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ORIGINAL ARTICLE

Efficacy and safety of everolimus and sunitinib in patients with gastroenteropancreatic neuroendocrine tumor

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Abstract
Purpose Efficacy of targeted agents, such as everolimus and sunitinib, has been demonstrated in prospective trials on patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Considering the heterogeneous clinicopathological characteristics of neuroendocrine tumors (NETs), evaluation of treatment outcomes in a real-world setting is necessary.
Methods Clinical records of 44 patients with GEP-NET who were treated with everolimus or sunitinib between March 2007 and October 2014 were retrospectively reviewed. Considering the distinct characteristics of pancreatic NETs (pNETs) and non-pancreatic gastrointestinal NETs (GI-NETs), efficacy analysis was performed separately.
Results Pancreas was the most common primary site ($n = 28$, 64%), followed by rectum ($n = 10$, 23%) and stomach ($n = 3$, 7%). Sunitinib and everolimus were administered in 27 (61%) and 17 (39%) patients, respectively. In patients with pNET, median progression-free survival (PFS) with everolimus and sunitinib was 16.6 months (95% CI 8.0–25.1) and 8.0 months (95% CI 0.0–17.4), respectively ($p = 0.51$). Among non-pancreatic GI-NET patients, median PFS with everolimus and sunitinib was 14.7 months (95% CI 2.4–27.0) and 1.7 months (95% CI 0.5–3.0), respectively ($p = 0.001$). Compared to patients treated with everolimus, tumor grade 3 (30 vs. 0%) and history of prior cytotoxic chemotherapy (70 vs. 50%) were more common in patients treated with sunitinib.
Conclusions Both everolimus and sunitinib were effective in GEP-NET patients. Outcomes of everolimus therapy in GEP-NETs were consistent with those reported elsewhere. Poor efficacy of sunitinib in non-pancreatic GI-NETs may be attributable to the baseline characteristics associated with poor clinical outcomes.

Keywords Neuroendocrine tumor · Gastroenteropancreatic · Everolimus · Sunitinib

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies that originate from neuroendocrine cells in various organs. NET can occur in different organs of the body, with gastrointestinal tract and pancreas being the most common primary sites [1]. Its prognosis depends on several clinicopathological factors such as the primary tumor site, tumor burden, stage at diagnosis, metastasis, and tumor grade according to the WHO 2010 classification. Thus, all of these factors should be considered in the management of patients with NET. The mainstay of treatment for resectable disease is surgery with curative intent. However, unresectable and metastatic tumors are incurable in most cases.

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With recent serial successes in large randomized phase 3 trials, more therapeutic options are now available for unresectable or metastatic gastroenteropancreatic NETs (GEP-NETs). These include somatostatin analogues [2], targeted agents [3–5], cytotoxic chemotherapy [6], and peptide receptor radionuclide therapy (PRRT) [7]. Everolimus and sunitinib are approved targeted agents for management of advanced GEP-NETs: everolimus for both gastrointestinal and pancreatic primary, and sunitinib for pancreatic primary tumors [3, 4]. Treatment with everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), was shown to improve progression-free survival (PFS) of patients with low- to intermediate-grade GEP-NETs, as compared to placebo, in the pivotal phase 3 RADIANT-3 [1] and RADIANT-4 trials [3]. Sunitinib is a multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI), which was shown to improve PFS of patients with well-differentiated pancreatic NETs (pNETs), as compared to placebo in a pivotal phase 3 trial [4].

Although the role of everolimus and sunitinib in patients with GEP-NETs is well established, it is still unclear where these agents should be positioned among the many available therapeutic options [8, 9]. Because baseline characteristics of study population for trials of each agent somewhat differed from each other in terms of tumor grades, functionality, primary tumor site and/or tumor burden, direct comparisons of the therapeutic options are not possible. Moreover, considering the very heterogeneous features of GEP-NETs, study populations in the prospective clinical trials do not entirely reflect the patients in daily clinical practice. Therefore, assessment of outcomes in real-world settings will help characterize the strengths and weaknesses of various treatment options and establish an appropriate continuum of care for GEP-NET patients.

The aim of this study was to evaluate the efficacy and safety of everolimus and sunitinib in clinical practice. Moreover, we sought to identify association of clinicopathological characteristics with treatment outcomes.

Materials and methods

In this study, clinical data pertaining to a total of 44 GEP-NET patients who were initiated on everolimus or sunitinib therapy at the Asan Medical Center, Seoul, Korea, between March 2007 and October 2014 were retrospectively analyzed. The study protocol was approved by the Institutional Review Board at the Asan Medical Center. All histological data were reviewed by two academic pathologists (MJS and SMH); tumors were graded according to the WHO 2010 classification system [10]. All patients were naive to both everolimus and sunitinib treatment.

The primary end point of this study was PFS, which was defined as the duration from the start of everolimus or sunitinib treatment to disease progression or death from any cause. Tumor response was assessed every 2–3 months and graded according to the Response Evaluation Criteria in Solid Tumors (RECIST, ver. 1.1) using the same imaging modalities as at baseline. Survival probabilities were estimated using the Kaplan–Meier method and compared using the log-rank test. The Chi-square test or Fisher exact test was used to assess categorical variables. A two-sided p value of <0.05 was considered statistically significant. SPSS version 21.0 (IBM, Chicago, IL, USA) was used for statistical analyses.

Considering the distinct differences in the clinicopathological characteristics of pNETs and non-pancreatic gastrointestinal NETs (GI-NETs), efficacy analysis was performed separately, while safety analysis included all patients. Efficacy outcomes, including response rate, PFS, and overall survival (OS), were evaluated in all patients who received at least one dose of everolimus or sunitinib. The safety analysis included all patients who visited the clinic at least once after initiation of treatment. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.03. Multivariate analyses were performed using Cox proportional hazards model to evaluate the influence of baseline clinicopathological characteristics on treatment outcomes.

Results

Patient characteristics

The pancreas was the most common primary site ($n = 28$, 64%) followed by the rectum ($n = 10$, 23%), stomach ($n = 3$, 7%), gallbladder ($n = 2$, 5%), and colon ($n = 1$, 2%). Sunitinib and everolimus were administered in 27 (61%) and 17 (39%) patients, respectively. Median age was 53 years (range, 29–81), and 27 patients (61%) were men. Eastern Cooperative Oncology Group (ECOG) performance status was 2 in four patients (9%) at the time of initiation of the treatment. All patients received everolimus or sunitinib for treatment of recurrent or metastatic disease. The liver was the most frequent metastatic site ($n = 40$, 91%), followed by the lymph nodes ($n = 15$, 34%), bone ($n = 6$, 14%), and peritoneum ($n = 3$, 7%). Among the 42 patients for whom histological review was available, most patients ($n = 36$, 86%) had well-differentiated tumor, while six patients (14%) had poorly differentiated tumor. Tumor grading according to the 2010 WHO classification was available in 41 patients, and four (10%), 32 (78%), and five (12%) patients had grade 1, 2, and 3

Table 1 Baseline characteristics

Characteristics	Pancreatic NET ($n = 28$)			Non-pancreatic GI-NET ($n = 16$)		
	Sunitinib ($n = 17$)	Everolimus ($n = 11$)	p value	Sunitinib ($n = 10$)	Everolimus ($n = 6$)	p value
Age, median (range), years	50 (29–81)	52 (33–77)	0.96	57 (35–67)	51 (42–70)	0.31
Gender						
Male	10 (59%)	8 (73%)	0.69	7 (70%)	2 (33%)	0.30
Female	7 (41%)	3 (27%)		3 (30%)	4 (67%)	
ECOG PS			0.69			0.50
0–1	16 (94%)	11 (100%)		8 (80%)	6 (100%)	
2	2 (6%)	0		2 (20%)	0	
Primary site			1.00			0.15
Pancreas	17 (100%)	11 (100%)				
Rectum				5 (50%)	5 (83%)	
Colon				0	1 (17%)	
Stomach				3 (30%)	0	
Gall bladder				2 (20%)	0	
Differentiation	$n = 16$	$n = 11$	0.62	$n = 10$	$n = 5$	0.52
Well differentiated	13 (81%)	10 (91%)		8 (80%)	5 (100%)	
Poorly differentiated	3 (19%)	1 (9%)		2 (20%)	0	
Tumor grade	$n = 15$	$n = 11$	0.32	$n = 10$	$n = 5$	0.55
1	0	2 (18%)		1 (10%)	1 (20%)	
2	14 (93%)	8 (73%)		6 (60%)	4 (80%)	
3	1 (7%)	1 (9%)		3 (30%)	0	
Carcinoid symptoms	2 (12%)	3 (27%)	0.35	0	0	1.00
Prior surgery	7 (41%)	5 (46%)	1.00	6 (60%)	3 (50%	1.00
Prior SSA	8 (47%)	6 (55%)	1.00	2 (20%)	2 (33%)	0.60
Concurrent SSA	2 (12%)	2 (18%)	1.00	0	0	1.00
Previous cytotoxic chemotherapy	5 (29%)	1 (9%)	0.35	7 (70%)	3 (50%)	0.61
1 line	4 (24%)	1 (9%)	1.00	5 (50%)	0	0.17
2–3 lines	1 (6%)	0		2 (20%)	3 (50%)	

NET neuroendocrine tumors, *GI* gastrointestinal, *ECOG PS* Eastern Cooperative Oncology Group performance status, *SSA* somatostatin analogues

tumors, respectively. Somatostatin analogs were previously administered in 18 patients (41%) and concurrently used with everolimus or sunitinib in four patients (9%). Cytotoxic chemotherapy was previously administered in 16 patients (36%); six patients (14%) received two or more lines of chemotherapy.

Baseline patient characteristics are summarized according to the primary tumor site and treatment in Table 1. In both pNET and non-pancreatic GI-NET groups, there was no significant difference with respect to baseline clinicopathological characteristics according to treatment administered. However, patients treated with sunitinib in the non-pancreatic GI-NET group tended to have poorer performance status (20 vs. 0%), grade 3 tumor (30 vs. 0%), and history of more frequent previous cytotoxic chemotherapy (70 vs. 50%) as compared to patients treated with everolimus.

Efficacy in pNET

In patients with pNET ($n = 28$), median PFS with either everolimus or sunitinib was 13.8 months [95% confidence interval (CI) 2.6–25.0 months] over a median follow-up duration of 18.5 months (range 3.3–96.7 months; Fig. 1a). There was no significant difference in PFS between everolimus and sunitinib ($p = 0.51$), as median PFS with everolimus ($n = 11$) and sunitinib ($n = 17$) was 16.6 months (95% CI 8.0–25.1 months) and 8.0 months (95% CI 0.0–17.4 months), respectively (Fig. 1b). Median OS with either everolimus or sunitinib was not reached at the time of analysis; 3-year OS rate was 53.1% (Fig. 1c). OS did not differ according to the treating agents ($p = 0.24$), as median OS with everolimus and sunitinib was not reached and 22.5 months (95% CI not available), respectively (Fig. 1d). Objective response rates according to

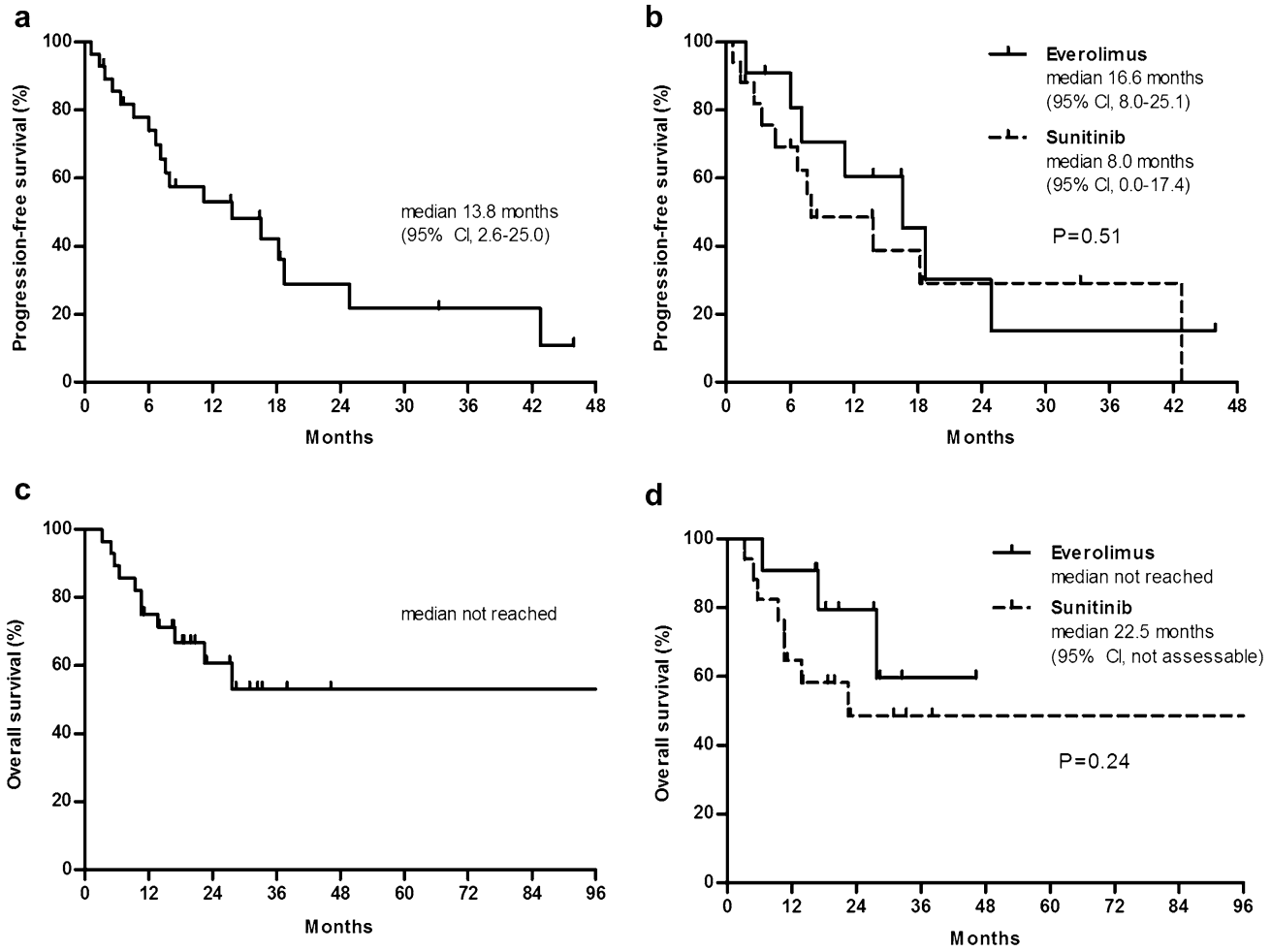

Fig. 1 Survival outcomes in patients with pancreatic neuroendocrine tumor. **a** Progression-free survival in overall population. **b** Progression-free survival according to treatment agent. **c** Overall survival in total study population. **d** Overall survival according to treatment agent

Table 2 Overall response

Response	Pancreatic NET ($n = 28$)			Non-pancreatic GI-NET ($n = 16$)		
	Sunitinib ($n = 17$)	Everolimus ($n = 11$)	p value	Sunitinib ($n = 10$)	Everolimus ($n = 6$)	p value
Partial response	3 (18%)	1 (9%)	1.00	0	1 (17%)	0.37
Stable disease	11 (64%)	8 (73%)		5 (50%)	5 (83%)	
Progressive disease	2 (12%)	1 (9%)		4 (40%)	0	
Not evaluable	1 (6%)[a]	1 (9%)[a]		1 (10%)[b]	0	

p values for comparison between patients with partial response and those with stable disease/progressive disease/not evaluable

NET neuroendocrine tumors, *GI* gastrointestinal

[a] Response assessment was not available because patients received treatment after metastasectomy

[b] Not evaluable; patient was lost to follow-up before the first response evaluation

the RECIST v1.1 were 18% with sunitinib and 9% with everolimus ($p = 1.00$; Table 2).

Due to failure of treatment with first targeted agent, seven patients subsequently received treatment with another targeted agent (sunitinib to everolimus in three patients and everolimus to sunitinib in four patients); median PFS in these patients was 2.3 months (95% CI 1.6–3.0 months).

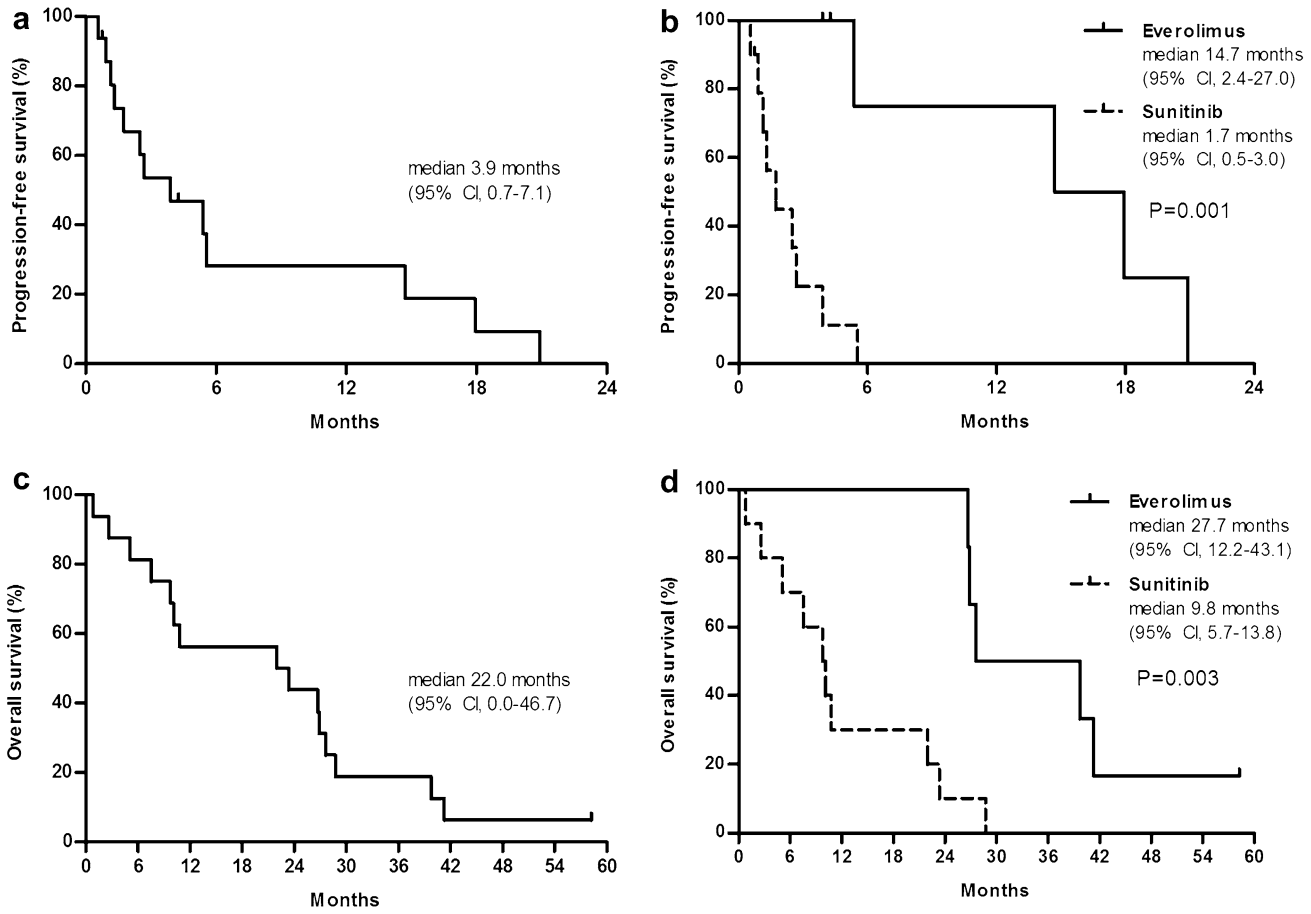

Fig. 2 Survival outcomes in patients with non-pancreatic gastrointestinal neuroendocrine tumor. **a** Progression-free survival in overall population. **b** Progression-free survival according to treatment agent. **c** Overall survival in total study population. **d** Overall survival according to treatment agent

Efficacy in non-pancreatic GI-NET

In patients with non-pancreatic GI-NET ($n = 16$), median PFS with either everolimus or sunitinib was 3.9 months (95% CI 0.7–7.1 months; Fig. 2a). Median PFS with everolimus ($n = 6$) was 14.7 months (95% CI 2.4–27.0 months) and that with sunitinib ($n = 6$) was 1.7 months (95% CI 0.5–3.0 months) ($p = 0.001$; Fig. 2b). Median OS with either everolimus or sunitinib was 22.0 months (95% CI 0.0–46.7 months; Fig. 2c): 27.7 months (95% CI 12.2–43.1 months) in the everolimus group, and 9.8 months (95% CI 5.7–13.8 months) in the sunitinib group ($p = 0.003$; Fig. 2d). One patient treated with everolimus achieved partial response with an objective response rate of 17% in the everolimus group, while no patient treated with sunitinib showed partial response. However, the difference was not statistically significant ($p = 0.37$; Table 2).

Predictive factors for PFS

With inclusion of all patients, univariate and multivariate analyses were performed to define the predictive factors for PFS (Table 3). On univariate analysis, primary tumor site [pancreatic vs. non-pancreatic GI; 13.8 months (95% CI 2.6–25.0) vs. 3.9 months (95% CI 0.7–7.1); $p = 0.008$], WHO tumor grade [grade 1 or 2 vs. grade 3; 14.7 months (95% CI 7.1–22.3) vs. 2.5 months (95% CI 0–5.0); $p = 0.004$], and previous cytotoxic chemotherapy before the administration of targeted agents [no vs. yes; 16.6 months (95% CI 8.2–25.0) vs. 2.6 months (95% CI 1.1–4.1); $p = 0.002$] were significantly associated with PFS. All these variables retained their statistically significant association with outcomes in the multivariate model. Although therapeutic agent (everolimus vs. sunitinib) showed marginal association with PFS ($p = 0.08$) on univariate analysis, the association was not significant in the multivariate model.

Table 3 Predictive factors for progression-free survival

Variables	Hazard ratio (95% CI)	*p* value
Univariate analysis		
Gender (male vs. female)	1.47 (0.70–3.10)	0.31
Pancreatic NETs versus non-pancreatic GI-NETs	0.37 (0.17–0.77)	0.01
Tumor grade (3 vs. 1/2)	4.56 (1.61–12.91)	<0.01
Sunitinib versus everolimus	1.97 (0.94–4.13)	0.08
Prior SSA	0.58 (0.28–1.22)	0.15
Prior surgery	0.73 (0.36–1.50)	0.40
Previous cytotoxic chemotherapy	3.15 (1.52–6.54)	<0.01
Multivariate analysis		
Pancreatic NETs versus non-pancreatic GI-NETs	0.39 (0.17–0.91)	0.03
Tumor grade (3 vs. 1/2)	6.64 (2.17–20.29)	<0.01
Previous cytotoxic chemotherapy	3.01 (1.30–6.96)	0.01

CI confidence interval, *SSA* somatostatin analogs, *NET* neuroendocrine tumors, *GI* gastrointestinal

Table 4 Adverse events associated with sunitinib and everolimus therapy

Adverse event	Sunitinib ($n = 27$)		Everolimus ($n = 17$)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Neutropenia	12 (44%)	9 (33%)	3 (18%)	0
Thrombocytopenia	5 (19%)	1 (4%)	2 (12%)	1 (6%)
Anemia	6 (22%)	5 (19%)	5 (29%)	0
Hand–foot syndrome	9 (33%)	2 (7%)	0	0
Fatigue	7 (26%)	1 (4%)	5 (29%)	0
Diarrhea	5 (19%)	3 (11%)	5 (29%)	0
Anorexia	5 (19%)	0	3 (18%)	0
Elevated liver enzyme	4 (15%)	0	2 (12%)	0
Edema	3 (11%)	0	0	0
Asthenia	3 (11%)	1 (4%)	2 (12%)	0
Stomatitis	2 (7%)	0	10 (59%)	1 (6%)
Nausea	2 (7%)	0	4 (24%)	0
Hypertension	2 (7%)	0	0	0
Constipation	2 (7%)	0	6 (35%)	0
Vomiting	1 (4%)	0	1 (6%)	0
Abdominal pain	1 (4%)	0	3 (18%)	1 (6%)
Skin rash	0	0	7 (41%)	0
Cough	0	0	5 (29%)	0
Pneumonitis	0	0	3 (18%)	2 (12%)

Safety profile

The most common cause of treatment discontinuation was disease progression ($n = 23$, 66%). Adverse events led to discontinuation of treatment in seven patients (20%); 3 (14%) receiving sunitinib [hemoperitoneum ($n = 1$), gastrointestinal bleeding ($n = 1$) and general weakness ($n = 1$)] and 4 (29%) receiving everolimus [pneumonitis ($n = 3$) and diarrhea/general weakness ($n = 1$)] ($p = 0.249$. Doses of sunitinib were reduced in 16 patients (59%). Most common cause for dose reduction was neutropenia ($n = 6$), followed by hand–foot syndrome ($n = 2$) and stomatitis ($n = 2$). In patients receiving everolimus, doses were reduced in five patients (29%) due to stomatitis ($n = 3$), neutropenia/thrombocytopenia ($n = 1$) and asthenia ($n = 1$). There was no significant difference in the rates of treatment discontinuation and dose reduction ($p = 0.07$) between patients treated with everolimus and sunitinib.

Data for safety analysis were available for all 44 patients (Table 4). No treatment-related mortality was observed in our study population. Neutropenia (44%) and hand–foot syndrome (33%) in the sunitinib group and stomatitis

(59%) and skin rash (41%) in the everolimus group were the most frequent adverse events for any grade. The most common grade 3–4 adverse events were neutropenia (33%), anemia (19%), diarrhea (11%), and hand–foot syndrome (7%) in patients treated with sunitinib and pneumonitis (12%) and stomatitis (6%) in those treated with everolimus.

Discussion

Our results showed that both everolimus and sunitinib were well tolerated and effective for patients with unresectable or metastatic GEP-NETs in a real-world clinical setting. Clinical outcomes and safety profile in our study were in line with the results of previous prospective trials. Although efficacy outcomes of sunitinib in patients with non-pancreatic GI-NET in our study were poor, this should be cautiously interpreted given the small sample size of patients harboring poor prognostic factors.

For patients with pNETs in this study, everolimus and sunitinib showed median PFS of 16.6 and 8.0 months, respectively. These are consistent with the results of previous phase 3 trials of everolimus and sunitinib [3, 4], the Korean phase 2 trial of everolimus [11], and the analysis of Western compassionate use program for everolimus [12]. In the pivotal phase 3 trials, median PFS with everolimus and sunitinib was similar as 11.0 and 11.4 months [4, 13]. In the current study, PFS with everolimus seems to be better than reported from previous studies (median 16.6 vs. 11–12 months); this might be associated with less pretreatment before the administration of everolimus, as only 9% of our patients with pNETs received prior systemic chemotherapy. Our results with sunitinib in patients with pNETs seem to be inferior to those reported from previous prospective studies using sunitinib (median 8.0 vs. 10–12 months) [4, 14]. This might be attributable to the inclusion of patients with poorly differentiated tumor (19%) in our study cohort for pNETs, given that previous prospective studies only included patients with well-differentiated tumors. After progression on first targeted agent, seven patients with pNETs subsequently received another targeted agent in this study. However, the median PFS in these patients was only 2.3 months; this might be due to the poor performance status and increased tumor burden at the time of initiation of second targeted agents.

Particularly in pNETs, because everolimus and sunitinib are approved for the same treatment setting, it is hard to define which agent should be administered first, although safety profile and patient vulnerability to agent-specific toxicities may sometimes help in the choice of treatment. In previous phase 2 study of pazopanib [15], the median PFS for patients who had previously received targeted agents, ranged from 4.0 to 12.4 months according to the various previous treatments (no prior biologic agents, previous multi-targeted TKI, mTOR inhibitor, or both multi-targeted TKI and mTOR inhibitor). These various results on the impact of previous targeted agents suggest that prospective randomized trial is the only way to define the optimal sequences of VEGFR-TKI and mTOR inhibitor in pNETs.

Although targeted agents have been widely investigated in non-pancreatic GI-NETs, recent RADIANT-4 study, which included advanced non-functional, grade 1 or 2 NET of lung or non-pancreatic GI origin is the only randomized phase 3 trial that demonstrated the statistically significant efficacy of targeted agent in non-pancreatic GI-NETs [3]. In the RADIANT-4 study, the median PFS with everolimus was 11.0 months, which was significantly better as compared to that in the placebo group (3.9 months). Our study also showed that the everolimus was effective in patients with non-pancreatic GI-NETs, with the associated median PFS of 14.7 months. Remarkably, all our patients with non-pancreatic GI-NETs had primary tumor in the colorectal origin. Considering only 30 (14%) patients in the everolimus group of the RADIANT-4 study had colorectal primary disease, our results reinforce that everolimus is effective in colorectal NETs.

Sunitinib, with a median PFS of 1.7 months, seems to be less effective for non-pancreatic GI-NETs as compared to everolimus in the current study and with prior prospective studies (mostly phase 2) for anti-angiogenic agents. Previous phase 2 study of sunitinib showed median PFS of 10.2 months in patients with non-pancreatic NET [14]. Other anti-angiogenic agents showed median PFS of 9.5 months (pazopanib) and 11.4 months (sorafenib plus bevacizumab) [11, 15]. Although no randomized phase 3 trials have assessed the efficacy of anti-angiogenic treatment over that of placebo or other treatments for patients with non-pancreatic GI-NETs, the results of previous single-arm studies indicate that activity of VEGFR-TKI cannot be precluded in non-pancreatic GI-NETs [14, 16, 17]. Considering these previous results on VEGFR-TKI, poor outcomes with sunitinib in our study may be associated with clinicopathological characteristics of included patients as 30% of patients had grade 3 tumors and 70% of patients previously had received one or more lines of cytotoxic chemotherapy.

Given that no randomized comparative trial of everolimus and sunitinib has been performed in patients with advanced GEP-NETs, our study may provide a good opportunity to compare the relative activity of both agents, even considering the potential selection bias introduced by the retrospective study design. In our study, patients with everolimus showed better median PFS

than those treated with sunitinib in either pNETs or non-pancreatic GI-NETs. Considering the very heterogeneous features of NETs and the retrospective nature of our study, current results should be interpreted in the context of more aggressive histological features and pretreatment in patients treated with sunitinib compared with those with everolimus, rather than inferior efficacy of sunitinib. This is supported by that, although everolimus showed marginal relationship for better PFS than sunitinib in the univariate analysis, the association was not significant on multivariate analysis after adjusting for other prognostic factors. In the current study, grade 3 tumor, previous cytotoxic chemotherapy, and non-pancreatic GI tumor origin were significant predictive factors for poor PFS. In particular, the median PFS of patients with grade 3 NETs was very poor (2.5 months with both everolimus and sunitinib).

Because not all patients respond to everolimus or sunitinib, biomarkers to predict the outcomes with these agents are essential to enhance the efficacy of targeted agents. However, there is no solid biomarker for everolimus or sunitinib despite intensive investigation including large phase 3 trials for various cancer types. Further efforts should be made to define potential biomarkers of these agents using novel technology such as next-generation sequencing or comprehensive gene-expression profiling.

This study has limitations in terms of small number of patients and the retrospective design and thus an inherent selection bias. However, considering most phase 2 trials for NET included 20–50 patients, our results may be representative of treatment outcomes in the real-world setting.

In conclusion, in the real-world setting, everolimus was universally effective in GEP-NETs and sunitinib showed comparable efficacy in pNETs. Although efficacy of sunitinib in patients with non-pancreatic GI-NETs was poor in this study, this might be due to the baseline characteristics associated with poor clinical outcomes in NETs. Grade 3 tumor, non-pancreatic GI origin, and previous cytotoxic chemotherapy were predictive factor for poor PFS in patients treated with targeted agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

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