Sunitinib in patients with pre-treated pancreatic neuroendocrine tumors: A real-world study

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ARTICLE INFO

ABSTRACT

Introduction: Besides data reported in a Phase-III trial, data on sunitinib in pancreatic Neuroendocrine Tumors (panNETs) are scanty.
Aim: To evaluate sunitinib efficacy and tolerability in panNETs patients treated in a real-world setting.
Patients and methods: Retrospective analysis of progressive panNETs treated with sunitinib. Efficacy was assessed by evaluating progression-free survival, overall survival, and disease control (DC) rate (stable disease (SD) + partial response + complete response). Data are reported as median (25th—75th IQR).
Results: Eighty patients were included. Overall, 71.1% had NET G2, 26.3% had NET G1, and 2.6% had NET G3 neoplasms. A total of 53 patients (66.3%) had received three or more therapeutic regimens before sunitinib, with 24 patients (30%) having been treated with four previous treatments. Median PFS was 10 months. Similar risk of progression was observed between NET G1 and NET G2 tumors (median PFS 11 months and 8 months, respectively), and between patients who had received ≥ 3 vs ≤ 2 therapeutic approaches before sunitinib (median PFS 9 months and 10 months, respectively). DC rate was 71.3% and SD was the most frequent observed response, occurring in 43 pts (53.8%). Overall, 59 pts (73.8%) experienced AEs, which were grade 1—2 in 43 of them (72.9%), grade 3 in 15 pts (25.4%), and grade 4 in one patient (1.7%). Six pts (7.5%) stopped treatment due to toxicity.

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Conclusions: The present real-world experience shows that sunitinib is a safe and effective treatment for panNETs, even in the clinical setting of heavily pre-treated, progressive diseases.

Introduction

Pancreatic Neuroendocrine Neoplasms (panNENs), although considered rare diseases, have been increasing in incidence and prevalence over the last few decades in both US and European countries [1,2]. According to the updated World Health Organization (WHO) classification [3], they are classified into four different categories (well differentiated pancreatic neuroendocrine tumors (panNETs) G1, G2, G3, and poorly differentiated pancreatic neuroendocrine carcinoma NEC G3), based on the proliferative index Ki67 and tumor morphology which, together with tumor burden, are considered the strongest prognostic factors affecting patients' clinical outcome [4–7].

The therapeutic scenario of panNETs has dramatically changed during the last few years, after the introduction of targeted agents everolimus and sunitinib which are effective in patients with advanced, well-differentiated progressive tumors [8,9].

Sunitinib is a multi-target agent which effectively inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and KIT. Its activity in panNETs was initially observed in a Phase 2 trial which reported an objective response rate of 16.7% [10]. Sunitinib activity in panNETs has been definitively confirmed in a multicenter Phase III trial in 2011 [9] which showed, without significantly affecting patients' quality of life [11], a doubling in median progression-free survival (PFS) of 11.4 months in patients receiving sunitinib compared to those treated with placebo, a figure that has recently been confirmed by the updated data analysis [12].

However, beyond the above-mentioned studies, very scarce data on panNET patients treated with sunitinib outside the regulatory trial setting have been published so far.

Thus, this study aimed at analyzing the efficacy and tolerability of sunitinib in patients with panNETs in a real-world clinical setting.

Patients and methods

This is an Italian nationwide retrospective analysis of patients with sporadic panNETs who received sunitinib based on compassionate use or local regulatory authority approval, with the following inclusion criteria: age >18 years, histologically proven diagnosis of panNET with well-differentiated morphology, locally advanced unresectable or metastatic disease, progressive disease (PD) documented by radiological examinations, ECOG performance status ≤2, availability of follow-up data collected according to the European Neuroendocrine Tumors Society (ENETS) guidelines [13]. Patients with familiar syndromes (i.e. Multiple Endocrine Neoplasia syndromes, Von Hippen Lindau syndrome) and patients with tumors with poorly differentiated morphology (panNECs) were excluded from this study.

All patients provided full informed consent before starting sunitinib treatment. This study was approved by the local ethics committee of the Rome ENETS Center of Excellence — Sant'Andrea Hospital.

Methods

Based on the drug dosing schedule [14], sunitinib was given at the standard dose of 37.5 mg daily until PD or intolerable toxicity occurred, or if informed consent was withdrawn by the patient.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events v. 3.0 [15], and were prospectively collected together with demographic, pathological, radiological and clinical data at each participating center. A unique computerized datasheet was subsequently created, and data was analyzed retrospectively.

At the time of data analysis, tumors were retrospectively divided according to the WHO 2017 classification [3] based on the histological data obtained from the pathological charts collected at each participating center, where the initial diagnosis was done. The tumor degree of differentiation was reported in all the pathological reports.

Sunitinib efficacy was assessed by evaluating PFS, OS, and disease control (DC) rate, which was estimated by the best overall response (defined as the best radiological tumor response achieved during treatment according to RECIST 1.0 criteria [16]). Patients were considered "responders" when DC (in terms of stable disease (SD), partial response (PR), or complete response (CR)) was achieved as best overall response, otherwise they were considered "non-responders".

Data is expressed as median and 25th–75th interquartile ranges (IQR). Progression-free survival was defined as the interval between sunitinib therapy initiation and treatment discontinuation due to PD or patient death from any cause, whichever occurred first. Overall survival was defined as the interval between sunitinib therapy initiation and death from any cause. Both PFS and OS were assessed using the Kaplan-Meier method, and the results were compared by log-rank test. Risk factor analysis to identify variables associated with increased risk of progression was performed by Cox proportional-hazard regression analysis. Statistical analysis was performed by Medcalc® v.17 software (MedCalc Software (www.medcalc.org)).

Results

A total of 80 patients, median age 59 years (IQR 28–67), were included in the present study. Patients' general features are

Table 1
Patients' general features.

Feature	N	%
Male gender	45	56.2
Non-functioning tumors	70	87.5
ECOG performance status		
0	58	72.5
1	19	23.8
2	3	3.7
WHO 2017[a] [3]		
NET G1	20	26.3
NET G2	54	71.1
NET G3	2	2.6
ENETS staging		
Stage II	1	1.3
Stage III	7	8.7
Stage IV	72	90

ENETS: European Neuroendocrine Tumor Society.
[a] Data available in 76 patients.

summarized in Table 1. Tumor grading was available in 76 patients (95%), and was assessed in all but one of them by Ki67 immuno-histochemical analysis (in the remaining patient, grading was assessed by mitotic count). Overall, median Ki67 was 5% (IQR 3%–10%), and most patients (71.1%) had NET G2 neoplasm.

A total of 43 patients (53.8%) had undergone surgery before sunitinib treatment. Although surgery had been considered radical in 15 of them (18.8%), all underwent disease recurrence during subsequent follow-up.

All but one patient (98.8%) had received previous medical anti-tumor treatments before sunitinib initiation. The most frequent treatments received were somatostatin analogs (76 patients, 95%), everolimus (64 patients, 80%), systemic chemotherapy (46 patients, 57.5%), and peptide receptor radionuclide therapy (PRRT) (45 patients, 56.3%). Overall, 53 patients (66.3%) had received three or more therapeutic regimens before sunitinib initiation, with 24 patients (30%) having been treated with four previous systemic treatments.

Median interval between initial panNET diagnosis and sunitinib initiation was 66 months (IQR 39.5–98 months). Median duration of treatment was 7 months (IQR 5–12 months). Somatostatin analogs therapy was associated with sunitinib in 47 patients (58.7%).

Efficacy

Overall, median PFS was 10 months (95% CI 7–12 months) (Fig. 1). A total of 53 patients (66.2%) experienced PD during sunitinib treatment. Similar risk of PD was observed between NET G1 and NET G2 tumors, median PFS being 11 months and 8 months, respectively (p = .522). No difference was observed in terms of risk of PD in patients who had received three or more therapeutic approaches before sunitinib initiation compared to those who had received two or less previous systemic treatments, median PFS being 9 months and 10 months, respectively (p = .632). Similar median PFS was observed in patients who had been pre-treated with everolimus compared to those who had not received it, median PFS being 10 months and 7 months, respectively (p = .802). Although not statistically significant, a double median PFS was observed in patients who received somatostatin analogs in combination with sunitinib compared to patients who were treated with sunitinib alone (12 months and 6 months, respectively; p = .152).

When risk factor analysis was performed, no variable was significantly associated with increased risk of progression (Table 2).

Median overall survival from sunitinib initiation was 40 months (95%CI 21–47 months) (Fig. 2). A total of 28 patients (35%) died during sunitinib treatment.

Overall, DC rate was 71.3% and SD was the most frequent observed response, being reported in 43 patients (53.8%). Furthermore, 14 responders (17.5%) achieved PR during treatment, whereas the remaining 23 patients (28.7%) were non-responders to sunitinib, since they underwent PD as best overall response.

Tolerability

Overall, 59 patients (73.8%) experienced AEs during sunitinib treatment, which were mild (grade 1–2) in most cases (n = 43, 72.9%). Grade 4 toxicity was reported in one single patient (1.7%) as
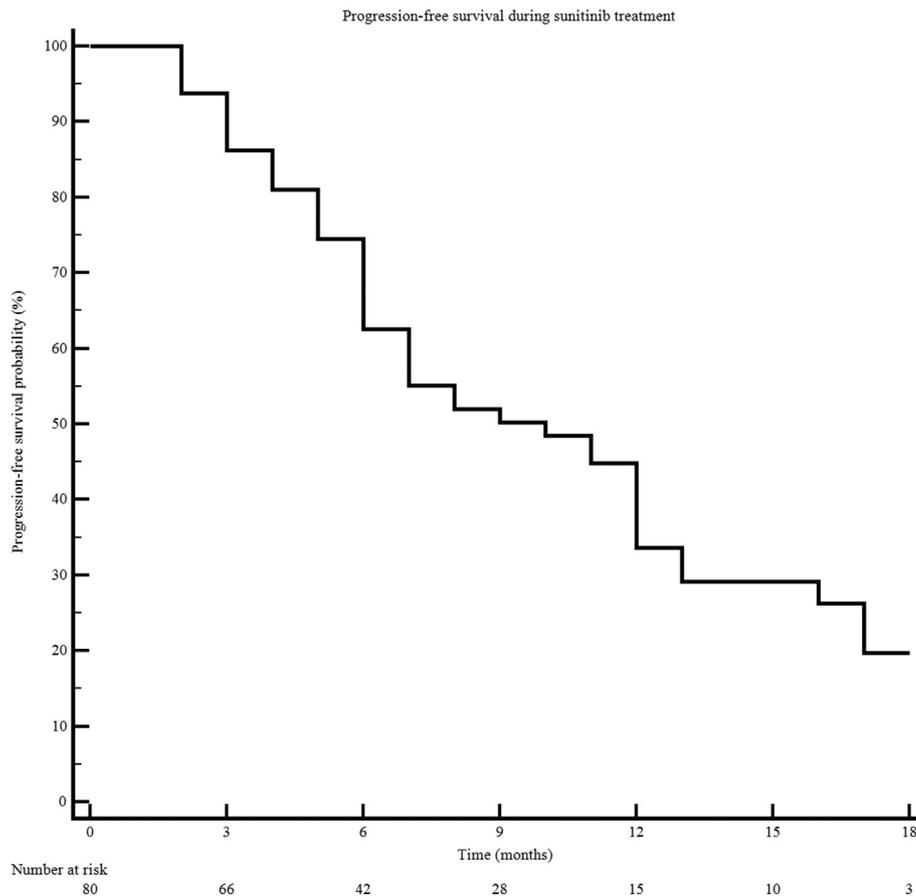

Fig. 1. Progression-free survival in 80 panNET patients during sunitinib treatment.

Table 2
Predictors for PD during sunitinib treatment.

Univariate analysis			
Variable	HR	95%CI	p
Performance status ECOG 1–2 vs 0	1.64	0.92–2.91	.089
NET G2 vs NET G1[a]	1.28	0.65–2.52	.459
Ki67[b]	1.01	0.96–1.07	.461
Concomitant somatostatin analog	0.68	0.38–1.21	.195
≥3 previous therapeutic lines (vs ≤ 2)	1.12	0.60–2.09	.709
Interval between NEN diagnosis and sunitinib beginning[c]	0.99	0.98–1.00	.292

[a] According with WHO 2017 classification [3].
[b] For each increasing Ki67% unit.
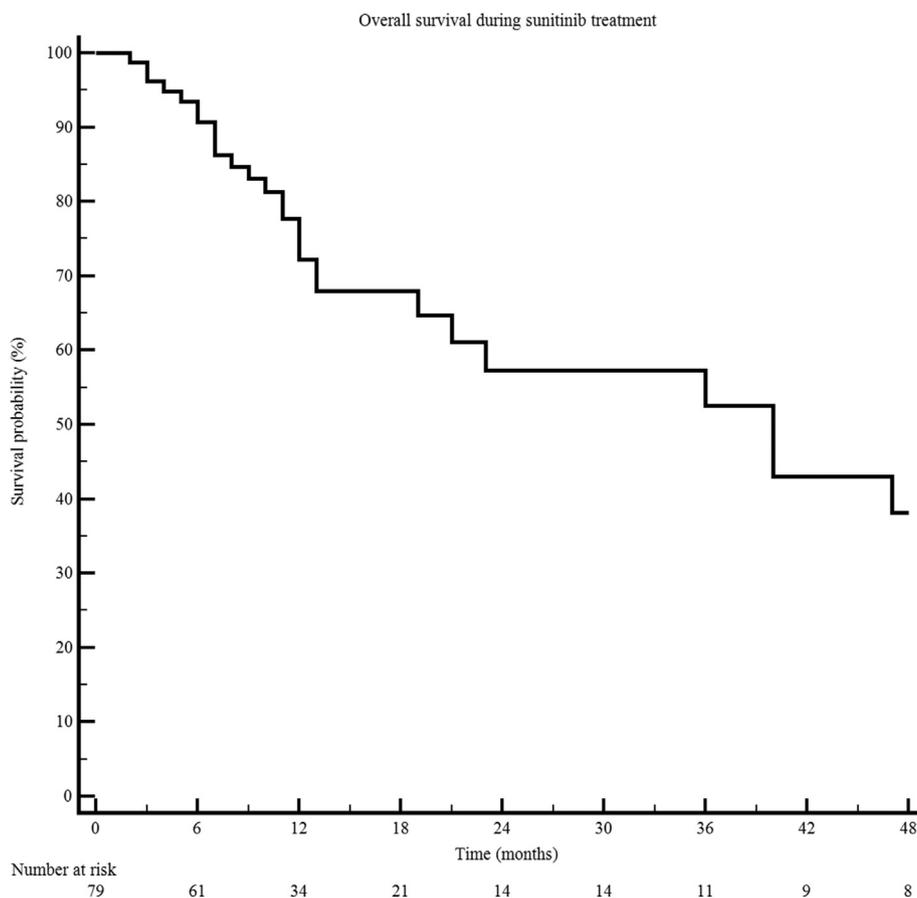[c] For each increasing month.

Fig. 2. Overall survival in 80 panNET patients during sunitinib treatment.

severe neutropenia, whereas grade 3 AEs occurred in 15 patients (25.4%). Most frequent AEs, occurring in >5% of patients, are detailed in Table 3. Due to toxicity, 32 patients (40%) required temporary sunitinib discontinuation, whereas a daily dose reduction was required in 24 patients (30%). A total of 6 patients (7.5%) definitively stopped treatment due to toxicity.

A similar safety profile was observed irrespective of the kind of previous treatments. In fact, of patients (n = 16) who experienced grade 3–4 AEs, 13 pts (81.2%) had received everolimus, 12 pts (75%) systemic chemotherapy, whereas 11 pts (68.7%) had been treated with PRRT.

Discussion

This study confirms activity and tolerability of sunitinib in patients with advanced, progressive panNETs even when heavily pre-treated.

Table 3
Most frequent adverse events during sunitinib treatment.

Adverse event	Overall	Grade 1-2	Grade 3-4
Hypertension	18 (22.5%)	15 (18.8%)	3 (3.8%)
Asthenia	18 (22.5%)	12 (15%)	6 (7.5%)
Diarrhea	16 (20%)	16 (20%)	–
Neutropenia	15 (18.8%)	8 (10%)	7 (8.8%)
Mucositis	14 (17.5%)	12 (15%)	2 (2.5%)
Palmar-plantar erythrodysesthesia	8 (10%)	7 (8.8%)	1 (1.3%)
Thrombocytopenia	7 (8.8%)	6 (7.5%)	1 (1.3%)
Stomatitis	5 (6.3%)	5 (6.3%)	–
Fever	5 (6.3%)	4 (5%)	1 (1.3%)

Table 4
Sunitinib in pancreatic neuroendocrine neoplasms.

	Median PFS	Median OS	DC rate
Phase III trial [9]	11.4 months	38.6 months	72%
Phase IV study, preliminary data [21]	11.1 months	37.8 months	NA[b]
Other studies (9[a], 20, 21, 22[a])	7.7—15.3 months	22.5 months − not reached	75%—86.7%
Present study	10 months	40 months	71.3%

DC = disease control (stable disease + partial response + complete response).
[a] This study reported 24.5% objective response rate (CR + PR).
[b] Main endpoint was time to progression.

Although approved by FDA and EMA in 2011 [14,17—19], data available on sunitinib in panNETs outside the multicenter Phase III trial [9] is scarce. Indeed, data from real-world studies may help physicians to fill the gap between the rigorous experimental design of regulatory trials and real clinical practice.

The study by Ito et al. [20] included only twelve patients with panNETs, confirming overall the major findings previously reported in the Phase III trial. A mixed population including 44 patients with pancreatic and gastrointestinal NETs was included in the paper by Yoo et al. [21], who observed a lower sunitinib activity in NETs other than pancreatic, as previously reported [10]. An additional retrospective analysis was published by Wang et al. [22] on 60 panNETs, mostly without previous systemic medical treatment (n = 53, 88.3%), again confirming sunitinib overall efficacy and safety. Furthermore, preliminary data from a completed Phase IV study has recently reported the treatment activity and safety also in naïve patients who received sunitinib as first-line therapy [23].

The present study reports the clinical experience on a relatively large set of heavily pre-treated panNET patients who received sunitinib in a real-world setting, with efficacy and tolerability data similar to that observed in the Phase III trial [9]. However, several differences in terms of patients' features and study design (prospective vs retrospective) need to be taken into account when comparing the present study with that trial. In fact, this study includes a significantly higher proportion of non-functioning tumor (87.5% vs 49%), with higher Ki67 (49.3% of patients with Ki67 > 5% vs 36%), longer interval between initial panNET diagnosis and sunitinib initiation (5.5 yr vs 2.4 yr), and a lower proportion of patients who had received surgery before sunitinib initiation (53.8% vs 88%). Although the number of previous therapeutic regimens was not specified in the Phase III trial, it is reasonable that the population evaluated in the present study includes more heavily pre-treated patients. In fact, almost all patients had received somatostatin analogs (95% vs 35% in the Phase 3 trial), and a significant proportion had also been pre-treated with everolimus or PRRT (80% and 56.3%, respectively, vs none in the Phase III trial). Conversely, a similar proportion of patients had been pre-treated with systemic chemotherapy (67.5% vs 66% in the Phase III trial). Based on these considerations, we can assume that a different population with more aggressive, heavily pre-treated patients and longer disease clinical history was included in the present study. This figure might be related to different reasons, including the late reimbursement approval for sunitinib in panNETs which, in Italy, occurred in 2015.

Nevertheless, the treatment efficacy was consistent with data reported by other studies performed in different clinical settings, in terms of median PFS, median OS, and DC rate (Table 4).

As far as the concomitant use of somatostatin analogs is concerned, a relatively high proportion of patients received the combined therapy (somatostatin analogs plus sunitinib) in the present study (58.7%), although most patients (87.5%) had non-functioning tumors. Although partly unexpected, this figure confirms the common clinical practice of maintaining somatostatin analogs when beginning targeted therapies irrespective of the tumor functional status, as reported by other studies [24—26]. The longer median PFS observed in patients who received the combined therapy in comparison with those who were treated with sunitinib alone might suggest a possible synergic activity between somatostatin analogs and targeted therapies. However, due to the relatively low number of patients and the retrospective study design, this hypothesis cannot be confirmed by significant solid data. Understanding the real impact of the association of somatostatin analogs to targeted agents on treatment efficacy still remains a challenge, given the conflicting results that have been reported on this topic so far [25,27—29].

Neither the comparison between NET G2 tumors vs NET G1 tumors nor the number of previous antitumor therapeutic lines were predictors for different response to sunitinib in terms of increased risk of PD (Table 2) (a comparison with NET G3 was not feasible due to the low number of patients included in this subgroup, n = 2). This figure seems to disagree with data from the Phase III trial (which reported a lower capability of sunitinib to reduce the risk of PD in patients with tumor with Ki67 > 5%, and with ≥2 previous therapeutic lines [9]), a difference which may be again related to the different patients' features. Interestingly, sunitinib efficacy was maintained in the subgroup of patients who had been pre-treated with everolimus.

As far as tolerability is concerned, neutropenia was confirmed as the most frequent grade 3—4 AE, with a proportion of study patients similar to that of the Phase III trial [9] (8.8% vs 12%, respectively). Conversely, several AEs (i.e. diarrhea, nausea, vomiting, fatigue, hair-color changes) were more rarely observed in this study, although their frequencies were similar to those reported by other studies investigating sunitinib in panNETs [21,22]. As previously reported [24], these differences may be due to the higher awareness of physicians who participated in the Phase III trial compared to the real-world clinical setting and, again, to the retrospective design of this study.

Conclusions

Despite inherent limitations mainly due to the retrospective study design, which is a common feature of the studies investigating NENs due to their rarity, the present real-world experience shows that sunitinib is a safe and effective treatment for panNETs, even in the clinical setting of heavily pre-treated, progressive diseases.

Acknowledgments

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