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Assessment of the safety and efficiency of sunitinib malate in metastatic neuroendocrine tumours of the pancreas (NEN G1/G2) depending on the number and type of earlier therapeutic lines — initial report

Ocena bezpieczeństwa i efektywność jabłczanu sunitynibu w przerzutowych guzach neuroendokrynnych trzustki (NEN G1/G2) w zależności od liczby i rodzaju wcześniejszych linii terapeutycznych — doniesienie wstępne

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Abstract

Introduction: The objective of this paper was to assess the safety and efficacy of sunitinib malate in patients with well-differentiated metastatic pancreatic neuroendocrine neoplasms (PNENs) who relapsed on standard therapy.

Material and methods: Overall, eight patients with well-differentiated pancreatic neuroendocrine tumours/neoplasm (NET/NEN G1/G2, Ki-67 < 20%), who had relapsed on a standard therapy approach, were treated. All had non-resectable, progressive disease. All received therapy using a standard dose of sunitinib malate. Adverse events were evaluated using NCI-CTC AE v. 3.0.

Results: Of the eight patients, seven had non-secretor and single secretor tumour (gastrinoma). Partial remission (PR) was noted in three patients (one after a single therapeutic line, two after two lines), five patients had stabilisation (SD) — including three individuals after three lines, one patient after two lines and another after a single line. Haematological adverse events: leukopenia (25%) — occurred in one patient after three lines and in one patient after two lines; anaemia (25%) — in one patient after three lines and in one patient after one therapeutic line. Mucocutaneous lesions were noted in 37.5% of patients after 2–3 lines of treatment. All of them experienced fatigue syndrome irrespective of the number of therapies. The majority of the patients simultaneously received somatostatin analogues, which did not exacerbate the toxicity profile. The median progression-free survival time (PFS) was 11 months.

Conclusions: Sunitinib may be considered as a fairly well-tolerated and effective therapeutic option in progressive non-resectable PNEN patients in the second and subsequent lines of treatment, irrespective of the types of treatment previously applied. **(Endokrynol Pol 2014; 65 (6): 472–478)**

Key words: *sunitinib; antiangiogenic therapy; SSA; somatostatin analogues; PRRT; peptide receptor radiotherapy; CTH; chemotherapy*

Streszczenie

Wstęp: Celem pracy była ocena bezpieczeństwa oraz analiza skuteczności jabłczanu sunitynibu u chorych z przerzutowymi wysokozróżnicowanymi guzami neuroendokrynnymi trzustki (PNET) w drugiej i kolejnych liniach leczenia.

Materiał i metody: Analizie poddano 8 pacjentów z wysoko zróżnicowanymi guzami neuroendokrynnymi trzustki (NEN G1/G2, Ki-67 < 20%), u których wystąpiła progresja choroby i otrzymali sunitynib. Wszyscy chorzy byli w stadium nieoperacyjnym. Sunitynib był podawany w standardowej dawce. Działania niepożądane oceniono na podstawie kryteriów NCI-CTC AE v. 3.0.

Wyniki: Leczono 8 pacjentów; 7 guzów nieaktywnych hormonalnie i 1 o typie gastrinoma. Częściową remisję (PR) uzyskano u 3 chorych (1 po 1 linii terapeutycznej, 2 — po 2 liniach), 5 chorych miało stabilizację (SD) — w tym 3 było po 3 liniach, 1 po 2 liniach i 1 po 1 linii terapeutycznej. Powikłania hematologiczne: leukopenia (25%) — wystąpiły u 1 pacjenta po 3 liniach i u 1 pacjenta po 2 liniach; niedokrwistość (25%) — u 1 pacjenta po 3 liniach i u 1 pacjenta po 1 linii terapeutycznej. U 37,5% chorych wystąpiły zmiany skórno-śluzówkowe po 2–3 liniach leczenia. U 100% chorych obserwowano zespół zmęczenia niezależnie od liczby terapii. Większość chorych jednocześnie otrzymywała SSA, co nie pogorszyło profilu toksyczności. Mediana czasu wolnego od progresji PFS (*progression free survival*) – wyniosła 11 miesięcy.

Wnioski: Sunitynib może być rozważany, jako dość dobrze tolerowana, skuteczna opcja terapeutyczna u chorych z nieresekcyjnymi PNET w drugiej oraz kolejnych liniach leczenia, niezależnie od rodzaju uprzednio zastosowanych metod.**(Endokrynol Pol 2014; 65 (6): 472–478)**

Słowa kluczowe: *sunitynib; terapia antyangiogenna; SSA; analogi somatostatyny; PRRT; peptydowa terapia radioizotopowa; CTH; chemioterapia*

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Introduction

Pancreatic neuroendocrine neoplasms (PNENs) are rare neoplasms of the digestive system originating from the Diffuse Endocrine System (DES). Most may constitute a component of the genetic syndromes of multiple endocrine neoplasia (MEN1, MEN2), von Hippel-Lindau (VHL), or neurofibromatosis type 1 (NF1). [1]. PNENs constitute from 2% to 10% of tumours in this organ, with an incidence rate of approximately 4–12 per 1,000,000 individuals. The number of new diagnoses has increased in recent years due to more sensitive diagnostic methods [2–4].

The therapeutic options for non-resectable, advanced PNEN patients are still unsatisfactory and limited. In the first line of treatment, it is common to apply biological therapies: somatostatin analogues (SSA) are recommended in the treatment of slow-growing NETG1 and NETG2 [5–7]. Chemotherapy is recommended in metastatic or locally-advanced, non-resectable NETG2 and NEC [8–9]. Systemic treatment with streptozotocin (STZ) and 5-fluorouracil (5-Fu) and/or adriamycin (ADM) gives an objective response rate ranging between 35 and 40% [10–12], while the combination of temozolomide and capecitabine used in the Strosberg study provided better results in terms of the objective response rate (ORR — 70%) [13]. Radionuclide therapy (PRRT) may be used in hormonally active and inactive NETG1/G2 tumours as well, but this finding is based only on non-randomised analyses [14–16].

In 2011, two new oral drugs were approved for the treatment of these tumours: the tyrosine multikinase inhibitor sunitinib; and the mammalian target of rapamycin kinase everolimus. Thus began a new era of targeted treatment for pancreatic neuroendocrine tumours [17–19].

Pre-clinical trials indicated that PNENs are supplied with a dense network of microvessels (hypervascularisation) and manifest high expression of vascular endothelial growth factor receptors (VEGFR1, VEGFR2, VEGFR3), platelet growth factor receptors (PDGFRα and PDGFRβ), stem cell factors (SCF), glial cell line-derived neurotrophic factors (GDNF) and many other signal pathways for neoangiogenesis [20]. Sunitinib malate and its active metabolite (SU011248) is an oral protein-tyrosine kinase inhibitor with strong antiangiogenic properties [17, 18]. This justifies the application of sunitinib in PNENs in particular NETG1 and NETG2 groups of patients. The drug has demonstrated a significant clinical improvement in terms of progression-free survival (PFS) in a double-blind, randomised trial compared to a placebo (median PFS 11.4 months *vs.* 5.5 months, HR 0.42; 95% CI: 0.26–0.66; $P < 0.001$), with an acceptable toxicity profile and maintenance of quality of life at a relatively good level [17].

The aim of this study was to analyse factors influencing the occurrence, type and severity of adverse events based on NCI-CTC AE v. 3.0 (*National Cancer Institute Common Terminology Criteria for Adverse Events 4.03)* related to sunitinib applied in subsequent therapeutic lines, as well as to analyse the efficiency of this treatment in patients with advanced, non-resectable, progressive, well-differentiated pancreatic neuroendocrine neoplasms (NETG1/G2), in terms of progression-free survival. The assessment encompassed all the patients receiving sunitinib therapy in Polish clinics from 2011 to 2013.

Material and methods

The analysis encompassed eight patients with histologically confirmed, well-differentiated PNENs — NENG1 with proliferation index Ki-67 $\leq$ 2% and NENG2 with 2% < Ki-67 < 20%), who were found during or upon completion of somatostatin analogue treatment (SSA: octerotide acetate — Sandostatin LAR®, lanreotide acetate — Somatuline Autogel®) and/or peptide receptor radionuclide therapy (PRRT) and/or chemotherapy (CTH) to have experienced progression of the neoplastic disease, and were therefore eligible for sunitinib therapy.

The histopathological diagnoses of these pancreatic neuroendocrine tumours took into consideration the requirements of the uniform international classification of the World Health Organization (WHO) and the European Neuroendocrine Tumour Society (ENETS) [21, 22]. Before the treatment, all patients had their serum chromogranin A (CgA) concentrations marked, and they were later controlled every three months. The state of somatostatin receptor expression was evaluated on the basis of somatostatin receptor scintigraphy (SRS; ^{99m}Tc-[HYNIC, Tyr3]-octreotide (HYNICTOC) Tektrotyd; Polatom, Poland).

The treatment was administered to patients with good performance status evaluated on the WHO scale (World Health Organization)/ECOG (Eastern Cooperative Oncology Group) at 0–1. Prior to the sunitinib therapy, concomitant diseases and complications of the past oncological treatment were taken into consideration. The performance of the bone marrow and the biochemical functions of the following organs were evaluated: the kidneys, the liver, the thyroid gland, as well as the circulatory system (cardiac ultrasound imaging, ECG and blood pressure measurement). Progression of the disease prior to sunitinib therapy was documented in CT and/or MRI.

Sunitinib was administered at a dose of 37.5 mg a day every day. The therapy was continued until progression or unacceptable toxicity occurred. The administration of sunitinib was halted when adverse events beyond grade 3 were noted based on NCI CTC AE *v.* 3.0 [23]. Continuation of the therapy was possible upon the improvement of the clinical condition below the 2nd degree. The drug dose was reduced by 12.5 mg in the event of prolonged adverse events related to sunitinib. The safety of the therapy was assessed based on the analysis of complications reported by the patients or examined in the laboratory.

The efficiency of the therapy was determined on the basis of radiological examination according to the criteria of the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.0. Examinations to assess the response to CT or MRI treatment were performed every 12 weeks.

An examination was performed to verify the correlation between the number and type of the individual therapeutic lines used before sunitinib therapy, and the sunitinib tolerance and the influence on the therapeutic benefit (the percentage of obtained responses and the progression-free survival time).

Results

The assessment encompassed eight patients receiving sunitinib therapy. The group comprised five women (62.5%) mean age 44 years (range 33 to 60) and three men (37.5%) mean age 47.2 years (range 29 to 67). The average age at the onset of the disease was 42.1 years (range: 26–63), while the age at the onset of the sunitinib therapy was 48.8 years (range: 29–67). All patients had PS WHO/ECOG of 0 except for two patients with WHO/ECOG of 1.

Three patients were diagnosed with NEN G1, and five with NEN G2. Among them, there were seven patients with hormonally inactive tumours and one with a gastrinoma tumour without concomitant MEN1 syndrome (MEN1, multiple endocrine neoplasia). A 29-year-old man was found to have a pathogenic R167W mutation (c.499C > T) in one allele of the VHL gene, which had clinical implications in the form of von Hippel-Lindau syndrome. Mean CgA in those patients was 115.56 ng/mL (range 2 to 442.4) (Table I).

All the patients underwent surgery on either a radical or a palliative basis. Three patients received radical surgery with removal of the primary pancreatic tumour (the R0 procedure), two patients underwent a cytoreduction procedure (the R1/R2 procedure), while the remaining three were administered exploratory laparotomy with collection of specimen for histopathological examination. Secondary cytoreduction was performed in three individuals (metastasectomy — surgical removal of metastases) in the liver, with one patient undergoing the procedure twice (Table II).

Table I. *Characteristics of patients and pancreatic tumour before sunitinib therapy*

Tabela I. *Charakterystyka pacjentów i cech guzów trzustki przed terapią sunitynibem*

Parameter	Result
Female/male	5/3
Mean age at initial diagnosis (years/range)	42.1 (29–67)
Mean age at sunitinib therapy (years/range)	48.9 (29–67)
NETG1/NETG2 (%)	3/5 (37/63%)
CgA (mean/range)	115.56 ng/mL (2–442)

Table II. *Characteristics of clinical parameters of a pancreatic tumour and metastatic lesions before sunitinib therapy*

Tabela II. *Charakterystyka parametrów klinicznych guza trzustki oraz zmian przerzutowych przed terapią sunitynibem*

Parameters		Results
Radical /non-radical/tumour sampling surgery (%)		3/2/3 (37.5/25/37.5)
Localisation of the primary tumour in the pancreas (%)	Head	2 (25%)
	Body	4 (50%)
	Tail	4 (50%)
Initial size of the tumour, T feature (mm/range)		81.5 (40–120)
Pre-sunitinib size of the tumour (mm/range)		45.3 (0–124)
Location of metastatic lesions	Liver mts (%)	7 (87.5)
	Lymph node mts (%)	4 (50%)
Local recurrence of pancreatic tumour (%)		5 (62.5)
Secondary cytoreduction (metastasectomy* (%)		3 (37.5%)

Sunitinib malate was used in the second and subsequent therapeutic lines for metastatic NEN tumours of the pancreas. During sunitinib therapy, SSA treatment — activated in the first line of treatment (87.5%) — was continued. One patient showed no expression of somatostatin receptors. Five patients (62.5%), before being put on sunitinib, received peptide receptor radionuclide therapy (PRRT), including one individual receiving such a therapy twice, with an interval of two years. Half of the patients (50%) had previously undergone chemotherapy (with five different schemes: cisplatin with etoposide, 5-fluorouracil with adriamycin, gemcitabine), including one individual undergoing two systemic treatment lines (Table III).

Assessment of therapeutic response

Partial remission (PR) was obtained in three patients. In the remaining patients, the response was assessed as stabilisation of the disease (SD) — including three

Table III. *Number and type of therapeutic lines before starting sunitinib therapy*

Tabela III. *Liczba i rodzaj linii terapeutycznych przed włączeniem sunitynibu*

Number of therapy lines before sunitinib therapy	Type of sytemic therapy before sunitinib treatment	Number of patients
Single	SSA	2
Two	Chemotherapy	2
	PRRT + SSA	1
Three	SSA	2
	Chemotherapy (two lines of systemic therapy)	
	PRRT	
Four	SSA	1
	Chemotherapy	
	PRRT (twice)	

SSA — somatostatin analogues therapy; PRRT — peptide receptor radionuclide therapy

patients with three lines of past treatment, one after two lines and one after one therapeutic line (Table IV).

Assessment of survival times

The longest period of sunitinib treatment was 39 months (from three cycles in a dose reduced to 25 mg due to third-degree dermatological complications). The patient had previously received two lines of treatment: somatostatin analogues and PRRT. The patient continues her sunitinib therapy. The median progression-free survival time including all patients (PFS) was 11.5 months.

Assessment of safety of sunitinib therapy depending on the number and type of past therapeutic lines

Most adverse effects related to sunitinib therapy were mild or moderate (degree of severity 1st or 2nd degree according to NCI CTC AE). Severe adverse events (in the 3rd and 4th degrees) referred to haematological complications: leukopenia (25%) — in one patient after three therapeutic lines, and in one patient after two lines; anaemia (25%) — in one patient after three lines, and in one patient after one therapeutic line. Mucocutaneous lesions were observed in three (37.5%) patients after 2–3 lines of treatment. Patients with haematological complications in the 3rd or 4th degree received prior chemotherapy.

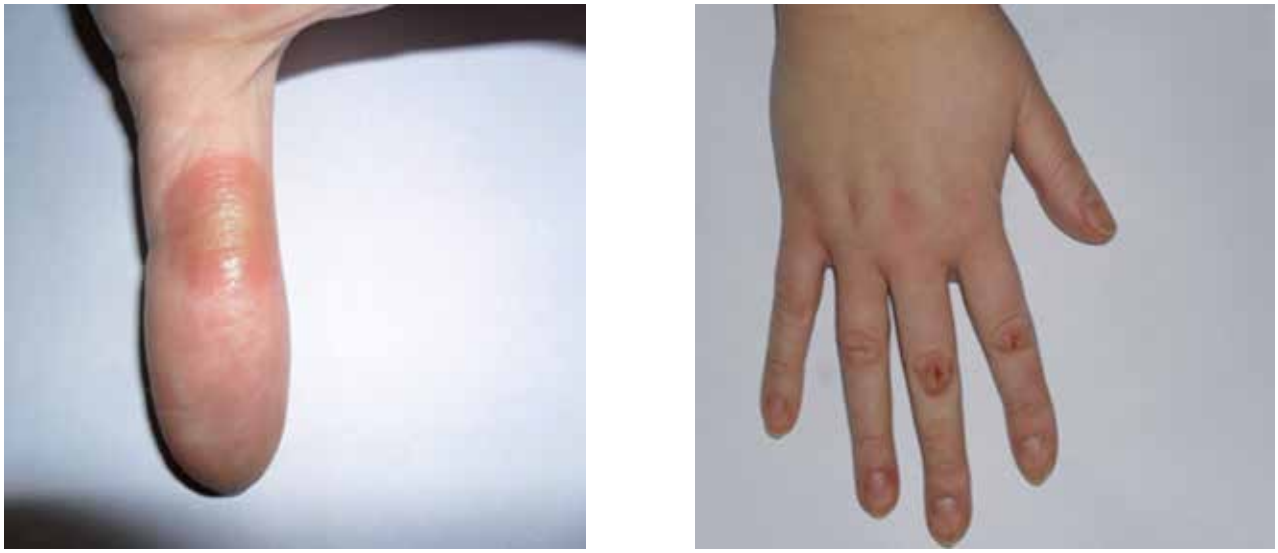
The treatment was terminated in two patients — in one after ten months of therapy, due to bleeding from the pancreatic head tumour (prior to sunitinib, he received only one line — SSA). The other patient, after

Table IV. *Type and severity of sunitinib adverse effects in the individual patients assessed according to the criteria of NCI CTC AE v. 3.0*

Tabela IV. *Rodzaj i stopień nasilenia działań niepożądanych sunitynibu u poszczególnych pacjentów ocenianych według kryteriów CTC AE v. 3.0*

Type and severity of toxicity (Degree 1–4)	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-8
Mucocutaneous	3	1	3	2	2	0	1	1
Hand-foot syndrome	3	0	2	0	1	0	1	1
Fatigue syndrome	2	2	1	2	2	1	1	1
Haematological:								
a) Leukopenia	a) 0	a) 4	a) 0	a) 0	a) 0	a) 0	a) 4	a) 0
b) Anaemia	b) 0	b) 2	b) 0	b)4	b) 0	b) 3	b) 2	b) 0
c) Thrombocytopenia	c) 0	c) 1	c) 0	c) 0	c) 2	c) 0	c) 1	c) 1
Dyspeptic symptoms (abdominal pains)	1	2	0	2	0	0	2	0
Nephrological	0	0	2	1	0	0	0	0
Cardiological	0	1	1	1	0	0	0	1
Tumour bleeding	0	0	0	4	0	0	0	0
Endocrinological (hypothyroidism)	0	0	2	0	0	0	0	2
Diarrhoea	1	2	2	2	2	1	1	1
Vomiting	0	0	0	2	0	0	0	0
Nausea	1	1	1	1	1	0	0	0
Constipation	1	0	0	0	0	0	0	0
Infection	2	3	1	2	1	0	0	0

0 — no symptoms; 1 — mild symptoms; 2 — moderate symptoms; 3 — serious complications ; 4 — life-threatening symptoms



Figures 1A, B. *Dermatological complications in the form of hand-foot syndrome (palmar-plantar erythrodysesthesia) — 3rd degree of CTC AE*

Rycina 1A, B. *Powikłania dermatologiczne w postaci zespołu ręka-stopa (erytrodyzestezja dłoniowo-podeszwowa) — 3 stopnia CTC AE*

12 months of sunitinib therapy, experienced immunity disorders complicated by severe pneumonia (he had previously received three therapeutic lines: SSA, PRRT and CTH with cisplatin).

All eight patients (100%) reported suffering from fatigue syndrome and diarrhoea (1st or 2nd degree) irrespective of the therapeutic lines administered prior to the sunitinib therapy. Half of the patients (50%) on sunitinib had previously been diagnosed and treated for arterial hypertension (concomitant disease). All of these patients were receiving anti-hypertensive therapy that required modification due to clinically significant incidents of increased arterial pressure. No patients manifested arterial hypertension as a new symptom induced by the tyrosine kinase inhibitor therapy.

Dermatological complications occurred in seven individuals (87.5%) in the form of mucosal damage, with two individuals experiencing 3rd degree effects. Five individuals suffered skin damage on their hands and feet in the form of palmar-plantar erythrodysesthesia, including one patient with 3rd degree effects. This patient had undergone four therapeutic lines before receiving sunitinib therapy (SSA, CTH and two courses of PRRT) (Figs. 1A, B).

Two patients were diagnosed with iatrogenic hypothyroidism that required hormonal supplementation (in one individual after two therapeutic lines — SSA and PRRT, in the other — after one line with SSA). The majority of the patients (87.5%), during their sunitinib therapies, received SSA, which had no influence on the exacerbation of the toxicity profile (Tables V and VI).

Discussion

Data concerning the effects of antiangiogenic therapy based on patient profiles, and on the number and type of therapies administered prior to sunitinib, is very limited and mainly derived from analysis of a few randomised clinical trials [17, 18].

There are ongoing efforts to determine the optimal therapeutic sequence for patients with pancreatic neuroendocrine neoplasms/tumours. The introduction of new molecular agents into clinical practice has significantly influenced the progress in PNENs treatment, both in terms of symptom control and antiproliferation effects [17–19].

This paper analyses the factors influencing the occurrence and severity of complications related to sunitinib malate — a multikinase inhibitor — applied in the second and subsequent therapeutic lines in patients with metastatic NETG1/G2. None of the patients received sunitinib in the first line of treatment. In all of the patients, irrespective of the number of previously administered therapeutic options, one could observe adverse events of varying severity, but primarily of low degree (1st and 2nd degree of NCI-CTC AE).

The greatest clinical benefits were observed in those patients who had undergone only somatostatin analogue therapy before sunitinib treatment (regardless of the type: 'cold' — SSA, or 'hot' analogues — PRRT). Efficacy and safety of sunitinib did not appear to be affected by such features as: the differentiation degree of the G1 and G2 tumour cells, the size of the original mass of the pancreatic tumour, the elevated CgA con-

Table IV. *Dependency between the number of therapeutic lines before sunitinib, the therapeutic response, and the duration of the response*

Tabela IV. *Zależność między liczbą linii terapeutycznych przed sunitynibem, odpowiedzią na leczenie i czasem trwania odpowiedzi*

	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-8
Number of therapeutic lines before sunitinib	4	3	2	1	2	3	2	1
The best therapeutic response [RECIST]*	SD	SD	SD	SD	PR	SD	PR	PR
PFS or duration of the response (months)	12	11	39	10	14	9	14	7
Severe adverse events [4] CTC AE]		Leukopenia		Anaemia			Leukopenia	

P-1 to P-8 — consecutive patients; *RECIST — Response Evaluation Criteria in Solid Tumour

Table V. *Summary of sunitinib adverse effects depending on the severity assessed on the basis of the criteria of CTC AE v. 3.0*

Tabela V. *Zestawienie działań niepożądanych sunitynibu w zależności od stopnia nasilenia ocenianego na podstawie kryteriów CTC AE v. 3.0*

Type and severity of toxicity (Degree 1–4)	No symptoms No. (%)	Degree 1 No. (%)	Degree 2 No. (%)	Degree 3 No. (%)	Degree 4 No. (%)
Haematological complications:					
a) Leukopenia	a) 6 (75)	a) 0	a) 0	a) 0	a) 2 (25)
b) Anaemia	b) 4 (50)	b) 0	b) 2 (25)	b) 1 (12.5)	b) 1 (12.5)
c) Thrombocytopenia	c) 4 (50)	c) 3 (37.5)	c) 1 (12.5)	c) 0	c) 0
Non-haematological complications related to sunitinib:					
Mucocutaneous	1 (12.5)	3 (37.5)	2 (25)	2 (25)	0
Hand-foot syndrome	3 (37.5)	3 (37.5)	1 (12.5)	1 (12.5)	0
Fatigue syndrome	0	4 (50)	4 (50)	0	0
Nephrological	6 (75)	1 (12.5)	1 (12.5)	0	0
Cardiological, including arterial hypertension	4 (50)	4 (50)	0	0	0
Tumour bleeding	7 (87.5)	0	0	0	1 (12.5)
Endocrynological, including hypothyroidism	6 (75)	0	2 (25)	0	0
Infections	3 (37.5)	2 (25)	2 (25)	1 (12.5)	0
Gastroenterological symptoms related to sunitinib:					
Abdominal pain	4 (50)	1 (12.5)	3 (37.5)	0	0
Diarrhoea	0	4 (50)	4 (50)	0	0
Vomiting	7 (87.5)	0	1 (12.5)	0	0
Nausea	3 (37.5)	5 (62.5)	0	0	0
Constipation	7 (87.5)	1 (12.5)	0	0	0

centration before activating the sunitinib therapy, the expression of somatostatin receptors, the secretional status of the tumour, or the number of therapeutic lines applied before sunitinib as opposed to the quality of the therapeutic lines (SSA, PRRT, chemotherapy).

Haematological complications (mainly neutropenia) were strictly related to the past chemotherapy treatment and increased the risk of infections during the sunitinib treatment (62.5%). The other toxicities due to this therapy were related to individual characteristics of the patients (e.g. a concomitant disease or clinical implications of the von Hippel-Lindau syndrome) as well as with the tumour parameters (e.g. infiltration of vessels and nerve plexuses, location of the tumour in the head of the pancreas). Simultaneous administration of SSA with tyrosine multikinase inhibitor did not affect the exacerbation of the treatment tolerance, its effects or the deterioration in quality of life [17, 24]. This observation is important from the clinical point of view, particularly in the light of the recent findings of the CLARINET study that confirm the antiproliferation action of lanreotide in PNENs [6].

In the first clinical analyses concerning sunitinib safety in PNENs, published in 2008, the therapy encompassed 109 patients, with 107 of them receiving sunitinib (including: carcinoids — 38.3%, and pancreatic tumours — 61.6%). Sunitinib was administered in the dose of 50 mg/day in a pattern of six weeks (four weeks of therapy with two weeks of interval). Among the PNENs patients, objective response rate (ORR) was achieved in 16.7% of the patients, stabilisation of the disease in 68%; slightly worse results were achieved in the group of carcinoids in terms of response, while comparable in terms of the median progression free survival time (7.7 months *vs.* 10.2 months). Over 80% of the patients in both groups survived for one year. 88.8% manifested fatigue syndrome induced during the treatment with the tyrosine kinase inhibitor, including over 27% in the 3rd degree of NCI CTC AE [18, 20]. Similar effects were indicated in the study by Raymond et al. [17], where sunitinib therapy with a dose of 37.5 mg daily encompassed 171 patients, obtaining the PFS rate of 11.4 months *vs.* 5.5 months in the placebo group [HR 0.42; 95% CI, 0.26–0.66; P < 0.001], which is confirmed in our small group of patients with the same PFS 11.5 months. Treatment efficiency in the form of objective response rate was obtained in 9.3% (95% CI, 3.2–15.4), but failed to be obtained in the placebo group. The most common adverse events related to the drug included: diarrhoea (59%), nausea (45%), vomiting (34%), malaise (34%), fatigue syndrome (32%), neutropenia (29%), abdominal pain (28%), arterial hypertension (26%), palmar-plantar erythrodysesthesia (23%), cachexia (22%), mucosal damage (22%), bleeding (20%), thrombocytopenia (17%) and others, similar to the findings of the Raymond study [17].

Conclusions

Sunitinib malate proved to be a fairly well tolerated and effective therapeutic option in patients with well-differentiated NETG1 and NETG2 neuroendocrine pancreatic tumours, when used in the 2nd and subsequent lines of treatment, irrespective of the number of previously administered pharmacological or radioisotope treatments. Further studies are needed to determine the optimal safe sequence of treatment methods.

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