Not All Patients with a Pancreatic Neuroendocrine Tumour Will Benefit from All Approved or Recommended Therapeutic Options: A Real-Life Retrospective Study

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Key Words

Safety · Neuroendocrine tumour · Pancreatic tumour · Therapeutic lines

Abstract

Background: At least nine therapeutic options are recommended or approved for pancreatic neuroendocrine tumour (pNET). The primary endpoint of this study was to determine the number of therapeutic lines given before death. Secondary endpoints were to determine toxic events as a function of number of therapeutic lines and of time. **Methods:** Patients with pNET treated between 1998 and 2010 at our centre were characterised. All therapeutic lines were recorded as well as tumour- or toxic-related deaths. Persistent treatment-related toxicity (PTRT) was defined as: chronic kidney disease, anaemia, thrombocytopenia, neutropenia, severe liver failure, cardiac failure and recurrent sepsis, precluding at least one other therapeutic option or second cancers. **Results:** Ninety-two patients were analysed. The median follow-up was 7 years. The 1-, 2- and 5-year overall survival rates

were 90, 81 and 51%, respectively. After 3 and 5 therapeutic lines, 23 and 50% of patients had died, respectively. After 3 and 5 lines, the frequency of toxic events was 8 and 24%, respectively. Overall, 17 toxic events were observed including 6 treatment-related deaths and 11 PTRT. After 1, 2 and 5 years of treatment, the frequency of toxic events was 6, 9 and 16%, respectively. **Conclusion:** Tumour- and toxic-related deaths as well as PTRT may preclude access to all therapeutic options in patients with pNET. Optimised risk benefit sequence should be investigated.

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Introduction

Pancreatic neuroendocrine tumours (pNET) represent less than 5% of neuroendocrine tumours, and more than 50% of patients present with metastases at the time of diagnosis [1, 2].

The therapeutic management of metastatic pNET aims to control both the functioning status of the tumour and

its growth. In the absence of cure and due to the prolonged survival of subgroups of patients with metastatic pNET, striking a balance between the risks and benefits of therapy is a constant concern for physicians. The historical therapeutic management of metastatic pNET comprises the use of surgery, imaging-guided locoregional therapies, streptozotocin-based chemotherapy and interferon [3–7]. More recently, following the results of retrospective studies, the use of temozolomide- or oxaliplatin-based chemotherapies has increased the number of therapeutic options [8–10]. In addition, peptide receptor radionuclide therapy (PRRT) has emerged as an option based on phase I–II trials and compassionate studies [11, 12]. Also, three positive placebo-controlled phase III trials have recently been published in pNET patients leading to the approval of three targeted therapies: sunitinib, everolimus and lanreotide [13–15]. Finally, treatment combinations are now emerging [16]. At present, patients may benefit from a long list of available therapeutic options, at least nine for patients suffering from metastatic pNET [17], and the question of the best strategy is now open for discussion.

To achieve progress in this field, one unanswered but critical question is the number of lines that patients with pNET could be administered before tumour-related death occurs. In addition, toxicity-related deaths but also the rate of persistent treatment-related toxicity (PTRT) may also affect the feasibility of sequential therapies and should also be known as well as the parameters that affect the safety of the respective treatments. Not only prospective trials with sequential design are necessary to solve this issue but also retrospective studies which provide long-term follow-up observation throughout the therapeutic management [18].

The primary endpoint of this retrospective study was to determine the number of therapeutic lines given before tumour- or toxicity-related death in patients treated for metastatic pNET in a single centre of expertise. Secondary endpoints were to determine toxic events defined as PTRT for more than 3 months or treatment-related death as a function of number of therapeutic lines and of time. Finally, in a preliminary exploratory analysis, we looked for the relationship between baseline characteristics and the presence of toxic events at any times.

Patients and Methods

Population

This retrospective study reviewed consecutive patients with metastatic unresectable pNET followed up in our institution between May 1998 and December 2010. Inclusion criteria were:

Table 1. Patient and tumour characteristic

	Patients (n = 92)
Median age [range], years	55 [22–78]
Male/female ratio	45/47
Functional syndromes	31 (34) ^a
Genetic status	
Sporadic	88 (96)
MEN1	3 (3)
NF1	1 (1)
Chromogranin A	
Unknown	18 (20)
Normal	18 (20)
Elevated	
>1–5 UNL	25 (27)
≥5–10 UNL	12 (13)
≥10 UNL	19 (20)
ENETS grade	
Unknown	19 (21)
1	29 (32)
2	38 (41)
3	6 (6)
Ki67	
Unknown	23 (25)
≤2	32 (35)
3–20	32 (35)
>20	5 (5)
Mitoses	
Unknown	31 (34)
<2	36 (39)
2–20	24 (26)
>20	1 (1)
Median primary tumour size [range], mm	55 [18–200]
Somatostatin receptor scintigraphy	
Unknown	22 (24)
Positive	61 (66)
Negative	9 (10)
Metastatic organs [range]	1 [0–4]
ENETS staging	
Stage III	4 (4)
Stage IV	88 (96)
Liver involvement	
Uncertain	26 (28)
≤30%	35 (38)
30–70%	19 (21)
≥70%	12 (13)
Patients treated	
Before 2006	45 (49)
From 2006 onward	47 (51)

Values are presented as n (%), unless otherwise indicated. MEN1 = Multiple endocrine neoplasia type 1; NF1 = neurofibromatosis type 1; UNL = upper limit of normal. ^a 31 functioning syndromes including 4 gastrin-, 1 GHRH (growth hormone-releasing syndrome)-, 7 serotonin-, 3 somatostatin-, 2 PTHRP (parathyroid hormone-related protein)-, 6 glucagon-, 1 VIP (vasoactive intestinal peptide)-, 6 insulin- and 1 ACTH (adrenocorticotrophic hormone)-dependent.

(1) reviewed well-differentiated architecture of NET based on biopsy or surgical specimens by one single pathologist, (2) TNM stage IV or unresectable stage III disease as defined by both scintigraphic and conventional imaging, and (3) at least one therapeutic line. Exclusion criteria were: (1) the lack of follow-up and (2) poorly differentiated neuroendocrine carcinoma.

The following parameters were recorded for all patients at the time of the first therapeutic intervention: age, gender, comorbidity (tobacco use, hypertension, dyslipidaemia, diabetes mellitus, obesity), routine biological tests before treatment (glycaemia, creatinine, ASAT, ALAT, bilirubin, haemoglobin, platelet, neutrophil counts), chromogranin A levels, inherited syndromes, functioning status, liver tumour involvement, number of invaded organs based on computed tomography and/or magnetic resonance imaging, grading as defined by the 2010 WHO classification, somatostatin receptor scintigraphy status, and the type and number of therapeutic lines.

Treatment

The following systemic therapeutic options were given and were considered as one therapeutic line: somatostatin analogues (SSA), interferon, sunitinib, everolimus, PRRT, dacarbazine, streptozotocin, 5-fluorouracil (5FU) or platin-based chemotherapies [3, 4, 6–8, 12, 15, 19]. In addition, transhepatic arterial chemoembolization (TACE) was also considered as a therapeutic line. Treatments were given according to recommendations and/or the main publications in the field and discussed within the setting of a multidisciplinary meeting for more than 20 years. The main characteristics of our strategy have previously been described [4, 16, 20–22].

Safety

Safety was recorded retrospectively according to National Cancer Institute (NCI) common terminology criteria for adverse events version 4 (CTCAE v4.0) during the follow-up. Drug-related toxic events were specifically analysed and defined as a lethal toxicity (grade 5) or as persistent treatment-related (grade 2–4) toxicity lasting more than 3 months (PTRT) after the last treatment administration which precluded at least one subsequent therapeutic line. PTRT included chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m²), anaemia (haemoglobin <8 g/dl), thrombocytopenia (<100,000/mm³), neutropenia (<1,500/mm³), jaundice (bilirubinaemia >50 µM), severe liver failure (prothrombin time <50%), cardiac toxicities [left ventricular systolic dysfunction: left ventricular ejection fraction (LVEF) <50%, heart failure], recurrent sepsis and second cancer. Toxic events were classified according to the type of organ: liver, renal, cardiac, haematological and infectious toxicities. Pretreatment echocardiography was routinely performed when cardiac toxicity was expected [23].

Statistical Analysis

The primary endpoint of this retrospective study was to determine the number of therapeutic lines given before tumour- or toxicity-related death in a population with advanced pNET. The baseline time was when the first line was initiated. The number of therapeutic lines was calculated from the date of the first line to the date of first PTRT or to the date of toxic- or tumour-related death or to the last date of follow-up.

The secondary endpoints were to determine toxic events defined as PTRT or related to death after 2, 3 and 5 therapeutic lines

Table 2. Type of therapeutic lines according to the line of treatment

Therapeutic lines	First line (n = 92)	Second line (n = 87)	All lines (n = 92)
SSA	23 (25)	10 (11)	47 (51)
Interferon	1 (1)	0 (0)	1 (1)
TACE	10 (11)	15 (17)	43 (47)
Dacarbazine-based CT	0 (0)	0 (0)	18 (20)
Streptozotocin-based CT	32 (35)	33 (38) ^a	64 (70)
Platin-based CT	20 (22)	13 (15)	53 (57)
Oxaliplatin-based	6 (6)	10 (11)	36 (39)
Cisplatin or carboplatin-based	14 (15)	3 (3)	17 (18)
Fluorouracil-based CT	3 (3)	3 (3) ^b	15 (16)
PRRT	2 (2)	2 (2)	26 (28)
Sunitinib	0 (0)	3 (3)	24 (26)
Everolimus	1 (1)	8 (9)	40 (44)

Values are shown as n (%). CT = Chemotherapy. ^a Streptozotocin-based chemotherapy + bevacizumab (3 patients) ^b 5FU + external beam radiotherapy (1 patient).

or at 1, 2 and 5 years of treatment. Toxic events and overall survival (OS) were estimated using the Kaplan-Meier method considering the time following the first therapeutic line or the number of lines. Associations between baseline characterization and presence or absence of toxic events at the end of follow-up were analysed with χ^2 (with or without Yates correction) or Fisher's exact test. A p value <0.05 was considered significant.

Results

Characteristics of the Population under Study

Among 146 consecutive patients with pNET referred to our institution between May 1998 and December 2010, 55 patients were excluded due to non-pNET morphology (n = 6), a localised intra-pancreatic tumour (n = 18), follow-up outside our institution (n = 27), and no systemic treatment initiated (n = 3). Finally, a total of 92 pNET patients (45 male and 47 female, median age 55 years, range: 22–78 years) with a diagnosis of unresectable/metastatic pNET were enrolled. The main patient characteristics are described in table 1. Forty-seven out of 92 patients were treated from 2006 onward at a time when all therapeutic options became available.

Description of Therapeutic Lines

Among 92 patients, the most frequent first therapeutic line was systemic chemotherapy given in 55 (60%) patients. Twenty-three patients (25%) received SSA, and 10 (11%) patients were treated with TACE as first-line therapy (table 2).

Fig. 1. OS in 92 patients with metastatic or unresectable pNET as a function of time since the first line.

Fig. 2. Percentage of death in 92 patients with metastatic or unresectable pNET as a function of the number of therapeutic lines.

During the course of the disease, nearly half of the population received SSA (51%), TACE (47%) or everolimus (44%). A quarter of the patients received PRRT (28%) or sunitinib (26%). Streptozotocin-, platin-, dacarbazine- and/or fluorouracil-based chemotherapies were given in

Fig. 3. Frequency of toxic events as a function of the number of therapeutic lines.

Fig. 4. Frequency of toxic events as a function of time (years).

64 (70%), 53 (57%), 18 (20%) and 15 (16%) cases, respectively. Among platin-based chemotherapies, 36 (39%) and 17 (18%) patients received oxaliplatin- and cisplatin-based chemotherapy during the course of the study or, as first line, in 6 (6%) or 14 (15%) cases, respectively (table 2).

Fig. 5. Toxic events according to organ: number of patients with a toxic event as a function of the type of toxic event. In each column, the number of treatment-related deaths is indicated in dark grey and the number of treatment-related toxicity without death is indicated in light grey.

OS as a Function of the Number of Therapeutic Lines
After a median follow-up of 79 months, 52 patients had died. The median OS was 5 years. The 1-, 2- and 5-year OS rates were 90% (95% CI: 82–95), 81% (95% CI: 72–88) and 51% (95% CI: 40–61), respectively (fig. 1). Deaths were classified as tumour- or treatment-related, others and unknown in 35 (67% of dead patients), 6 (12%), 4 (8%) and 7 (13%) cases, respectively. The causes of treatment-related deaths were as follows: cardiac failure (n = 2), liver failure (n = 2), infection (n = 1) and second cancer (n = 1). After 2, 3, 4 and 5 therapeutic lines, 15, 23, 38 and 50% of patients had died (fig. 2).

Toxic Events

Toxic events were observed in 17/92 patients (18%). Among the 17 toxic events, 6 treatment-related deaths (35%) and 11 permanent toxicities (65%) occurred. After 1, 2, 3, 4 and 5 lines, the frequency of toxic events was 4, 7, 8, 19 and 24%, respectively (fig. 3). One, 2 and 5 years after the first-line treatment, the frequency of toxic events was 6, 9 and 16%, respectively (fig. 4).

The classification of toxic events by organ was as follows: nephrotoxicity (6 patients, no death), cardiac toxicity (5 patients including 2 treatment-related deaths), haematological malignancy (2 patients, no death), fatal liver failure (2 patients), fatal second cancer (1 patient) and fatal infection (1 patient) (fig. 5).

Renal and cardiac toxicities are detailed in table 3. Concerning nephrotoxicity, 5 patients experienced grade 2 (n = 4) and grade 3 (n = 1) chronic kidney disease and

1 patient experienced haemolytic uremic syndrome with renal insufficiency. None of these toxicities were lethal. Concerning cardiac toxicity, 2 patients died of cardiac toxicity including acute heart failure with QT prolongation (n = 1) and acute coronary syndrome after a 5FU infusion followed by left ventricular systolic dysfunction (n = 1). Three patients experienced grade 3 or 4 heart failure related to left ventricular systolic dysfunction. Toxic therapeutic sequences are described in table 3.

The median duration of follow-up was 83 and 69 months for patients who experienced toxic events and for those who did not, respectively; therefore, more patients treated before 2006 experienced toxic events. In a preliminary analysis, we attempted to correlate the baseline tumour and patient characteristics with the onset of toxic events. No significant relationship was found between baseline characteristics of the patients and tumours including functioning status, liver involvement or number of metastatic organs. A trend was found for more frequent toxic events in patients with Ki67 >10%: 31% of patients with toxic events. Age >55 years was significantly more frequent in patients with toxic events (table 4).

Discussion

Our study aimed to answer the following pragmatic question: how often are pNET patients able to receive all available therapeutic options? Indeed, the therapeutic landscape of advanced pNET patients has recently been

Table 3. Detailed characteristics of patients with renal and cardiac toxicities

Sex	Age, years	Comorbidities	Systemic therapeutic lines	Local therapy	Organ toxicity	Cause of toxicity-related death
F	58	Diabetes	DS, SSA, 5FUS, everolimus	Cementoplasty (bone)	Nephrotoxicity, CKD grade 2	–
M	60	Tobacco use, hypertension, diabetes, prostate carcinoma	GEMOX, CDDP, 5FU, FOLFOX, PRRT, sunitinib	Distal pancreatectomy	Nephrotoxicity, CKD grade 2	–
F	56	Hypertension, dyslipidaemia, acute coronary syndrome	CDDP, SSA	None	Nephrotoxicity, CKD grade 2	–
F	61	Hypertension	DS	None	Nephrotoxicity, CKD grade 3	–
F	66	Diabetes	DS, SSA, PRRT, everolimus, FOLFOX	None	Nephrotoxicity, CKD grade 2	–
M	55	Dyslipidaemia, tobacco use	SSA, everolimus, sunitinib	Pancreaticoduodenectomy, liver radiofrequency ablation, liver stereotactic radiation therapy	Nephrotoxicity, haemolytic and uremic syndrome, CKD	–
M	76	Tobacco use, diabetes, hypertension	SSA, DS (525 mg/m ²), 5FUD	TACE	Acute coronary syndrome	Cardiac toxicity (not detailed)
M	57	Hypertension, diabetes	SSA, DS	None	Left ventricular systolic dysfunction	–
M	57	Diabetes, dyslipidaemia, coronary artery bypass graft surgery	DS (400 mg/m ²), 5FUS, SSA, PRRT	TACE, distal pancreatectomy	Left ventricular systolic dysfunction	–
M	74	Diabetes, dyslipidaemia, hypertension, aortic valve disease	DS (550 mg/m ²)	Distal pancreatectomy	Heart failure, left ventricular systolic dysfunction, conduction disorders	–
F	50	None	DS	TACE (chromogranin A)	Heart failure, left ventricular systolic dysfunction, conduction disorders	Heart failure

Regarding treatment options given in patients experiencing toxic events, 6 patients with renal failure received various therapeutic lines including PRRT, streptozotocin- or platin-based chemotherapy, TACE, sunitinib, or everolimus. Otherwise, all the patients with cardiac failure had received doxorubicin-based chemotherapy and TACE. The cumulative dose of doxorubicin-based chemotherapy (systemic and TACE) was below the recommended cumulative dose of 550 mg/m².

DS = Doxorubicin-streptozotocin; D = Dacarbazine; 5FUS = 5 fluorouracil-streptozotocin; GEMOX = oxaliplatin-gemcitabine; FOLFOX = 5 fluorouracil-oxaliplatin; CDDP = cisplatin-etoposide; CKD = chronic kidney disease.

diversified [17, 24]. To the best of our knowledge, this is the first study to describe the history of therapeutic interventions in pNETs in the real-life setting.

Baseline characteristics of the population under study can be considered as representative of an advanced pNET population. Even if the vast majority of the systemic options used in this population are approved or recommended options in 2016, this was not true for 18% of patients who received cisplatin-based chemotherapy [25]. This rate of prescription may be explained by the retrospective nature of our study, the evolution of WHO classification including the recent recognition of NET G3 subgroups and the still debated role of cisplatin-based chemotherapy in aggressive NET.

In our population of patients with advanced pNET at diagnosis and with a 5-year survival rate of 51%, in accordance with previous studies [21], we found that when 5 therapeutic lines had been administered, 50% of patients had died. In addition, after 3 lines of therapy, 23% of patients had died and toxic events had already occurred in 8% of patients. Tumour- or toxicity-related death was the main cause of discontinuation of therapy. The basic conclusion of this result is that not all pNET patients will benefit from all approved or recommended therapeutic options and therefore the ranking of drug administration matters.

During the course of therapeutic interventions, treatment-related deaths and PTRT occurred in 6 and 12% of

Table 4. Baseline tumour and patient characteristics in the groups of patients with and without toxic events

	Toxic event (n = 17)		No toxic event (n = 75)		p
	evaluable patients, n	results, n (%)	evaluable patients, n	results, n (%)	
Functioning syndrome	17	4 (24)	75	27 (36)	0.32*
Ki67 >10%	13	4 (31)	56	9 (16)	0.2**
Liver involvement >70%	17	2 (12)	74	8 (11)	0.59**
Metastatic organs >1	17	2 (12)	75	12 (16)	0.49**
Age >55 years	17	14 (82)	75	56 (75)	0.03*
CKD >1.5 ULN	16	1 (6)	67	0 (0)	0.19**
Bilirubin >1.5 ULN	14	1 (7)	61	2 (3)	0.46**
Transaminases >3 ULN	14	2 (14)	64	1 (2)	0.08**
Haemoglobin <10 g/dl	16	2 (12)	63	5 (8)	0.43**
Comorbidities ^a	17	12 (70)	75	45 (60)	0.41*
First therapeutic line initiated before 2006	17	14 (82)	75	31 (41)	0.005*

CKD = Chronic kidney disease; ULN = upper limit of normal. ^a Comorbidities: tobacco use, hypertension, dyslipidaemia, diabetes mellitus, obesity. Grade is provided according to * χ^2 test; ** Fisher's exact test.

cases, respectively. The frequency of toxic events was 8, 19 and 24% after 3, 4 and 5 lines, respectively, suggesting cumulative toxicity. Even though these rates are pretty low, efforts should be expended to make this number close to zero. Sparing critical organs from becoming toxicity targets of several lines of treatment is becoming a key objective in patients with advanced pNET due to the increasing number of options available. Renal and cardiac dysfunctions were the most frequent in terms of toxicity. Preliminary recommendations can be derived from our study to decrease the risk of toxic events. Cisplatin-based chemotherapy, a well-known nephrotoxic drug, should be omitted in pNET patients in the absence of protocols as recently evaluated. Indeed, the best level of evidence available suggests no added value of cisplatin-based chemotherapy in NET patients [22, 25, 26]. Of note, several other medical options used in pNET patients have been reported to alter renal function, and their interaction should be closely monitored in the near future. Streptozotocin-based chemotherapy led to renal failure in less than 10% of patients [4, 7, 27]. Although renal failure is uncommonly described, increased serum creatinine has been reported with sunitinib in 18% of patients [14, 28, 29] as well as with everolimus in 46% of cases [30]. Among patients receiving sunitinib in other malignancies, the incidence of creatinine elevation, whatever the grade, ranges from 12.4 to 65.6% [28, 31, 32]. However, renal function was deteriorated in 57% of patients with pre-existing renal impairment at the start of therapy with tyrosine ki-

nase inhibitors [33]. Laboratory abnormalities including elevated serum creatinine levels, whatever the grade, during everolimus treatment have been reported in 50–77% of patients in some series [34, 35], while grade 3/4 occurred in less than 1%.

In addition, the heart was the second most frequently affected organ. In our study, follow-up was performed in accordance with French recommendations when available [23]. Doxorubicin and 5FU are well-known causes of cardiac toxicity. Although the cumulative dose of 550 mg/m² of doxorubicin was not exceeded in these patients, intra-patient variability may affect its tolerance as well as when it is given simultaneously with TACE which remains an unstandardised procedure. Several medical options used in pNET patients have been reported to also alter cardiac function, and their interaction should be closely monitored in the near future. Cardiac toxicities may have been underestimated in previous trials since follow-up did not include routine baseline/follow-up electrocardiography and/or echocardiography. In 2 phase III studies with sunitinib in gastrointestinal stromal tumours and metastatic renal cell carcinoma, the frequency of cardiac-related adverse events was reported in 11–13% of cases including 3% of grade 3 toxicity [28, 29]. No change in the LVEF was reported with sunitinib in a trial with patients with gastrointestinal stromal tumour, but 10% of patients with metastatic renal cell carcinoma experienced a change in LVEF [31, 36]. No cardiac disorder has been reported in phase III trials with sunitinib or

everolimus in neuroendocrine tumours [14, 15], but case reports on cardiac failure have been published [37]. In addition, treatments at risk of cumulative toxicity should be identified and their use rationalised. Toxic events were found to be cumulative and time related. Only future prospective studies analysing the evolution of patient and tumour characteristics but also treatment sequences in a time-dependent manner will properly answer the key question of the mechanism of the onset of toxic events. Our preliminary analysis suggests that the use of a more aggressive sequence of therapy in pNET patients, with high Ki67 and control of comorbidity, especially in older patients, should be cautiously evaluated.

The limitations of this study include its retrospective design and the period-dependent availability as well as the modality of treatment prescriptions since the start of the study. In line with that comment, our population received mainly systemic chemotherapy or SSA as first-line treatment, a picture that may change in the near future. The frequency of toxicities is underestimated because we only described toxicities which contraindicate other ther-

apeutic lines. In addition, only the first residual toxicities were taken into account. Finally, the prescription of cisplatin-based chemotherapy even if reflecting the real-life setting cannot be considered as recommended. The strengths of the study are the multidisciplinary team management with the same senior team from the outset, the use of all available options since 2005 and the low rate of loss to follow-up.

In conclusion, after 3 and 5 therapeutic lines, 23 and 50% of patients had died and the frequency of toxic events was 8 and 24%, respectively. Not all patients with pNET will benefit from all approved or recommended therapeutic options. The best treatment sequence should be investigated.

Disclosure Statement

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