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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Does sunitinib have a patient-specific dose without diminishing its antitumor effect on advanced pancreatic neuroendocrine neoplasms?

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Abstract

Purpose Because it is unknown whether adjusting the dose of sunitinib can benefit patients with pancreatic neuroendocrine neoplasms (Pan-NENs), this retrospective study examined maximum tumor shrinkage rates and prognoses in patients with and without low doses of sunitinib administration.

Methods Eighty-seven patients with metastatic and unresectable neoplasms, treated with sunitinib for > 1 month, were divided into a low-dose (LD) or high-dose (HD) group. The tumor response rates were investigated over time using computed tomography according to the response evaluation criteria in solid tumors criteria.

Results The LD and HD groups included 42 and 45 patients, respectively. There were no differences in baseline characteristics (tumor size, Ki-67 index, mitosis, and differentiation) between the two groups. Progressive disease (PD), stable disease (SD), and partial response (PR) were observed in 16.7, 54.8, and 28.6% of patients in the LD group, respectively, and in 13.3, 60, and 26.7% of patients in the HD group, respectively. There were no differences in tumor shrinkage rates between the two groups ($p = 0.87$). The 3-year progression-free survival rates for the LD and HD groups were 2.4% and 2.3%, respectively ($p = 0.67$), and the 3-year overall survival rates were 57.9% and 70.5%, respectively ($p = 0.76$). The occurrence of adverse events was similar between the two groups (61.9% vs. 60.0%, $p > 0.95$).

Conclusions Dose reduction of sunitinib did not alter tumor shrinkage rates or prognoses for patients with advanced Pan-NENs.

Keywords Neuroendocrine tumor · Sunitinib · Low dose · Liver metastasis · Unresectable

Introduction

The detection of pancreatic neuroendocrine neoplasms (Pan-NENs) has gradually increased because of advances in diagnostic technologies (Yao et al. 2008; Ito et al. 2015). The 5-year survival rate of patients with Pan-NENs is below 43% (Pape et al. 2004). Systemic drug therapy is the standard treatment for unresectable and metastatic tumors, whereas surgery is the optimal treatment for localized diseases. Molecular targeted therapy involving everolimus and sunitinib are usually used for patients with neuroendocrine tumors, grades 1 and 2 (NET-G1/G2) (Pavel et al. 2016). It has recently been reported that sunitinib prolongs the survival rate of grade 3 (NET-G3) patients to the same degree as NET-G1/G2 patients (Mizuno et al. 2018).

Sunitinib is a multitargeted tyrosine kinase inhibitor that acts on vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and other kinases (Abrams et al. 2003; Mendel et al. 2003; Murray et al. 2003). VEGF is a key molecule for angiogenesis in Pan-NENs (Casanovas et al. 2005). Malignant Pan-NENs express stem-cell factor receptors, VEGF receptors, and PDGF receptors (Fjallskog et al. 2003). A phase III trial involving 171 patients with well-differentiated tumors from 42 research centers in 11 countries compared sunitinib with a placebo and showed that the median progression-free survival (PFS) rates in the sunitinib group were significantly prolonged (11.4 vs.

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5.5 months) with an objective response rate (ORR) of 9.3% (Raymond et al. 2011). The study reported an overall survival (OS) improvement of 9.5 months in the sunitinib group compared with the placebo group (38.6 vs. 29.1 months) (Raymond et al. 2011).

However, severe adverse clinical events occasionally require dose adjustment. There has been a report that 20% of patients receiving a routine schedule with standard doses of sunitinib led to treatment discontinuation (Yoo et al. 2017). Those patients required dose reductions to mitigate toxicity, thereby reducing drug exposure which in turn may compromise efficacy. For metastatic renal cell carcinoma (mRCC), sunitinib treatment modification may help improve efficacy outcomes by prolonging the duration of treatments (Boegemann et al. 2018). However, for Pan-NENs, the efficacy and safety of treatment modification has not been elucidated.

Therefore, this study aimed to evaluate the efficacy and safety of sunitinib treatment modification in patients with Pan-NENs. To this end, the present study provided valuable insights into the current use of sunitinib scheduling and dose modifications.

Methods

Patients and methods

Between 2002 and 2018, 243 patients with Pan-NENs were treated at the Tokyo Medical and Dental University. Eighty-seven patients who were administered sunitinib for > 1 month and who underwent computed tomography (CT) or magnetic resonance imaging (MRI) before and after sunitinib administration were included in this study (Fig. 1). The median daily dosage (MDD) in this study (22.5 mg/day) was calculated from all dosages and durations of administration (MDD = all dosage/duration). The patients were divided into a low-dose (LD, $n = 42$) or high-dose (HD, $n = 45$) group according to their MDD.

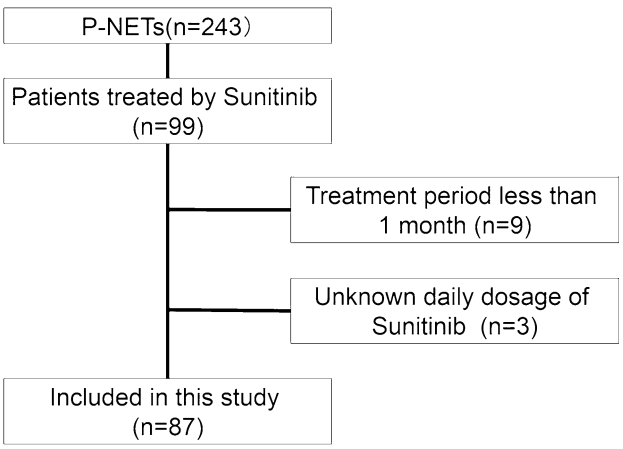

Fig. 1 The study design

Generally, patients receive 18.75 mg (525 mg/28 days) of sunitinib as an initial daily dose at our hospital. In cases of grade 2 toxicity, the initial dose is reduced to 12.5 mg/day. In the absence of grade 2 or higher toxicities, the dosage is increased to 37.5 mg (1050 mg/28 days). If grade 2 side effects develop during the increased dose, it is reduced back to 18.75 mg/day. Patients have never been administered > 50 mg/day, with the maximum dose administered being 37.5 mg/day.

Background characteristics assessed included age, gender, genetic syndromes such as multiple endocrine neoplasia type 1, tumor functionality, tumor locations, synchronous lymph nodes, liver metastases, and surgical procedures. All patients were examined at least every 2–6 months via laboratory tests and CT or MRI with a bolus injection of a contrast medium. A minimum of two radiologists diagnosed patient progressions and relapses. Progression-free survival (PFS) rates were measured from the start of sunitinib administration to the first day of progression or death owing to any cause. Moreover, we examined the best response during the entire administration period according to the response evaluation criteria in solid tumors (RECIST) criteria. We conducted a prognostic survey of all patients in December 2018.

The following pathological findings were analyzed: tumor size, immunohistochemical findings such as the Ki-67 index, and hormone production. According to the World Health Organization (WHO) 2017 classification of tumors of the endocrine organs, tumors were classified into four grades in terms of histological differentiation, mitotic indices, and Ki-67 proliferative indices. NET-G1s were defined as being well-differentiated with mitotic counts of > 2/10 high-power field (HPF) and with a Ki-67 index of < 3%. NET-G2s were defined as being well-differentiated with mitotic counts of 2–20/10 HPF and with a Ki-67 index of 3%–20%, while NET-G3s were well-differentiated, had mitotic counts of > 20/10 HPF, and a Ki-67 index of > 20%. Neuroendocrine carcinomas (NEC-G3s) were defined as having poor differentiation, mitotic counts of > 20/10 HPF, and a Ki-67 index of > 20%. For tumors with a discrepancy between the Ki-67 index and mitotic count, the higher grade was assigned according to the WHO recommendations. We quantified the Ki-67 proliferative index and mitotic count by counting at least 500 cells in "hot spots".

All study procedures were approved by the Human Research Ethics Committee of Tokyo Medical and Dental University (Approval ID: 1080), and written informed consent was obtained from each participant.

Statistical analysis

Statistical comparisons for significance of clinicopathological features were performed using the Chi squared test or Fisher's exact test with a single degree of freedom. Continuous variables were expressed as median (range) and evaluated by the nonparametric Mann–Whitney *U* test, unless otherwise stated. Categorical variables were compared using Fisher's exact test. Survival curves were created using the Kaplan–Meier method and compared via log-rank tests. Significant variables were subjected to univariate analysis using the Cox proportional hazards model. All statistical analyses were performed with Easy R (EZR, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

This study included 87 Pan-NEN patients treated with sunitinib at a single high-volume center in Japan (Table 1). The median observation period was 23 months. The median duration of sunitinib treatment was 6 months. The median patient age was 54 years (range, 18–83 years). Forty male and 47 female patients were included in this study. Six patients had genetic diseases such as multiple endocrine neoplasia type 1 or von Hippel–Lindau disease. The median maximum primary tumor size was 30 mm. The primary tumor site was the pancreas head in 43 patients (49.4%). Liver and lymph node metastases were observed in 73 (87.9%) and 37 (42.5%) patients, respectively. The median Ki-67 index was 9.6%, and the median mitotic index was 2/10 HPF. Chromogranin A, synaptophysin, and CD-56 showed positive staining in 77 (89%), 79 (91%), and 67 (77%) cases, respectively. Patients had the following tumors: nonfunctional tumors ($n = 71$), insulinomas ($n = 9$), gastrinomas ($n = 4$), vasoactive intestinal peptide-producing tumors ($n = 2$), and glucagonomas ($n = 1$). According to the 2017 WHO classification, 84 patients had gradable tumors, and 12, 50, 14, and eight patients had NET-G1, NET-G2, NET-G3, and NEC-G3 tumors, respectively. Specimens from three patients were inadequate, and it was not possible to grade those specimens using the WHO criteria.

Thirty patients underwent resections before sunitinib treatment and 25 underwent resections after sunitinib treatment. Twenty-nine patients had systemic chemotherapy, such as platinum-based regimens, before sunitinib administration. Table 1 compares the background characteristics of the LD and HD groups and reveals no significant differences between the two groups.

Tumor response to sunitinib in the LD and HD groups

The median maximum tumor reduction rate was 15.2% in the 87 patients. Figure 2a, b shows the best response during the entire administration period according to the RECIST criteria. In the LD group, partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 12 (28.6%), 23 (54.8%), and 7 (16.7%) patients, respectively. In the HD group, PR, SD, and PD were observed in 12 (26.7%), 27 (60%), and 6 (13.3%) patients, respectively. There was no significant difference between the two groups as determined by the maximum response rate ($p = 0.9$). As shown in Fig. 2c, d, similar time courses were observed in both the groups after the start of sunitinib administration. One month after administration, patients whose target tumors increased in size did not achieve PR in either group. Conversely, any patient who achieved PR once did not achieve PD.

Adverse events

No treatment-related mortality was observed in our study population. As shown in Table 1, adverse events were observed in 26 (61.9%) and 27 (60.0%) patients in the LD and HD groups, respectively. There was no significant difference between the two groups in the occurrence of adverse events ($p > 0.95$). Table 2 compares the adverse events between the two groups for the higher tumor grades, with severe adverse events observed in 4 (9.5%) and 4 (8.8%) patients in the LD and HD groups, respectively. There was no significant difference between the two groups in the occurrence of grade 3 or higher adverse events ($p > 0.95$).

Prognosis

The median PFS after starting sunitinib was 6.2 months (95% confidence interval [CI], 3.8–9.7) in the LD group and 5.5 (95% CI, 3.3–7.2) months in the HD group ($p = 0.667$) (Fig. 3a). There was no significant difference between the two groups. Figure 3b shows the OS after starting sunitinib. There was no significant difference between the two groups ($p = 0.764$). Figure 3c shows the OS of patients with NET-G3. There was no difference in the OS between the two groups ($p = 0.384$). The median OS rate was 48.2 months in the LD group and 39.5 months in the HD group ($p = 0.764$). Figure 3d shows the OS rate with NEC-G3. There was no difference between the two groups ($p = 0.433$).

Table 1 Clinical or tumor factors and sunitinib treatment

Patient factor	$n=87$		
Sunitinib	< 22.5 mg/day ($n=42$)	≥ 22.5 mg/day ($n=45$)	p value
Clinical characteristic			
Age: years, median (range)	55 (18–81)	54 (19–83)	0.7
Gender: male/female, *n*	19/23	21/24	> 0.95
Before surgery, *n* (%)	15 (35.7)	15 (37.8)	> 0.95
After surgery, *n* (%)	11 (26.2)	14 (31.1)	0.6
Prior systemic chemotherapy, *n* (%)	14 (33.3)	15 (33.3)	> 0.95
Genetic syndrome			
MEN type 1	4 (9.5)	0 (0)	0.1
VHL disease	1 (2.4)	1 (2.2)	> 0.95
Tumor factor			
Maximum mm size, median (range)	30 (5–110)	30 (5–150)	0.7
Location			
Head	18 (42.9)	25 (55.5)	0.3
Body/tail	24 (57.1)	20 (44.4)	
Ki-67 index: %, median (range)	7 (2.1–71)	11.15 (1–90)	0.5
Mitosis:/10 HPF, median (range)	2 (0–60)	2 (0–72)	0.8
Liver metastasis, *n* (%)	35 (83.3)	38 (84.4)	> 0.95
Lymph node metastasis, *n* (%)	19 (45.2)	18 (40.0)	0.7
Chromogranin A positive, *n* (%)	38 (90.5)	39 (86.7)	0.5
Synaptophysin positive, *n* (%)	39 (92.9)	40 (88.9)	0.4
CD56 positive, *n* (%)	35 (83.3)	32 (71.1)	0.1
Tumor functionality, *n* (%)			
Nonfunctioning	31 (73.8)	40 (88.9)	0.3
Insulinoma	6 (14.3)	3 (6.7)	
Gastrinoma	3 (7.1)	1 (2.2)	
VIPoma	2 (4.8)	0 (0)	
Glucagonoma	0 (0)	1 (2.2)	
2017 WHO classification, *n* (%)			
G1	4 (9.5)	8 (17.8)	0.6
G2	27 (64.3)	23 (51.1)	
NET-G3	5 (11.9)	9 (20.0)	
NEC-G3	4 (9.5)	4 (8.9)	
Unknown	2 (4.8)	1 (2.2)	
Sunitinib treatment			
Months of treatment: median (range)	7.5 (1–48)	5 (1–45)	0.3
Adverse events, *n* (%)	26 (61.9)	27 (60.0)	> 0.95

MEN multiple endocrine neoplasia, *VHL* von Hippel–Lindau, *HPF* high-power field, *VIP* vasoactive intestinal peptides, *WHO* World Health Organization, *NET* neuroendocrine tumor, *NEC* neuroendocrine carcinoma

Discussion

The present study provided evidence that dose reduction of sunitinib in response to a patient's individual symptoms did not change tumor shrinkage rates or patient prognoses. Moreover, there was no change in PFS or OS rates in patients with NET-G3 or NEC-G3. As a result, the frequency of adverse events in patients with reduced doses of sunitinib was comparable to that in patients with relatively high doses of sunitinib, although there was no difference in baseline characteristics between the two groups. This is the first study to elucidate whether tumor shrinkage rates decrease after reducing the dose of sunitinib in patients with Pan-NENs.

A previous study included relatively stable tumors with low Ki-67 indices (Raymond et al. 2011). Except for poorly differentiated tumors, a subgroup analysis of a phase III trial of sunitinib for Pan-NENs revealed that sunitinib was ineffective in 29 cases with Ki-67 indices > 5%, while it was

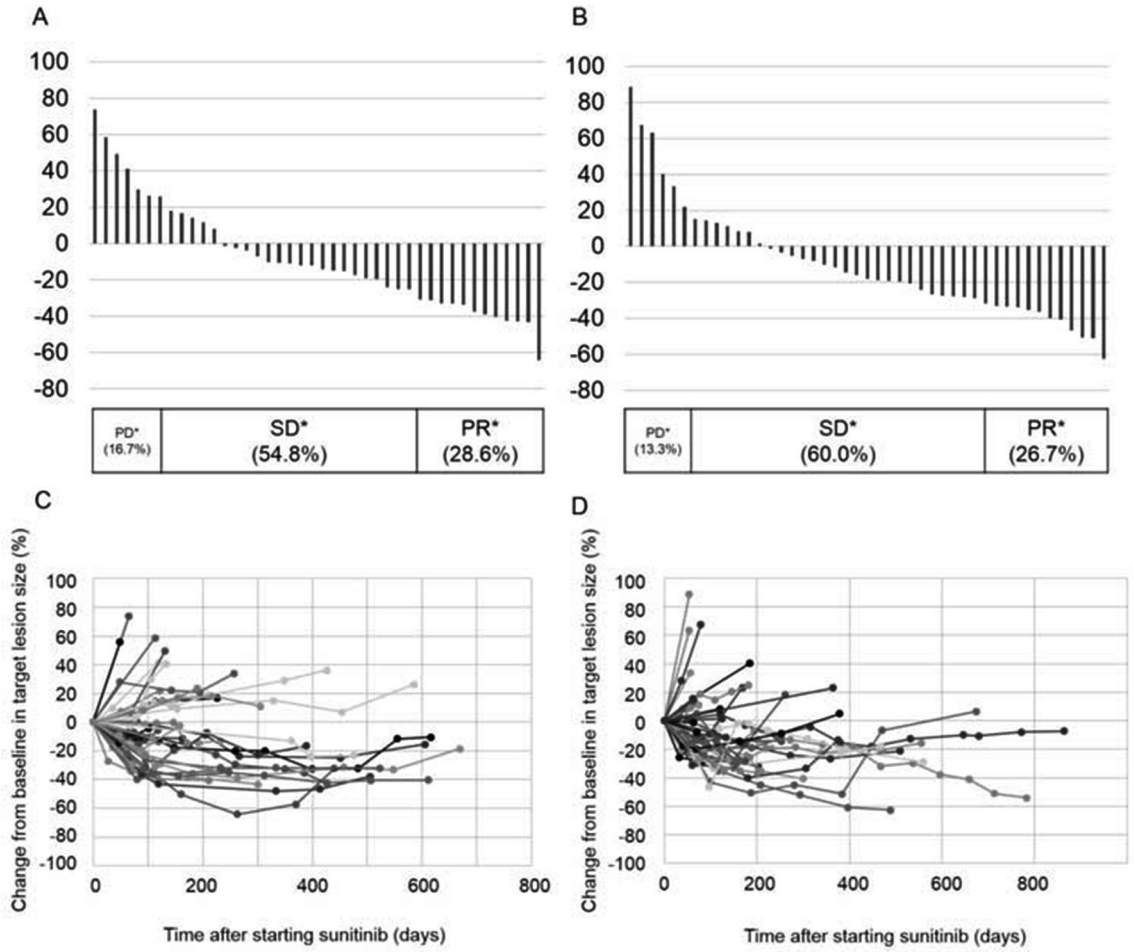

Fig. 2 Maximum tumor shrinkage rates (MTSRs) and the target tumor size time course for each patient after sunitinib administration. **a** The MTSR in the low-dose group ($n=42$). **b** The MTSR in the high-dose group ($n=45$). **c** The time courses in the low-dose group ($n=42$). **d** The time courses in the high-dose group ($n=45$). Note that there was no difference in MTSR between the low- and high-dose groups. *PD* progressive disease, *SD* stable disease, *PR* partial response

Table 2 Treatment-related adverse events (Grades 3/4)

Sunitinib	< 22.5 mg/day ($n=42$)	≥ 22.5 mg/day ($n=45$)	p value
Thrombocytopenia	0 (0)	2 (4.4)	0.5
Leukopenia	1 (2.4)	0 (0)	0.5
Tumor lysis syndrome	1 (2.4)	0 (0)	0.5
Hand-foot syndrome	1 (2.4)	1 (2.2)	> 0.99
Edema	1 (2.4)	1 (2.2)	> 0.99

effective in 41 cases with Ki-67 indices < 5%. In that study, the number of patients with hepatic and extrahepatic metastases was 95% and 24%, respectively. Nonfunctional tumors were observed in 72% of patients (Raymond et al. 2011). In a phase II study in Japan that classified tumors according to the 2004 WHO classification and that excluded poorly differentiated tumors, no data on Ki-67 or mitotic indices were shown (Ito et al. 2013). In that study, the number of patients with nonfunctional tumors and those with liver metastasis were 83% and 100%, respectively. Moreover, only patients with no disease progression in the last 12 months before starting sunitinib were targeted. Given that only patients with very slow-growing tumors were recruited, the cohort may not have included patients with Ki-67 indices > 20%. However, the present study included NET-G3 (16.1%) and NEC-G3 (9.2%) patients. The median Ki-67 index was 9.6% and the mitotic index was 2/10 HPF. The number of patients with liver and lymph metastases was 83.9% and 42.5%, respectively. Nonfunctional tumors were observed in 82% of patients, suggesting that the present study included patients with aggressive tumors with high Ki-67 indices.

In past studies, patients basically received 37.5 mg/day sunitinib on a continuous daily dosing schedule, and dose reduction was permitted to manage adverse events (Raymond et al. 2011; Ito et al. 2013). In the phase III trial,

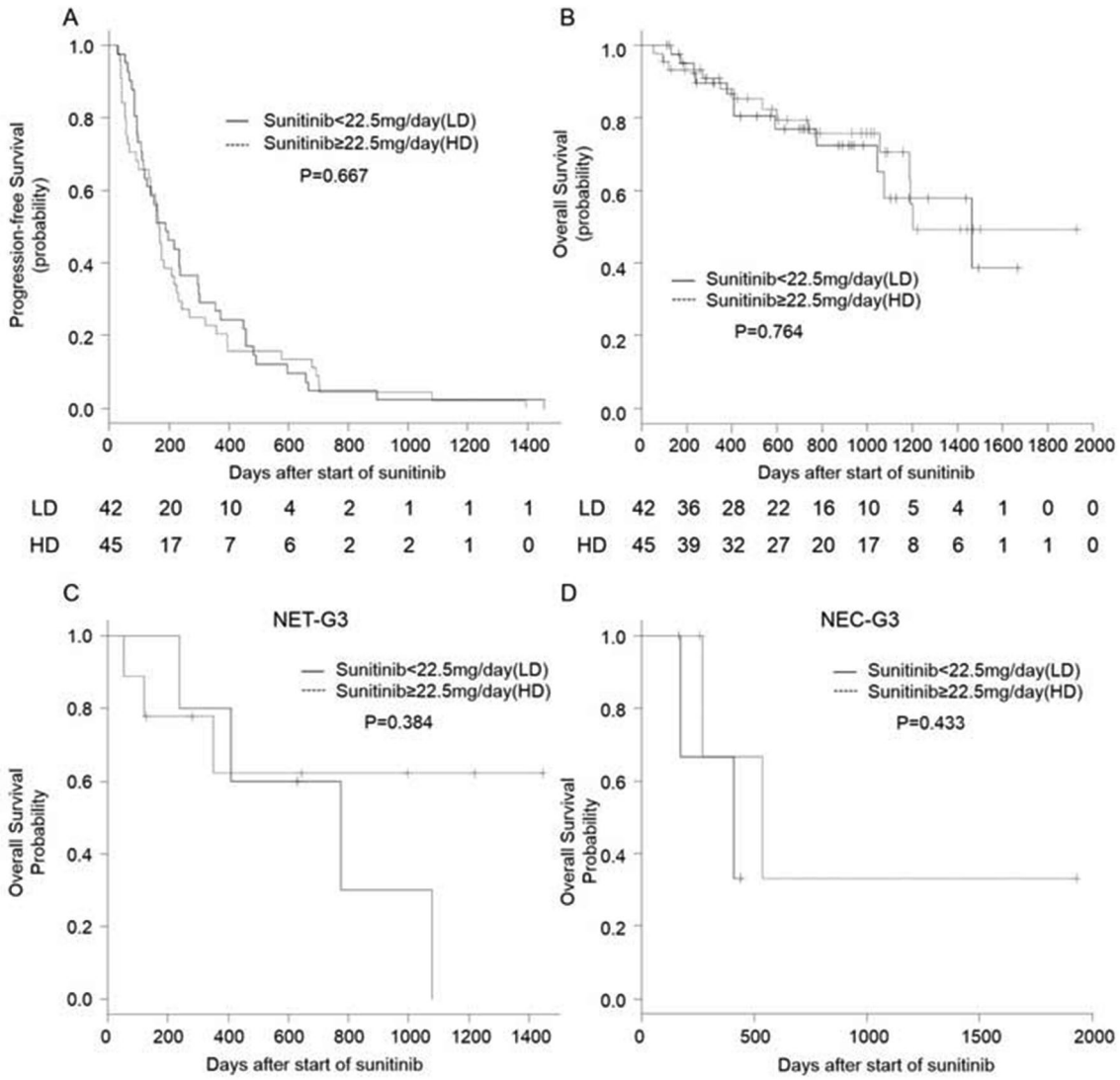

Fig. 3 Progression-free survival (PFS) and overall survival (OS) probabilities after sunitinib administration comparing the low-dose (LD) group and the high-dose (HD) group (log-rank test). **a** PFS: there was no significant difference ($p=0.7$). **b** OS: there was no significant difference ($p=0.8$). **c** OS in NET-G3 patients: there was no significant difference ($p=0.4$). **d** OS in NEC-G3 patients: there was no significant difference ($p=0.4$). *OS* overall survival, *LD* low dose, *HD* high dose, *NET-G* neuroendocrine tumor-grade, *NEC* neuroendocrine carcinoma

treatment interruptions and a dose reduction to 25 mg/day were permitted to manage adverse events, with a subsequent increase in dose if toxicity of grade 2 or higher did not occur. Patients received sunitinib for a median duration of 4.6 months (Raymond et al. 2011). In the aforementioned phase II trial, dose reductions to 25 mg/day were also permitted based on individual tolerances, although the definition of individual tolerance was not clear. The median duration of treatment with sunitinib was 9.8 months (Ito et al. 2013). In the present study, the initial daily dose of sunitinib was 18.75 mg/day, and it could be increased to 28 mg in the absence of grade 2 or higher toxicity. The median duration of treatment with sunitinib was 6 months. The duration may be short because patients undergo R0/1 surgeries or reduction surgeries when tumor shrinkage is achieved.

Past studies have also demonstrated the maximum shrinkage rate of tumors. In a phase III trial, the CR (complete response), PR, SD, and PD rates were 2, 7, 63, and 14%, respectively, and the ORR was 9.3% (Raymond et al. 2011). Moreover, in a Japanese phase II trial, the CR, PR, SD, and PD rates were 0, 50, 42, and 8%, respectively, and the ORR was 50% (Ito et al. 2013). In the present study, the ORR was 16.7% for the LD group and 13.3% for the HD group. The CR, PR, SD, and PD rates were 0%, 17%, 55%, 29%, respectively, in the LD group and 0, 13, 60, 27%, respectively, in the HD group. There was no significant difference between

the two groups as determined by the maximum response rate ($p = 0.9$). The PR rate for the current study was higher than that of a phase III trial (Raymond et al. 2011), but lower than that for a phase II Japanese study (Ito et al. 2013), although the LD and HD groups included 21.4% and 28.9% cases with Ki-67 indices ≥20%, respectively. In the phase II Japanese study, patients with poorly differentiated tumors were excluded (Ito et al. 2013). Moreover, only stable patients with no disease progression in the last 12 months before starting sunitinib were included (Ito et al. 2013). These results indicate that patient characteristics may result in a difference in the prognosis between the phase II study in Japan and the present study.

In the phase III study, PFS and OS rates were 11.4 and 38.6 months, respectively (Faivre et al. 2017; Raymond et al. 2011). The present study showed that the median PFS rate was 6.2 months in the LD group and 5.9 months in the HD group. The present study included patients with aggressive tumors with high Ki-67 indices, although the phase III study excluded poorly differentiated tumors. The difference in baseline characteristics may contribute to the difference in PFS rates. Moreover, the present study illustrated that drug responses were evaluated according to the tumor reduction rate 1 month after sunitinib treatment (Fig. 2a, b), with results similar to those of the Japanese phase II study (Ito et al. 2013).

The phase III study reported that 22% of patients who received sunitinib discontinued its use because of adverse events (Raymond et al. 2011). Moreover, Wang et al. reported that 35.2% of patients who received the standard sunitinib dosage of 37.5 mg/day had the dose reduced to 25 mg/day or discontinued owing to the occurrence of adverse events (Wang et al. 2017). They also reported that the steady-state serum concentrations showed no significant differences between the 37.5 mg/day group and the 25 mg/day group. It is important to sufficiently understand the properties of the drug so as to avoid adverse events and establish drug efficacies. They suggested that it is feasible to reduce the dosage to 25 mg/day for patients who are unable to tolerate a sunitinib dose of 37.5 mg/day (Wang et al. 2017). In the present study, the rate of adverse events related to sunitinib was 60.9%. Consequently, patients receiving sunitinib treatments at the standard dose and schedule required reductions in drug dose and exposure. This study showed that there was no significant difference between the two groups in the occurrence of grade 3 or higher adverse events. Moreover, no patients discontinued the standard dosage of 37.5 mg/day owing to adverse events. Our protocol (i.e., low initial dosage, gradual dose increase, and rapid dose reduction before the development of any adverse events) may result in low rates of severe adverse events for both groups.

On the other hand, higher sunitinib blood levels have been associated with longer PFS rates, OS rates, and higher ORRs in RCC patients (Houk et al. 2010). Sunitinib has been regarded as a first-line therapy for mRCCs (Vazquez et al. 2012). On an average, 50% of patients receiving sunitinib treatment at the standard dose and schedule required dose reductions to mitigate toxicity, thereby lowering both dose intensity and drug exposure which in turn may compromise efficacy (Motzer et al. 2007; Motzer et al. 2013). In this context, in addition to adverse event mitigation, sunitinib treatment modification may help improve efficacy outcomes in mRCCs by prolonging the duration of treatments (Boegemann et al. 2018). However, the efficacy of sunitinib treatment modification was unknown in Pan-NENs.

The present study has some limitations. First, it was an observational retrospective study. Second, all treatments were performed on predominately Asian patients. Third, the observational period was short because patients underwent surgery when tumor shrinkage was achieved. However, the large number of patients in this cohort may help minimize the selection bias.

In conclusion, low-dose sunitinib treatment did not alter the tumor shrinkage rates or the prognoses of patients with advanced Pan-NENs. Low doses of sunitinib allowed patients to continue treatments for longer periods of time while potentially maximizing the efficacy of sunitinib. This can lead to additional treatments such as conversion surgery.

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Compliance with ethical standards

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

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