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Complications of Treatment

Practical management of sunitinib toxicities in the treatment of pancreatic neuroendocrine tumors

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ABSTRACT

Pancreatic neuroendocrine tumors (pNETs) are infrequent malignancies which manifest in both functional (hormone-secreting) and more commonly non-functional (non-secreting) forms. The oral multitargeted tyrosine kinase inhibitor sunitinib and mammalian target of rapamycin (mTOR) inhibitor everolimus are approved as targeted therapies for patients with well-differentiated, non-resectable disease and evidence of disease progression. The recent approval of sunitinib for the management of advanced pNET is based on a continuous daily dosing (CDD) schedule that differs from the intermittent 4 weeks on/2 weeks off (4/2) schedule approved for sunitinib in advanced renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). Therefore, although clinicians may be familiar with therapy management approaches for sunitinib in advanced RCC and GIST, there is less available experience for the management of patients with a CDD schedule. Here, we discuss the similarities and differences in the treatment of pNET with sunitinib compared with advanced RCC and GIST. In particular, we focus on the occurrence and management of sunitinib-related toxicity in patients with pNET by drawing on experience in these other malignancies. We aim to provide a relevant and useful guide for clinicians treating patients with pNET covering the management of events such as fatigue, mucositis, hand–foot syndrome, and hypertension.

Introduction

Pancreatic neuroendocrine tumors (pNETs) are generally regarded as infrequent malignancies. However, the reported incidence of pNETs is increasing, with Surveillance, Epidemiology and End Results (SEER) records showing a clear upward trend for the period 1973–2003 [1]. In the US alone, a conservative estimate of prevalence in 2004 was 32,353 individuals [1]. pNETs are associated with favorable survival relative to other tumor types. For individuals with well-differentiated (grades 1 and 2) regional disease, the median survival is 9.25 years, with 5-year survival rates of 62%; for those with metastatic disease, these values fall to 2.25 years and 27%, respectively [1].

pNETs are divided into two groups (functional and non-functional) according to whether or not the tumor secretes a biologically active substance. pNETs are predominantly non-functional and thus are not associated with hormone hypersecretion syndromes. Diagnosis of such tumors is often serendipitous at early stages; advanced-stage diagnosis usually stems from symptoms arising from tumor bulk. Of patients with advanced disease, 60–85% have liver metastases at diagnosis [2,3]. Where surgical resection is possible, it is the treatment option of choice for both locoregional and metastatic disease according to the National Comprehensive Cancer Network (NCCN) treatment guidelines [3]. Where disease is non-resectable and patients are symptomatic, or have clinically significant tumor burden or progressive disease, treatment options include hepatic regional therapy, cytoreductive surgery, cytotoxic chemotherapy, and somatostatin analogues to control symptoms arising from hormone hypersecretion (NCCN treatment guidelines) [3]. The development of targeted agents for pNET has primarily focused on the vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR). Sunitinib and everolimus, targeting the VEGF/VEGFR and mTOR pathways, respectively, have recently been approved for the treatment of non-resectable pNET. Although conventional tumor response rates (per Response Evaluation Criteria in Solid Tumors; RECIST) are low, these agents are associated with significant

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improvements in progression-free survival (PFS) [3] and both agents have been added to the standard armamentarium for the treatment of non-resectable pNET in the clinical setting. At the time of its approval in the European Union in December 2010, sunitinib represented the first new treatment option approved for pNET for 20 years; approval by the US Food and Drug Administration followed in May 2011 [4,5].

Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor of VEGFRs, platelet-derived growth factor receptors (PDGFRs), KIT, FLT3, CSF-1R, and RET [6] approved in the US and EU for the treatment of progressive, well-differentiated pNET in patients with unresectable locally advanced or metastatic disease. Phase II results indicating that sunitinib could provide benefit to patients with pNET [7] were confirmed by a placebo-controlled phase III trial conducted in 171 patients with well-differentiated, malignant pNET. This trial was discontinued early after an independent data review showed greater mortality (21 vs. 9 deaths) and inferior PFS (median 5.5 months vs. 11.4 months) in the placebo group [8]. The hazard ratio (HR) for progression or death with sunitinib was 0.42 (95% confidence interval [CI] 0.26–0.66; $p < 0.001$); the HR for death alone was 0.41 (95% CI 0.19–0.89; $p = 0.02$) in the first reported analysis. Similar results were reported from a retrospective analysis of patients treated in routine clinical practice [9].

Sunitinib is also approved for the treatment of metastatic renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST) after imatinib therapy. A difference in sunitinib dosing schedules for pNET and RCC/GIST (see below), together with the potential impact of disease-specific co-morbidities in pNET, provides a rationale for the development of toxicity management guidelines specifically for the various healthcare providers treating patients with pNET. Furthermore, as a new treatment modality for pNET directed against a new target, the side-effect profile of sunitinib differs substantially from established pNET therapies and may be unfamiliar to healthcare providers who have previously treated patients with established cytotoxic agents. Specific guidance on sunitinib therapy management in pNET will thus be of benefit and interest to all multidisciplinary team members who participate in patient care, including medical oncologists, endocrinologists, gastroenterologists, nurses, dermatologists, podiatrists, and nutritionists. However, as sunitinib has longer-standing approval for RCC and GIST, the relative wealth of experience of side-effect management in these tumor types, from both clinical trials and clinical practice, will be drawn upon as a rich initial starting point for the optimization of disease management in patients with pNET.

Sunitinib dosing and titration

The recommended dosing regimen for pNET is 37.5 mg taken orally once daily continuously without a scheduled off-treatment period (continuous daily dosing [CDD]) [10]; this differs from the dosing regimen for GIST and advanced RCC, which is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

Factors impacting on the development of the CDD dosing regimen included efficacy, safety, flexibility of dosing, and convenience. Based on similar pharmacokinetic parameters, specifically mean dose-corrected trough concentrations, for sunitinib and its active metabolite SU12662 on a CDD schedule in a phase II study of patients with GIST [11] and on Schedule 4/2 in a phase III trial in the same tumor type [12], a CDD of 37.5 mg might reasonably be expected to deliver the equivalent dose-intensity over a 6-week period and same overall plasma exposure without intervals off treatment. Furthermore, data from RCC studies suggested an off-treatment rebound in putative pharmacodynamic biomarkers (including plasma VEGF and plasma sVEGFR-2) [13,14]. In contrast, on-treatment changes in levels of these soluble proteins were sustained throughout treatment on a CDD schedule [15]. Thus, there was a theoretical possibility that a CDD regimen might offer an efficacy advantage. Recently, Schedule 4/2 and CDD have been directly compared in the renal EFFECT trial. This trial reported that, for the treatment of RCC, there was no significant difference in the incidence of commonly reported adverse events (AEs), but there was a statistically significant difference in favor of Schedule 4/2 in 'time to deterioration', a composite endpoint of death, progression, and disease-related symptoms [16]. The investigators concluded that adherence to the approved 50 mg dose administered on Schedule 4/2 remains the treatment goal for patients with RCC.

The conclusion from the renal EFFECT trial that adherence to dose and schedule is the key therapy goal is fundamental to maintaining treatment efficacy with sunitinib. Although the sunitinib prescribing information recommends dose interruptions and/or dose adjustments of 12.5 mg increments based on individual safety and tolerability [10], it is preferable to avoid deviating from the approved dose and schedule where possible. This approach is underpinned by results of a meta-analysis of sunitinib trial data, mainly from patients with RCC or GIST, which showed that higher exposure to sunitinib was associated with longer time to tumor progression, longer overall survival (OS), a higher probability of objective response, and greater tumor shrinkage [17]. In the same analysis, increased exposure to sunitinib was also associated with increased incidence of specific AEs, namely fatigue, neutropenia, and diastolic hypertension. Moreover, it is becoming apparent that specific AEs may actually be biomarkers of treatment effect, as might be expected for on-target toxicities arising from the mode of action of sunitinib [18]. Although emerging biomarker data pertain to RCC and GIST and require prospective confirmation [19–24], these data provide a compelling rationale for managing AEs in a proactive and timely manner in order to maintain dose intensity and compliance with therapy in the long term, thereby allowing efficacy to be maintained.

In accordance with prescribing information for sunitinib, a dose reduction should be considered where sunitinib is co-administered with strong CYP3A4 inhibitors or grapefruit juice, and a dose increase may be necessary if patients are receiving CYP3A4 inducers.

Adverse-event profile

In the pNET phase III trial, the most frequently occurring AEs in patients treated with sunitinib 37.5 mg/day on a CDD schedule were diarrhea (59% of patients), nausea (45%), asthenia (34%), vomiting (34%), and fatigue (32%), mainly of grade 1 or 2 severity, although diarrhea, asthenia, and fatigue were of grade 3 or 4 severity in 5% of patients [8,10,16]. Events occurring at similar frequencies in patients receiving sunitinib and those on placebo were vomiting (34% vs. 30%), asthenia (34% vs. 27%), and fatigue (32% vs. 27%). In the sunitinib arm, neutropenia was reported as a grade 3/4 AE in 12% of patients and hypertension was the most frequently reported grade 3/4 non-hematologic AE (10%) [8]. This frequency pattern of AEs is consistent with that seen in earlier trials of sunitinib (CDD) in a variety of tumor types [11,15,25]. It is also similar to the AE profiles reported from a phase II study of carcinoid and pNETs (Table 1) [7,8] and from the RCC phase III trial [10], both of which utilized Schedule 4/2 dosing, as well as the randomized phase II RCC study that directly compared Schedule 4/2 and CDD [16].

Discontinuation due to AEs occurred in 15% of patients who received sunitinib in the phase III pNET trial; the AEs most frequently associated with discontinuation were fatigue (4%), diarrhea (2%), and cardiac failure (2%) (Table 2) [7,8,11,15,16,25].

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Table 1
Adverse events occurring in >15% of patients with pNET receiving sunitinib on a CDD schedule in the phase III trial, and patients with carcinoid or pNET receiving sunitinib administered according to Schedule 4/2 in the phase II trial.

Event	pNET Phase III CDD[a] sunitinib *N* = 83 [8]			Carcinoid and pNET Phase II Schedule 4/2[b] sunitinib *N* = 107 (pNET *n* = 66) [7]		
	All grades, *n* (%)	Grade 1 or 2, *n* (%)	Grade 3 or 4, *n* (%)	All grades, *n* (%)	Grade 1 or 2, *n* (%)	Grade 3 or 4, *n* (%)
Diarrhea	49 (59)	45 (54)	4 (5)	70 (65)	65 (61)	5 (5)
Nausea	37 (45)	36 (43)	1 (1)	57 (53)	51 (48)	6 (6)
Asthenia	28 (34)	24 (29)	4 (5)	NR	NR	NR
Vomiting	28 (34)	28 (34)	0	32 (30)	25 (23)	7 (6)
Fatigue	27 (32)	23 (28)	4 (5)	95 (89)	69 (64)	26 (24)
Hair-color changes	24 (29)	23 (28)	1 (1)	34 (32)	34 (32)	0
Neutropenia	24 (29)	14 (17)	10 (12)	90 (84)	54 (50)	36 (34)
Abdominal pain	23 (28)	19 (23)	4 (5)	NR	NR	NR
Hypertension	22 (26)	14 (17)	8 (10)	17 (16)	6 (6)	11 (10)
HFS	19 (23)	14 (17)	5 (6)	18 (17)	16 (15)	2 (2)
Anorexia	18 (22)	16 (19)	2 (2)	30 (28)	27 (25)	3 (3)
Stomatitis	18 (22)	15 (18)	3 (4)	34 (32)	32 (30)	2 (2)
Dysgeusia	17 (20)	17 (20)	0	52 (49)	52 (49)	0
Epistaxis	17 (20)	16 (19)	1 (1)	NR	NR	NR
Headache	15 (18)	15 (18)	0	25 (23)	24 (22)	1 (1)
Insomnia	15 (18)	15 (18)	0	11 (10)	11 (10)	0
Rash	15 (18)	15 (18)	0	28 (26)	27 (25)	1 (1)
Thrombocytopenia	14 (17)	11 (13)	3 (4)	73 (68)	64 (60)	9 (8)
Mucosal inflammation	13 (16)	12 (14)	1 (1)	11 (10)	8 (8)	3 (3)
Weight loss	13 (16)	12 (14)	1 (1)	NR	NR	NR
Constipation	12 (14)	12 (14)	0	NR	NR	NR
Back pain	10 (12)	10 (12)	0	NR	NR	NR

CDD, continuous daily dosing; HFS, hand–foot syndrome; NR, not reported; pNET, pancreatic neuroendocrine tumor.

[a] Raymond et al. [8] adverse events were defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Events listed are those of any grade that occurred in >15% of patients in either the sunitinib arm (shown above) or the placebo arm (please refer to Raymond et al.) [8].

[b] Kulke et al. [7] adverse events were defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0. Events listed are those of any grade that occurred in >10% of patients and also occurred in the phase III study in either the sunitinib or the placebo arm. Adverse events occurring in >15% (all grades) of the patients in the phase II study, but not reported in the phase III study, were: skin discoloration (36.5%), glossodynia (33.6%), myalgia (32.8%), oral pain (24.3%), flushing (19.6%), dyspepsia (18.7%), paresthesia (17.8%), and periorbital edema (15.9%).

Table 2
Dose intensity, dose adjustments, and discontinuations related to safety in studies of sunitinib.

Study	No. of patients	Dose intensity (%)	Dose reductions (%)	Dose interruptions (%)	Discontinuation due to AEs (%)
CDD (37.5 mg daily) in various cancers					
George et al. [11] Phase II GIST	60	NR	23	77	7
Escudier et al. [15] Phase II RCC	107	93	43	65	15
Novello et al. [25] Phase II NSCLC	47	NR	29.8	36.2	25.5
Raymond et al. [8] Phase III pNET	86 sunitinib	91.3	31	30	17
	85 placebo	100.6	11	12	8
Motzer et al. [16] Phase II RCC	143	78	43	62	17
Schedule 4/2 in various cancers					
Motzer et al. [16] Phase II RCC	146	91	36	65	16
Kulke et al. [7] Phase II	107 (41 carcinoid and 66 pNET)	NR	47.7	62.6	10.2

AE, adverse event; GIST, gastrointestinal stromal tumor; NR, not reported; NSCLC, non-small cell lung cancer; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma.

Overall, 31% of patients required at least one dose reduction. Rates of discontinuations due to AEs ranged from 7% to 25.5% across the various tumor types in which CDD of sunitinib has been studied (Table 2) [7,8,11,15,16,25]. For comparison, 10.2% of patients with carcinoid or pNET receiving sunitinib on Schedule 4/2 discontinued due to AEs (Table 2) [7] and very similar discontinuation rates were reported when the two dosing schedules were directly compared in RCC (Table 2) [16].

Management of toxicities

The welcome advent of more efficacious therapies directed against new molecular targets in pNET is associated with a unique, and potentially unfamiliar, range of toxicities. Therapy management for targeted agents poses new challenges for healthcare professionals and, ultimately, for patients. Successful disease management requires a multi-stranded approach incorporating proactive AE prevention, AE management (with vigilant monitoring to allow early intervention and thus the possibility of preventing deterioration), and patient education [26]. We describe methods by which these goals may be achieved for specific toxicities associated with sunitinib. In addition, as a result of the experience of the safety profile of sunitinib in clinical trials, the sunitinib prescribing information recommends that a number of parameters should be monitored at baseline and during sunitinib treatment [10]. We intend to provide guidance for physicians and patients encountering these events in the clinic, outside of the proscriptive environment of clinical trial protocols. As a practical guide to AE management, Table 3 provides 'at a glance' actions and considerations to aid healthcare providers who are unfamiliar with toxicities that may occur during treatment with sunitinib.

Fatigue

Fatigue and asthenia were frequently reported AEs in the pNET phase III trial, occurring at 32% and 34% overall, respectively; rates

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Table 3
Recommended management strategies for key sunitinib-related toxicities by treatment stage and toxicity grade.[a]

Adverse event	Baseline assessment	During therapy	Toxicity grade 1–2[b]	Toxicity grade 3–4[b]
Hypertension				
Action	Measure BP	Monitor BP (may include home monitoring)	BP < 160/<100 (but elevated, i.e. ⩾140 / ⩾90) Vasodilatory antihypertensive agents (e.g., ACE inhibitors and angiotensin II receptor antagonists) are preferred to calcium channel blockers (see below), diuretics and β-blockers	BP ⩾ 160/⩾100 Interrupt sunitinib temporarily until hypertension is under control Grade 3: withhold dose until toxicity is grade ⩽1 or BP has returned to baseline, then resume treatment at the same dose level. If the toxicity recurs with grade 3 severity, reduce the dose by 1 level Grade 4: withhold dose until toxicity is grade ⩽1 or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the clinician
Notes	Actively screen for hypertension and treat as appropriate	If sunitinib is interrupted to enable control of hypertension, treatment may be resumed once BP is appropriately controlled	Avoid CYP4503A4 inhibitors such as diltiazem and verapamil (calcium channel blockers); this is not an issue with the dihydropyridine class of calcium channel blockers [28] Use caution with β-blockers and calcium channel blockers that cause PR elongation	Uncontrolled hypertension is associated with onset of cardiotoxicity Refer to national or institutional guidelines according to local practice
Fatigue				
Action	Establish baseline activity levels	Monitor and grade fatigue	Continue at same dose level	Interrupt sunitinib temporarily until fatigue is grade ⩽1 or has returned to baseline Grade 3: then resume treatment at the same dose level. If the toxicity recurs with grade 3 severity, reduce the dose by 1 level Grade 4: then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the clinician
Notes	Institute preventive measures: adequate nutrition, moderate exercise, counselling regarding lifestyle	Responds to interruption of therapy, if necessary	Consider alternative physical cause (e.g., anemia, thyroid dysfunction, insomnia, dehydration, etc.) or psychological cause (e.g., depression)	
Oral mucositis/stomatitis				
Action	Ensure good oral hygiene	Monitor and grade oral mucositis	Continue at same dose level	Interrupt sunitinib temporarily until mucositis/stomatitis is grade ⩽1 or has returned to baseline Grade 3: then resume treatment at the same dose level. If the toxicity recurs with grade 3 severity, reduce the dose by 1 level Grade 4: then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the clinician
Notes	Consider early use of mouthwashes containing steroids, antibiotics, antifungals or anaesthetics, as appropriate	Mouthwashes containing alcohol should be avoided Hot, spicy or acidic foods may exacerbate symptoms	Advise use of soft toothbrushes and sensitive/pediatric toothpaste Dose reductions are not usually necessary for oral mucositis alone; however, consider interruption or dose modification for multiple toxicities	
Skin rash/hand–foot syndrome				
Action	Skin examination	Re-examine and grade skin toxicity	Continue at same dose level	Interrupt sunitinib temporarily until skin rash/hand–foot syndrome is under control Grade 3: withhold dose until toxicity is grade ⩽1 or has returned to baseline, then resume treatment at the same dose level. If the toxicity recurs with grade 3 severity, reduce the dose by 1 level Grade 4: withhold dose until toxicity is grade ⩽1 or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the clinician
Notes	Patient education is essential: moisturize hands and feet (including the use of urea-based creams [29]), avoid rubbing (e.g., ill-fitting shoes), manicure/pedicure, etc.	Skin toxicity may be reduced by avoiding hot showers, reducing sun exposure, and wearing loose-fitting clothing	May require removal of blisters or use of hydrocolloidal dressings May require strong analgesia (topical or systemic) Monitor for superadded infection which may require antibiotics May require referral to a dermatologist	

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Table 3 (*continued*)

Adverse event	Baseline assessment	During therapy	Toxicity grade 1–2[b]	Toxicity grade 3–4[b]
Diarrhea				
Action	Establish baseline function	Monitor and grade diarrhea	Continue at same dose level	Interrupt sunitinib temporarily until diarrhea is under control Grade 3: withhold dose until toxicity is grade ⩽1 or has returned to baseline, then resume treatment at the same dose level. If the toxicity recurs with grade 3 severity, reduce the dose by 1 level Grade 4: withhold dose until toxicity is grade ⩽1 or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the clinician
Notes	Advice: avoid caffeine, lactose-containing foods, fatty or high-fiber foods and fruits (except pectin-containing fruit [e.g., apples and bananas); keep well hydrated	Consider alternative causes: pancreatic insufficiency (steatorrhea), infection, drugs (e.g., laxatives, antibiotics, etc.)	Oral hydration Oral anti-diarrheals	As above + supportive measures (e.g., intravenous fluids) Consider infective diarrhea and treat appropriately
Hematologic toxicity				
Action	Check baseline blood count	Complete blood counts should be performed at the beginning of each treatment cycle	Continue at same dose level	Grade 3: withhold dose until toxicity is grade ⩽2 or has returned to baseline, then resume treatment at the same dose level. If the toxicity recurs with grade 3 severity, at the discretion of the clinician, reduce the dose by 1 level Grade 4: withhold dose until toxicity is grade ⩽2 or has returned to baseline, then reduce the dose by 1 level and resume treatment
Notes		Additional monitoring if suspicion of infection (e.g., fever, chills, prolonged viral infection, etc.) or bleeding		Consider prophylactic antibiotic treatment if prolonged neutropenia merits Neutropenia with concomitant infection may be treated with granulocyte-colony stimulating factor (NCCN treatment guidelines for prevention and treatment of cancer-related infections) [30]
Thyroid dysfunction				
Adverse event	Baseline assessment	During therapy	Hypothyroidism	Hyperthyroidism
Action	TSH at baseline	Re-check every 12 weeks or symptom-directed	Thyroxine replacement therapy (in line with institutional standard)	Treat hyperthyroidism (in line with institutional standard)
Notes	Additional thyroid tests only as clinically indicated; follow-up based on institutional standard (may include free T4, T3, thyroglobulin)	Aim to keep TSH in normal range	Dose modifications of sunitinib usually not required May require involvement of endocrinologist	

ACE, angiotensin-converting enzyme; BP, blood pressure; NCCN, National Comprehensive Cancer Network; TSH, thyroid-stimulating hormone.

[a] Recommendations are based on information in the study protocol for the placebo-controlled phase III trial of sunitinib in pNET [8], which was based on data from a phase I study of sunitinib [27], and from studies of sunitinib in renal cell carcinoma (except where specifically referenced otherwise).

[b] Toxicity CTCAE v4.0.

of grade 3/4 events were 5% each [8,10]. Four percent of patients receiving sunitinib discontinued due to fatigue. Recent retrospective analyses of data from sunitinib trials in RCC and GIST have linked asthenia and fatigue with improved outcomes, tentatively identifying these AEs as potential biomarkers of sunitinib efficacy [22,31]. Fatigue, often the most limiting toxicity associated with sunitinib treatment, develops during the first month of treatment, with the highest incidence frequently noted after 2–3 months. It should, however, be remembered that clinical presentation of fatigue does not necessarily reflect the underlying cause. Fatigue may be a treatment-induced event *per se*; however, it may also result from confounding side effects (such as hypothyroidism or asthenia), or incidental events (for example, occult tumor hemorrhage and related anemia), underlying disease, or may result from emotional distress or depression, physical distress, or dehydration [32,33]. Fatigue arising from confounding side effects requires management specific to the underlying event; analytical abnormalities indicative of, for example, anemia or hypothyroidism should be corrected, and disease- and treatment-related co-morbidities such as anorexia and cachexia should be closely monitored [32,34]. Key preventative and supportive management approaches are summarized in Table 3. Some patients may require an initial reduction to a 25 mg dose [4], with a number subsequently needing an intermittent dosing schedule at this dose (2 weeks on therapy followed by 1 week off therapy [Schedule 2/1], which has been associated with reduced toxicity in patients with metastatic RCC [35]).

Oral toxicity, stomatitis, and mucositis

Although an overall stomatitis rate of 22% was reported in the phase III pNET trial, treatment with sunitinib is associated with a

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variety of oral disorders; thus, the sunitinib prescribing information presents a composite AE 'stomatitis/oral syndromes' capturing a wider range of relevant AE reporting terms, with dysgeusia reported separately [10]. The rate documented for 'stomatitis/oral syndromes' is 48% with a grade 3/4 rate of 6%, very similar to the rates reported for stomatitis/mucositis for RCC [10]. In contrast to the oral toxicities associated with cytotoxic chemotherapy and arising from local tissue damage and inflammation, those seen with sunitinib appear to stem from functional irritation of the mucosa and the underlying mechanisms are yet to be elucidated [32]. Mucositis often occurs during the first month of treatment, but the highest severity is seen during the second and third months [27]. Symptomatic management of sunitinib oral toxicities is via dietary modification and oral care, with early intervention achieving better control of mucositis (Table 3). As might be expected from the preponderance of grade 1/2 events, dose adjustments/interruptions for oral toxicity are seldom necessary. Dose modification should, however, be employed for more severe toxicities and is associated with rapid symptom relief.

Dermatologic AEs: rash and hand–foot syndrome (HFS)

Several dermatologic AEs were among the frequently reported AEs in the phase III pNET trial. Hair color changes occurred in 29% of patients (1% grade 3/4), palmar–plantar erythrodysesthesia (hand–foot syndrome; HFS) in 23% (6% grade 3/4), rash in 18% (0% grade 3/4), and dry skin in 15% of patients (0% grade 3/4). The dermatologic effects of sunitinib are potentially explained by deregulation of signaling pathways; a paracrine feedback loop initiated by VEGF links keratinocytes and endothelial cells, and stromal secretion of PDGF from matrix fibroblasts may play a role in the biology of the skin dermis (reviewed by Aparicio-Gallego et al) [18]. It is also possible that VEGF may be involved in the formation and repair of skin capillaries or that skin toxicity may arise from the action of sunitinib on the focal adhesion kinase (FAK) pathway (Aparicio-Gallego et al 2011 and references therein) [18]. Hair depigmentation (Fig. 1) may result from inhibition of c-KIT signaling as this pathway is integral to melanocyte proliferation, differentiation, and pigment production [32,36,37].

As with sunitinib in RCC, in pNET skin rashes rarely require dose reduction and symptoms tend to decrease over time. Measures to manage rash are outlined in Table 3.

Hand–foot syndrome, characterized by alterations in the dermal vasculature and minor endothelial changes at grades 1 and 2, and more extensive vascular changes combined with layers of keratinocyte necrosis and intra-epidermal cleavage at grade 3 and 4, can be a painful and debilitating condition. A number of possible underlying mechanisms have been identified (reviewed by Kollmannsberger and colleagues) [32]. However, it seems likely that sunitinib disrupts endothelial cell survival and repair mechanisms and, when these mechanisms are inhibited in the high-pressure areas of the hands and feet (which are subject to routine daily trauma through activities such as walking and hand washing), these areas fail to repair and develop the characteristics of HFS [32,36].

Patient education regarding HFS is perhaps more important than for other sunitinib-associated AEs. Ideally, patients should be encouraged to take care of their hands and feet from the onset of treatment, including the use of urea-based creams [29] (Table 3).

Fig. 1. Example of hair and skin depigmentation following chronic treatment with sunitinib.

Gastrointestinal symptoms

Gastrointestinal (GI) toxicities were prominent among patients treated with sunitinib in the phase III pNET trial; however, little is known about the causative mechanism [18,32]. Although the majority of patients treated on this trial experienced diarrhea (59%), for most patients the severity of diarrhea was mild or moderate; severity increased (grade 3/4) in only 5% of patients [8,10].

Typically, the onset of sunitinib-associated diarrhea occurs after approximately 3 weeks of therapy and is rarely seen to initiate beyond 6 months. It is sometimes difficult to distinguish sunitinib-associated diarrhea from diarrhea derived from the disease or from that resulting from the somatostatin analogs that are commonly administered to these patients. A number of preventative and supportive measures have been put forward for controlling diarrhea (see Table 3). Clinical experience with sunitinib CDD in pNETs has shown that severe diarrhea rapidly resolves a few days following treatment discontinuation. However, most cases of diarrhea occurring in sunitinib-treated patients with pNET are grade 1–2 and are generally managed successfully by oral hydration and oral antidiarrheal agents. Dose modification is rarely necessary. During the phase III pNET trial, grade 3–4 non-hematologic toxicities triggered treatment interruption until symptoms resolved to grade $\leqslant$1, with reintroduction of sunitinib either at the same dose level (reinforcing patient education for grade 3 toxicity) or at the lower dose level of 25 mg.

Nausea and vomiting occurred at frequencies of 45% and 34%, respectively, in the phase III pNET trial but, as with diarrhea, these AEs were generally mild or moderate in severity and grade 3/4 events were rare [4,8,10]. As with fatigue, nausea and vomiting in pNET are not necessarily related to sunitinib treatment. When treating nausea and vomiting in patients with pNET, co-morbidities such as altered levels of electrolytes arising from diarrhea (e.g., hyponatremia, hypokalemia), fatigue, and hyporexia should be considered and treated as appropriate. Preventative measures for nausea and vomiting are dietary: a bland diet is recommended, with small portions taken frequently, and with a higher than customary intake of fluids. Spicy, fatty, and salted foods should be avoided. Early treatment with anti-emetic agents such as metoclopramide or alizapride is desirable, while administration of proton pump inhibitors will protect the mucosa [33,34,36]. However, as proton pump inhibitors may interfere with sunitinib absorption and metabolism, they are not recommended to be administered within 2 h of sunitinib [34]. Ondansetron and other related drugs are not routinely recommended for the treatment of vomiting induced by sunitinib since they may interfere with the metabolism of sunitinib through the CYP3A4 pathway. Dose adjustments should seldom be necessary for nausea and vomiting but, as for diarrhea, severe events should result in dose adjustments as they did in the phase III trial.

Thyroid dysfunction

Hypothyroidism was reported in 6/83 patients (7%) receiving sunitinib in the phase III pNET trial; all cases were grade 1/2 in

severity [8]. Although the mechanisms by which sunitinib modulates thyroid function are yet to be defined, candidates include antiangiogenic effects, inhibition of iodine uptake, destructive thyroiditis, thyroid peroxidase inhibition, and reduction of vascularity by capillary regression and/or constriction [18,36,38]. For sunitinib in RCC, hypothyroidism was reported as early as 1–2 weeks after initiation of therapy and the incidence tended to increase over time [32]. In addition, a recent meta-analysis reported a relationship between longer duration of sunitinib treatment and increased incidence of all-grade hypothyroidism [39]. Based on our clinical experience, we suspect that the onset of hypothyroidism in pNET treated with sunitinib is later than is seen with the higher dose used to treat RCC; data are, however, currently lacking.

A number of authors have proposed algorithms for treating hypothyroidism in patients with RCC [32,38,40], which concur that regular surveillance of thyroid function is warranted from baseline onwards. Overt hypothyroidism should be treated with hormone replacement therapy utilizing typical doses of levothyroxine to normalize concentrations of thyroid-stimulating hormone (TSH) and resolve symptoms. Asymptomatic subclinical hypothyroidism should be monitored and treated if hypothyroidism becomes overt [32,38]. For patients with pNET, we recommend that thyroid function tests are checked at least every 12 weeks unless concomitant symptoms (e.g., fatigue) suggest thyroid dysfunction (Table 3). Sunitinib dose modifications for thyroid dysfunction are generally not required; the condition is usually treated with hormone replacement therapy and the dose maintained. However, should dose modification be implemented for grade 3 or 4 events, hormone replacement therapy should be closely monitored in order to avoid hyperthyroidism and possible cardiovascular events.

Neutropenia

As has been noted in patients with RCC [18], most patients with pNET receiving sunitinib develop hematologic toxicity. Neutropenia is the most commonly observed hematologic toxicity and is the one associated with the highest incidence of grade 3/4 severity [10]. The phase III trial in patients with pNET reported neutropenia as an AE in 29% of patients receiving sunitinib according to the CDD schedule, with 12% experiencing grade 3/4 severity [8]. Despite identification of this as laboratory finding, there were no reported cases of febrile neutropenia [8]. For sunitinib in RCC, neutropenia is reported as occurring mainly during the first treatment cycle, without progression in later cycles, and is usually short-lived [36].

Neutropenia arising from sunitinib treatment of patients with pNET appears to be linked to neutrophil margination, rather than true neutropenia. This conclusion is based on observed cases of neutrophil levels returning to the normal range within 24 h of corticosteroid administration.

Table 3 outlines preventative measures and treatments for hematologic toxicity.

Cardiovascular events and hypertension

Hypertension was experienced by 26% of patients with pNET receiving sunitinib in the phase III trial; 10% of patients had events of grade 3/4 severity [8,10]. Retrospective analyses of experience from treatment of RCC and GIST has demonstrated that hypertension is an on-target effect of sunitinib associated with improved clinical outcomes. The incidence of hypertension-related AEs is generally low and manageable [19,20]. Hypertension is a prominent class-effect AE associated with VEGF-1 targeted treatment (tyrosine kinase inhibitors and bevacizumab) [20,41]. Recent guidelines for the management of hypertension in patients treated with anti-angiogenic agents concluded that dose reductions, schedule changes, and treatment discontinuations are rarely necessary, with the majority of patients well controlled with one or two antihypertensive medications [41]. We have also found this to be the case in patients with pNET treated with sunitinib. In patients with RCC, Larochelle and co-workers noted that the need for antihypertensive therapy is dictated by the magnitude of the rise in blood pressure, the underlying cardiovascular status of the patient, and additional risk factors that may be present [41]. Furthermore, cardiovascular damage is not usually associated with short-term increases in blood pressure [41]. All of these key points also pertain to patients with pNET treated with sunitinib.

Preventive and supportive measures are summarized in Table 3. Antihypertensive therapy should be closely monitored during sunitinib dose adjustment in order to avoid the induction of hypotension.

QT-prolongation. Sunitinib has been associated with cardiovascular events when used to treat patients with RCC or GIST [10,42,43]. Only hypertension was reported as frequently occurring in the pNET study [8]. However, the sunitinib prescribing information states that sunitinib has been shown to prolong the QT interval in a dose-dependent manner, which may lead to an increased risk of ventricular arrhythmias including torsade de pointes (observed in <0.1% of sunitinib-exposed patients) [10]. Sunitinib should therefore be used with caution in patients with a history of QT interval prolongation, those taking antiarrhythmics, or those with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Periodic monitoring (electrocardiograms and electrolytes [magnesium, potassium]) should be considered and additional monitoring for signs and symptoms of congestive heart failure (CHF) employed. The dose of sunitinib should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline [10].

Thromboembolic events. These were not reported in patients treated with sunitinib in the phase III pNET trial. However, should these events be encountered, they have previously been successfully treated with low molecular weight/subcutaneous heparin for periods of 3–6 months without bleeding complications. Maintenance or interruption of sunitinib administration during treatment is at the discretion of the treating physician, but should be employed for patients in cardiorespiratory compromise with reintroduction at the same dose level. Sunitinib should, however, be withdrawn for life-threatening events. Oral anti-vitamin K should be avoided during heparin treatment as it interacts with both sunitinib and heparin. Treatment of asymptomatic pulmonary embolism should be on a patient-by-patient basis, balancing risks and benefits, and be agreed in consultation with the patient.

Discussion

The importance of adhering to therapy, in terms of dose, schedule and duration of treatment, cannot be overstated. Both patient and physician have key roles to play in achieving this important goal: physicians in managing side effects to minimize the burden imposed on patients, and patients in persevering with therapy and working with physicians on therapy management despite underlying disease burden. In fact, this is an oversimplification as the treating physician does not, or rather should not, act alone. Achieving the best supportive care for pNETs requires a multidisciplinary team. The multifactorial nature of this disease, with the possibility of the appearance of carcinoid syndrome, diarrhea, vomiting, flushing, skin rash, palpitations, and other symptoms arising from tumor release of various active peptides, makes the participation of different medical specialties imperative. In addition, several of the more common side effects of sunitinib benefit from specialist care. Medical oncologists, oncology nurses,

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endocrinologists, gastroenterologists, dermatologists, cardiologists, nutritionists, and podiatrists are among the specialties that bring essential expertise to the care of patients with pNET receiving sunitinib.

Patients must also be fully committed to their treatment goals; patient education is key to achieving this and also provides some measure of familiarity in what must be a new and worrying situation. It is also reasonable to expect that patients who understand the importance of remaining on therapy at full dose and who are knowledgeable about the likely side effects and how they can be treated or avoided will be better placed to work with the medical team to optimize their duration and experience of therapy. Furthermore, although data are not currently available in pNET, preliminary data in RCC and GIST suggest that certain AEs may function as biomarkers of sunitinib treatment effect [21–23,31,44,45], and may be viewed by the patient as positive indicators of treatment benefit. Patients are likely to be encouraged if they are made aware that, unlike conventional chemotherapy, AEs with sunitinib tend to improve over time rather than worsen. From another perspective, patient education regarding the importance of adhering to dose and schedule is also critical as sunitinib is a self-administered agent [34].

Another aspect that should be considered in the practical management of AEs is that sunitinib side effects fall into two categories:

(1) those that might limit the dose (e.g., asthenia, HFS) vs.
(2) those that are potentially preventable/treatable (diarrhea, hypertension, hypothyroidism).

Potentially dose-limiting toxicities are difficult to manage preventatively/treat and, should the toxicity become severe, are thus more likely to require dose modification/interruption. Patients who require dose reduction often continue to derive benefit from treatment. If, however, tumor progression occurs during the first 3 months of treatment at the reduced dose, dose re-escalation with the intent to re-control the disease via optimization of drug exposure should be considered. Preventable/treatable toxicities should be managed with the intention to maintain dose and schedule as far as possible while also maintaining quality of life. For example, analysis of patient-reported outcomes data from the phase III pNET trial showed that throughout the 10-cycle assessment period there was no difference between the placebo and sunitinib treatment groups for global health-related quality of life; cognitive, emotional, physical, role, and social functioning; or in other symptoms and scales with the single clinically significant exception of diarrhea [8], a toxicity that is both preventable and manageable without dose adjustment. To our knowledge, this type of analysis has not been conducted for any other targeted agent evaluated for the treatment of pNET.

In addition to optimizing sunitinib therapy with respect to toxicity management (the scope of this review), future studies may identify other ways to optimize therapy, for example, by further monitoring pharmacokinetics or evaluating pharmacodynamic endpoints (e.g. on-target adverse events or biochemical markers). One such study, an international open-label trial of the efficacy and safety of sunitinib in patients with progressive, well-differentiated pNET (EudraCT, 2011-004363-74) is recruiting patients (planned enrollment, $n = 80$), and, as part of its secondary outcomes (primary endpoint, PFS), will assess potential relationships between plasma drug concentrations and selected safety, biomarker, and efficacy endpoints. The insights gained from the approaches to AE management established in the treatment of RCC and GIST are a valuable resource and should be used to inform management strategies in pNET. However, in administering a continuous daily dose of sunitinib to patients with pNET, physicians must be vigilant and continue to optimize care of these patients as we gain greater experience with this dosing regimen. Ideally, we should aspire to personalizing therapy and therapy management, not only for sunitinib but other targeted therapies, such as everolimus and, indeed, chemotherapy and radionuclide therapy. This could be achieved by identifying biomarkers not only for a better clinical outcome, but also for predicting toxicity. This is not an unrealistic goal; there are already indications that germ-line polymorphic variants have the potential to predict both lack of response and toxic effects in patients with RCC treated with sunitinib [46]. In the fullness of time, it is to be hoped that advances of this type will allow us to select the best treatment options for both efficacy and experience of therapy for our patients.

Conflict of interest statement

JWV has received honoraria from Pfizer, Novartis, Keocyt and Ipsen, and institutional grant funding from Novartis, Keocyt and Pfizer. SF has received honoraria from Pfizer and Novartis (personal, compensated). RAH has served as an advisor for Novartis, Bayer, Lilly, and Celgene. EG has served as an advisor and given lectures for Pfizer, Novartis and Ipsen. ER has received consulting fees and research grants from Pfizer, Novartis and Ipsen (personal, compensated).

Author contributions

All persons listed as authors contributed to preparing the manuscript and meet International Committee of Medical Journal Editors (ICMJE) criteria for authorship. JWV proposed the concept for the manuscript.

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