%)	8 (44%)	1 (8%)	
Tumour mass	18 (25%)	12 (27%)	3 (17%)	3 (25%)	
Incidental finding	10 (14%)	6 (14%)	2 (11%)	2 (17%)	
Jaundice	5 (7%)	3 (7%)	0 (0%)	2 (17%)	
Asthenia/weight loss	4 (6%)	2 (5%)	1 (6%)	1 (8%)	
Diarrhoea	3 (4%)	1 (2%)	1 (6%)	1 (8%)	
Other	4 (6%)	3 (7%)	1 (6%)	0 (0%)	
Ki-67 index	18 [10–60]	15 [10–60]	20 [10–50]	18 [10–42]	0.31[a]
Grade 3 tumours	23 (31%)	10 (23%)	8 (44%)	5 (42%)	0.16
Stage (number of M+ sites)					
III	13 (18%)	5 (11%)	4 (22%)	4 (33%)	0.41
IV (1 M+ site)	30 (40%)	18 (41%)	8 (44%)	4 (33%)	
IV (≥2 M+ sites)	31 (42%)	21 (48%)	6 (33%)	4 (33%)	
Hepatic metastases	60 (81%)	39 (89%)	13 (72%)	8 (67%)	0.11
Extra-hepatic metastases	31 (42%)	21 (48%)	6 (33%)	4 (33%)	0.54
Treatment prior to first-line chemotherapy					
Primary tumour surgery	28 (38%)	15 (34%)	5 (28%)	8 (67%)	0.088
Metastatic surgery	14 (19%)	9 (20%)	0 (0%)	5 (42%)	0.0071
Somatostatin analogue	9 (12%)	6 (14%)	1 (6%)	2 (17%)	0.69
Radiotherapy	4 (5%)	1 (2%)	1 (6%)	2 (17%)	0.11
Time since diagnosis, months	3.8 [0.1–73.6]	5.3 [0.1–44.1]	1.6 [0.4–73.6]	13.5 [0.1–72.1]	<0.001[a]
Duration of chemotherapy, months	4.8 [1.4–29.4]	5.5 [1.4–29.4]	4.4 [2.3–17.4]	4.4 [2.1–15.9]	0.63[a]
Follow-up duration, months	25.6 [1.0–136.0]	28.1 [1.0–136.0]	25.7 [2.3–88.4]	19.8 [3.7–53.1]	0.60[a]
OS,[c] months	36.3 (25.2–50.0)	37.9 (20.8–NE)	27.1 (20.9–NE)	40.9 (17.1–NE)	0.94[b]

Values are presented as n (%) or median [range] unless specified otherwise. p value: Fisher exact tests, otherwise specified. NE, not evaluable; M+ site, metastatic site; STZ-BC, streptozocin-based chemotherapy; P-BC, platinum-based chemotherapy; D/T-BC, dacarbazine/temozolomide-based chemotherapy; OS, overall survival. [a] Kruskal-Wallis tests. [b] log-rank test. [c] Median (95% CI).

There were 42 men (57%) and the median age of the population was 55.5 years (range: 33.6–78.7) (Table 1). The main presenting symptom was abdominal pain in 20 patients (28%). Seven patients (10%) had functioning tumours, including 3 gastrinomas. Sixty-one patients (82%) were stage IV, including 31 (42%) with 2 or more metastatic sites. Sixty patients (81%) had liver metastases. The median value of the Ki-67 index was 18 (range: 10–60), including 51 patients (69%) classified as grade 2 and 23 (31%) as grade 3. Surgery of the primary tumour before first-line chemotherapy was performed in 28 patients (38%) and metastatic surgery in 14 (19%). Nine patients (12%) received somatostatin analogues and 4 (5%) were treated with radiotherapy before first-line chemotherapy. No difference in any of these characteristics was found between grade 2 and grade 3 patients (data not shown).

Overall Survival

The median duration of follow-up (started at the onset of first-line chemotherapy) was 25.6 months (1.0–136.0), without any difference according to the first-line chemotherapy regimen received (Table 1). Forty-five deaths were recorded during the study.

The median OS for the whole cohort was 36.3 months (25.2–50.0), with 1-, 3-, and 5-year survival rates of 83% (75–92), 50% (39–64), and 29% (18–46), respectively. In the multivariate analysis, only surgery of the primary tumours was found to be positively associated with OS (HR = 0.38, 95% CI: 0.19–0.78, p = 0.008). A non-significant trend for poorer prognosis was found for patients with grade 3 tumours (HR = 1.81, 95% CI: 0.90–3.63, p = 0.095). The median OS was 50.0 months (33.4–not evaluable [NE]) for patients undergoing primary tumour sur-

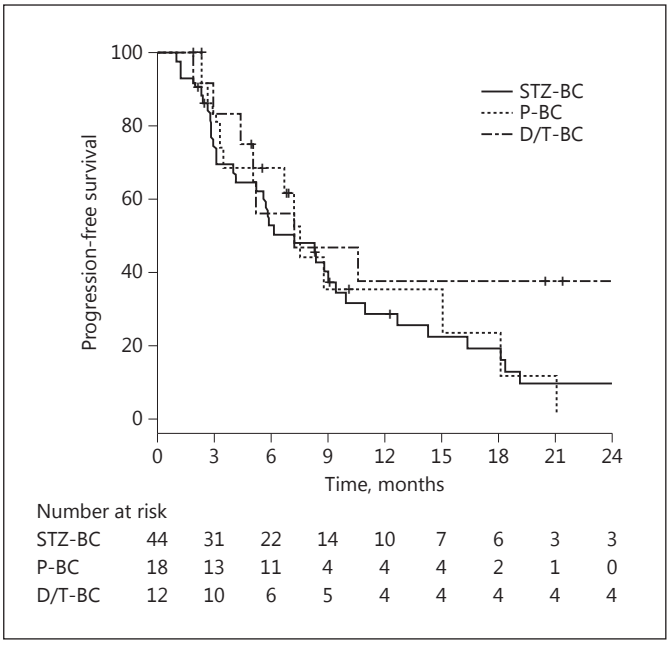

Fig. 2. Progression-free survival according to the first-line chemotherapy regimen ($n = 74$). Test log-rank $p = 0.51$. STZ-BC, streptozocin-based chemotherapy; P-BC, platinum-based chemotherapy; D/T-BC, dacarbazine/temozolomide-based chemotherapy.

gery, and 27.1 months (19.1–42.8) for patients without primary tumour surgery ($p = 0.023$). The median OS was 37.9 months (26.0–71.3) for patients with grade 2 tumours, and 20.9 months (17.1–NE) for patients with grade 3 tumours ($p = 0.54$).

First-Line Chemotherapy

Regarding the chemotherapy regimen, 44 patients received STZ-BC (including STZ + doxorubicin [$n = 33$], STZ + 5-fluorouracil [5-FU] [$n = 8$], STZ + 5-FU + bevacizumab [$n = 2$], and STZ + epirubicin [$n = 1$]), 18 patients received P-BC (including cisplatin + etoposide [$n = 16$] and carboplatin + etoposide [$n = 2$]), and 12 patients received D/T-BC (including temozolomide alone [$n = 2$], temozolomide + capecitabine [$n = 4$], dacarbazine + 5-FU [$n = 2$], and dacarbazine + 5-FU + epirubicin [$n = 4$]). The median delay between the diagnosis of metastasis and the onset of first-line chemotherapy was 3.8 months (0.1–73.6).

There was no difference between the 3 groups in terms of age, grading of the tumour, the number of metastatic sites at diagnosis, and primary tumour surgery (Table 1). Metastatic surgery prior to first-line chemotherapy was more frequent in the D/T-BC group (42%, 5 patients) than in the STZ-BC group (20%, 9 patients) and in the P-BC group (no patient) ($p = 0.0071$). In addition, the median length of time from diagnosis of metastasis was 5.3 months (0.1–44.1), 1.6 months (0.4–73.6), and 13.5 months (0.1–72.1) for the STZ-BC, the P-BC, and the D/T-BC group, respectively ($p < 0.001$) (Table 1).

The median duration of first-line chemotherapy was 4.8 months (1.4–29.4), with no differences between the 3 groups. Forty-nine patients received full-dose chemotherapy, while 14 received reduced-dose chemotherapy, without any difference between the groups (missing data for 11 patients).

PFS and Rates of Response to First-Line Chemotherapy

The median PFS was 7.2 months (5.7–9.9) for the whole population. In univariate analysis, there was no difference in median PFS according to the type of first-line chemotherapy regimen: 7.2 months (95% CI: 5.2–11.0), 7.5 months (95% CI: 3.5–NE), and 7.2 months (95% CI: 5.0–NE) in the STZ-BC group, the P-BC group, and the D/T-BC group, respectively ($p = 0.51$) (Fig. 2).

In multivariate Cox regression analysis, grade 3 (HR = 2.15, 95% CI: 1.18–3.92, $p = 0.012$) and age over 55 years (HR = 1.84, 95% CI: 1.06–3.18, $p = 0.030$) were significantly and independently associated with shorter PFS, but there was only a non-significant trend for a better median PFS for the D/T-BC group compared to the STZ-BC group (HR = 0.52, 95% CI: 0.24–1.13, $p = 0.099$) (Table 2). Median PFS was longer in patients with grade 2 tumours (8.8 months, 95% CI: 6.7–15.0) than in those with grade 3 tumours (5.6 months, 95% CI: 3.5–10.5, $p = 0.074$). Primary tumour surgery was not associated with PFS. When STZ-BC and D/T-BC were grouped together and compared to P-BC, no significant difference was observed regarding PFS (data not shown).

According to the RECIST, an OR after first-line chemotherapy was observed in 21 patients (29%); 25 (34%) had stable disease and 27 (37%) had progressive disease. The response rates did not differ significantly between the 3 groups (Table 3). Again, no difference was observed with regard to grade (data not shown).

Treatments Received following First-Line Chemotherapy

The median of the total number of treatment lines (either chemotherapy or biotherapy) was 2 (1–9), with no difference regarding the first-line chemotherapy regimen ($p = 0.28$). Fifty-eight patients (78%) received a second line of treatment: 5 received STZ-BC, 10 P-BC, 13 D/T-

Table 2. Progression-free survival (Cox regression analysis) (n = 74)

Risk factors	Patients, n (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p	HR (95% CI)	p
Chemotherapy regimen					
STZ-BC	44 (59%)	1.00		1.00	
P-BC	18 (24%)	0.96 (0.50–1.86)	0.90	0.89 (0.46–1.74)	0.73
D/T-BC	12 (16%)	0.65 (0.31–1.36)	0.26	0.52 (0.24–1.13)	0.099
Age >55 years	40 (54%)	1.48 (0.87–2.50)	0.15	1.84 (1.06–3.18)	0.030
Grade 3 tumours	23 (31%)	1.67 (0.95–2.95)	0.076	2.15 (1.18–3.92)	0.012
Stage IV	61 (82%)	1.31 (0.64–2.69)	0.46	1.71 (0.80–3.64)	0.16
Surgery of primary tumour	28 (38%)	0.90 (0.52–1.54)	0.69	–	–
Metastatic surgery	14 (19%)	0.80 (0.40–1.59)	0.53	–	–

Factors with an HR >1 are associated with decreased progression-free survival. STZ-BC, streptozocin-based chemotherapy; P-BC, platinum-based chemotherapy; D/T-BC, dacarbazine/temozolomide-based chemotherapy.

Table 3. PFS and response rates by first-line chemotherapy regimen (n = 74)

	STZ-BC (n = 44)	P-BC (n = 18)	D/T-BC (n = 12)	p value
Median PFS in months (95% CI)	7.2 (5.2–11.0)	7.5 (3.5–NE)	7.2 (5.0–NE)	0.51
Response rate (n = 73 eligible for analysis)				
Objective response	11 (26%)	4 (22%)	6 (50%)	0.37
Stable disease	13 (30%)	10 (56%)	2 (17%)	
Disease progression	19 (44%)	4 (22%)	4 (33%)	

p values: log-rank test (median PFS); Kruskal-Wallis test (response rate). STZ-BC, streptozocin-based chemotherapy; P-BC, platinum-based chemotherapy; D/T-BC, dacarbazine/temozolomide-based chemotherapy; PFS, progression-free survival.

BC, and 15 another regimen of chemotherapy; 15 were treated with targeted therapies. Finally, 36 patients received 3 or more lines of treatment.

Discussion

In a population of intermediate to highly proliferative and advanced pNET patients with Ki-67 indices >10%, our study underlines 2 important results: (1) STZ-BC was the first-line regimen most frequently used by French investigators, but P-BC was still used in 24% of the cases, demonstrating an absence of consensus between local physicians, and (2) an age >55 years and grade 3 NET were significantly and independently associated with shorter PFS, whereas the chemotherapy regimen used (STZ-BC, P-BC, and D/T-BC) did not influence PFS – which challenges the current ENETS or NCCN guidelines [22, 39]. The cut-off of a Ki-67 index ≥10% was chosen to select intermediate to highly proliferative pNETs based on recent ENETS guidelines [21–25], prognostic influence as demonstrated in surgical series, and also its association with higher uptake of fluorodeoxyglucose.

In our study, focusing on intermediate or highly proliferative pNETs, the median OS was shorter (36.3 months) than in previous studies on stage IV pNETs [5, 9, 11, 12, 16]. In line with this, other features also highlight the aggressiveness of the disease in our population: functioning tumours were rare (10%), 31% of the patients were classified as grade 3, and only 38% of the patients had previously undergone primary tumour surgery. Median OS is mainly influenced by primary tumour surgery, as previously reported [14, 40–42].

In the absence of known response predictors, and head-to-head comparisons of medical options for pNET patients, there is a lack of consensus regarding the best first-line therapy for pNET. According to current guidelines, chemotherapy is recommended for patients with

aggressive pNET, and the type of regimen is based on the differentiation status, which refers to both the morphology and the proliferative index. Historically, STZ-BC has been considered the standard treatment for aggressive pNET, and P-BC for the treatment of pNEC. In how far the Ki-67 proliferative index alone contributes to the antitumour impact of these regimens is open to debate [30, 36, 43–46]. Recently, the use of P-BC for aggressive NET was re-challenged, and D/T-BC was proposed as an alternative strategy to the historical STZ-BC regimen [27, 47, 48]. A few studies have specifically addressed the role of P-BC in patients classified into the newly described grade 3 NET category, which represents 31% of the population of our study. Although a lower rate of response to P-BC was found for grade 3 NET compared to NEC, some degree of tumour response was reported, ranging from 0 to 17% [29, 36, 38]. In addition, Sorbye et al. [31] reported an 11% partial response rate with P-BC in patients with NENs defined by a Ki-67 index <55%.

A median PFS of 7.2 months and an OR rate of 29% were found in our study regardless of the cytotoxic regimen used, calling for prospective studies and translational research to rationalise the best strategy for any given patient. Indeed, we were unable to demonstrate that alkylating agents (STZ-BC and D/T-BC combined) were associated with longer PFS when compared to a P-BC regimen. Meanwhile, a cytotoxic regimen with alkylating agents, since associated with better tolerance, may be favoured [49–52]. Walter et al. [51] recently confirmed that O^6-methylguanine-DNA methyltransferase status was associated with higher response rates to alkylating agent-based chemotherapy. Such a molecular marker, if prospectively confirmed, could be the first step towards a kind of individualised strategy.

Efforts were made to perform an in-depth evaluation of the heterogeneity of the population characteristics studied. Although no major differences in key prognostic parameters were observed across the 3 groups of patients, the number of metastatic surgeries as well as the length of time from diagnosis to chemotherapy initiation were found to be significantly different (i.e., less frequent and shorter) in the P-BC subgroup. In addition, a non-significant trend towards more aggressive prognostic features, such as a higher percentage of grade 3 tumours and a lower frequency of primary tumour surgery, was also observed among pNET patients who received P-BC. Overall, the selection of patients with a high Ki-67 index may have optimised the P-BC but not the STZ-BC or D/T-BC results and converged into comparable results from these different lines of chemotherapy in this patient population [46]. Indeed, both median PFS and OR rates among pNET patients who received STZ-BC or D/T-BC were found to be in the low range of results provided by previous studies [17, 27, 46, 51, 53–56]. In line with this comment is the remark that the fact that patients with grade 3 pNET experienced a shorter median PFS than those with grade 2 pNET also shows that Ki-67 alone is not a good predictor of chemotherapy.

Our results should be interpreted with caution, due to the multicentre and retrospective design of our study as well as the heterogeneity of the population and the regimen used. In addition, safety was not evaluated. However, this study is, to our knowledge, the first to attempt an analysis of the results of various first-line chemotherapy regimens in a population of intermediate or highly proliferative pNET patients with reviewed morphology for differentiation.

In conclusion, patients with intermediate or highly proliferative well-differentiated pNETs may benefit from 1 of the 3 chemotherapy regimens. Increased age and grade 3 tumours were associated with shorter median PFS. Randomised studies searching for response predictors and the best efficacy-tolerance ratio are required to personalise treatment strategies.

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Author Contributions

Conception and design: all authors; collection of data: all authors; assembly and analysis of data: G.R. and A.R.-R.; data interpretation: G.R., E.B., F.-X.C.-B., G.C., T.W., O.H., and V.R.; manuscript writing: G.R., E.B., F.-X.C.-B., G.C., T.W., O.H., C.L.-B., and A.R.-R.; final approval of the manuscript: all authors.

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