Practical management of toxicities associated with targeted therapies for advanced gastroenteropancreatic neuroendocrine tumors

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Abstract	Neuroendocrine tumors are heterogeneous, rare malignancies that arise most frequently in the gastroenteropancreatic tract (GEPNET). The therapeutic armamentarium for the treatment of GEPNETs has expanded significantly over the last two decades, however the ideal sequencing strategy remains controversial. As this disease may be relatively slow-growing, patients are expected to be treated for longer periods, so that even mild toxicities can influence quality of life, compliance and outcome in the long run. Prospective data on optimal adverse event management are lacking and recommendations are largely based on expert opinion and drug prescribing information. This review summarizes practical recommendations for toxicity management associated with the most commonly used GEPNET treatment options and stresses important focus points for future clinical trials.

Keywords Neuroendocrine tumor, somatostatin analogue, peptide receptor radionucleotide therapy, interferon-α, everolimus, sunitinib, toxicity management

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Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors arising from the diffuse endocrine system with a diverse range of functional and behavioral characteristics. NENs most frequently originate within the gastroenteropancreatic system (60-70%) and bronchopulmonary tract (25%). They are historically regarded as infrequent malignancies, with an incidence of 2.53/100,000/year as reported by the RARECARE working group [1]; however, both incidence and prevalence appear to be rising in recent decades [2,3]. The 2017 WHO classification of tumors of endocrine organs has recently been published to provide us

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with an update on the classification of pancreatic NENs [4], but it is likely to be implemented in all NENs in the near future. It now splits up NENs according to histological features and measurement of a proliferative marker index, the Ki-67 (%). Well-differentiated neuroendocrine tumors (NETs) are clearly distinguished from poorly-differentiated neuroendocrine carcinomas (NECs), the latter being characterized by a small-cell or large-cell histological pattern, aggressive clinical behavior and a very high Ki-67, usually around 70%. Well-differentiated NETs are further subdivided according to the Ki-67 into low-grade G1 tumors (Ki-67 <3%), intermediate-grade G2 (Ki-67 between 3-20%) and a new subgroup, the well-differentiated high-grade G3 NETs with a Ki-67 >20%, often around 40%.

The most common primary sites for gastroenteropancreatic neuroendocrine tumors (GEPNETs) are stomach, appendix, small intestine, rectum, pancreas and colon. Patients may present either with symptoms provoked by hormonal hypersecretion (30% of cases) or, if non-functional, by symptoms of local growth (mass, obstruction, or bleeding). The most prevalent functional syndrome is the carcinoid syndrome, covering a spectrum of symptoms such as diarrhea, flushing, wheezing and valvular heart disease (carcinoid heart disease). Extension beyond the primary tumor usually involves locoregional lymph nodes and more than half of the patients present with distant metastases at diagnosis. The most frequent metastatic site is the liver, followed by peritoneal, bone, lung, and brain metastases. Rarely, metastases can be seen in the heart, the breast, or the skin.

Balancing risks and benefits in GEPNET treatment

Thorough clinical assessment (symptoms, potential distinct functional syndromes, patient characteristics), together with primary tumor location and delineation of the tumor's grade and TNM stage as well as its somatostatin receptor (SSTR) expression profile, will guide treatment decision-making in these patients. In the advanced setting, treatment aims at controlling tumor growth and symptoms, while preserving and improving quality of life. As this disease may be relatively slow-growing, patients are expected to be treated for longer periods; thus, even mild toxicities can influence quality of life, compliance and outcome in the long run.

Surgery represents the only potentially curative option in this disease. Aggressive surgical strategies, such as *en-bloc* resection of primary tumor and metastases or even liver transplantation in highly selected cases, are to be considered when judging therapeutic options. Locoregional techniques, such as ablation, chemo- and/or radio-embolization and stereotactic body radiation therapy are often applied to treat metastases.

Current targeted therapy options for advanced GEPNETs include somatostatin analogues (SSAs), interferon (IFN)-α, peptide receptor radionucleotide therapy (PRRT) and the molecular targeted agents everolimus and sunitinib. Remarkably, none of these systemic therapies can be graded as meaningfully clinically beneficial according to the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) [5].

This review summarizes practical recommendations for toxicity management associated with these treatments. Cytotoxic chemotherapy remains the mainstay of advanced NEC treatment and can be a treatment option in advanced pancreatic NETs (pNETs); however, its specific adverse event management lies beyond the scope of this article.

SSAs

Most NETs express several SSTRs at high levels, with SSTR2 acting as the predominant subtype [6]. However expression levels and predominant subtype can vary between NET tumor types [7]. Somatostatin is a natural polypeptide playing an inhibitory role in pituitary, pancreatic and gastrointestinal (GI) hormone secretion, through its high affinity binding to all five SSTR subtypes (SSTR1-5). Its therapeutic use is limited by a very short circulation half-life of around 2 min. This led to the development of synthetic SSAs with longer half-lives, initially intended to palliate hormonal symptoms in functional GEPNETs.

Octreotide and lanreotide are synthetic octapeptides with high affinity for SSTR2 and moderate affinity for SSTR5. Octreotide was the first to be approved in 1988 for the treatment of hormonal syndromes and has a half-life of 1.5-2 h. It needs to be injected subcutaneously at a dose of 150-500 μg, 3-4 times a day. Octreotide long-acting repeatable (LAR) depot formulation is a slow-release product incorporating octreotide in microspheres of biodegradable polymer. Octreotide LAR (10, 20, or 30 mg) is typically administered intramuscularly every 4 weeks. Likewise, lanreotide has a depot formulation, called lanreotide autogel, available in 60, 90 and 120 mg, administered deep subcutaneously every 4 weeks. Both octreotide and lanreotide have shown comparable efficacy with regard to symptomatic control rates for carcinoid syndrome in 60-72% and 55-75% of cases, respectively [8-11].

As suggested in preclinical studies, SSAs also exhibit antiproliferative activity in NETs, which is more difficult to explain than their antisecretory effects. SSTR activation on the tumor cells might trigger direct antiproliferative mechanisms through the PI3K/Akt/mTOR pathway, inducing tumor suppressor gene expression, cell cycle arrest and apoptosis [12]. Indirect antiproliferative effects through inhibition of growth factor secretion and antiangiogenic activity have also been suggested [13]. A significant antitumor activity of SSAs was documented in two phase 3, prospective, randomized, placebo-controlled trials. The PROMID trial established the efficacy of octreotide LAR 30 mg every 4 weeks in inoperable or metastatic, functional or non-functional, well-differentiated G1 midgut NETs, especially in patients with resected primary and low hepatic tumor burden [14,15]. The more recent CLARINET study clearly demonstrated the antiproliferative effect of lanreotide autogel 120 mg every 4 weeks in inoperable or metastatic, non-functional, well-differentiated G1 and G2 (Ki-67 <10%) GEPNETs, regardless of tumor burden [16]. Both depot formulations, octreotide LAR and lanreotide autogel, are currently the most used SSAs in clinical practice.

With over 25 years of clinical experience with SSAs, it is safe to state that they are generally well tolerated. GI side effects (diarrhea, steatorrhea, abdominal cramps, flatulence, and nausea) are reported most frequently, but tend to be mild to moderate in severity. Patients should be informed that GI toxicity often decreases in intensity over time or resolves spontaneously during further treatment. Supportive measures should be taken and in case of overt steatorrhea, pancreatic enzymes should be substituted. Altered cholecystokinin secretion causes cholelithiasis in up to 50% of SSA treated GEPNET patients, which can be complicated by bilious attacks, acute cholecystitis or biliary pancreatitis occurrence [17]. Therefore, prophylactic cholecystectomy can be considered in patients receiving SSAs. Octreotide and lanreotide have the potential to alter glucose homeostasis and cause hyperglycemia; however, their exact impact remains debatable. Patients with known glucose intolerance or diabetes mellitus should be instructed to maintain strict blood glucose monitoring nevertheless. Rare side effects include hypoglycemia, hair loss, hypothyroidism, headache, myalgia, acute hepatitis, hyperbilirubinemia, site injection reaction, obstipation, paralytic ileus, bradycardia and QTc prolongation [6]. Higher doses of octreotide LAR (>30 mg/4 weeks) are frequently used in clinical practice to treat refractory carcinoid syndrome symptoms based on small retrospective and prospective studies [18]. Interestingly, none of these studies reported increased toxicity with the use of a higher dosage or a decreased dosing interval [19].

Pasireotide (SOM230) is a next-generation SSA with high affinity for SSTR1-3 and SSTR5, available in a short acting subcutaneous form and an LAR form, injected intramuscularly

every 4 weeks. Its place in GEPNET treatment is currently unclear after a randomized phase 3 trial failed to prove an advantage in carcinoid symptom control when compared to high-dose octreotide LAR [20]. Moreover, despite a safety profile similar to that of first-generation SSAs in general, pasireotide induces a higher frequency and degree of hyperglycemia (11 vs. 0%) [20].

IFN-α

IFNs are cytokines mediating antiviral, antiproliferative and antitumor activities. IFN-α has been used for the treatment of certain solid malignancies, such as melanoma and NETs; however, its mode of action is complex and remains to be further elucidated. It targets tumor cells directly, inducing cell cycle arrest and apoptosis on the one hand and acting through immunomodulation and antiangiogenesis on the other [6]. In the GEPNET indication, IFN-α is usually given as a subcutaneous injection at a dose of 3-5 million units three times a week or, alternatively, as weekly injections of 50-180 μg long-acting pegylated IFN-α. Because of its unfavorable toxicity profile, IFN-α is rarely used as first-line therapy (except in case of SSTR negative NETs [21]) and is mainly used as an additive to other treatment or as bridging while waiting for initiation of other therapy, such as embolization or PRRT. According to ENETS guidelines, IFN-α is an established and approved second-line (add-on) therapy for refractory carcinoid syndrome or functional pNETs [22]. It can also be considered as an antiproliferative therapeutic option in GEPNETs; however, prospective data are scarce and largely inconclusive [6,22].

Compared to SSAs, IFN-α is associated with more side effects, some of them occurring early on during the induction phase (i.e., flu-like symptoms, neutropenia, thrombocytopenia), while others are linked to a prolonged duration of therapy (i.e., fatigue, depression/anxiety). Routine laboratory monitoring is recommended before the start, after 2, 4 and 12 weeks, and every 3 months thereafter (complete blood count with differential, creatinine, electrolytes, liver function enzymes, creatinine kinase, thyroid stimulating hormone, triglycerides, and serum glucose) [23]. Recommendations for toxicity management are summarized in Table 1 [6,23-25].

Telotristat ethyl

Although SSAs achieve a reasonably high rate of symptom control in carcinoid syndrome, around 20% of patients suffer from persistent and debilitating symptoms [9,26]. In these refractory cases high doses of SSAs, association of IFN-α or switching of SSAs are often attempted, along with efforts to reduce tumor burden. Telotristat ethyl, a first-in-class, small-molecule, oral tryptophan hydroxylase inhibitor, suppresses the rate-limiting step in serotonin production. The drug has been approved by the Food and Drug Administration (FDA)

and European Medicine Agency (EMA) at a dose of 250 mg t.i.d. for the treatment of SSA-refractory carcinoid syndrome and is given in addition to the SSA administration [27]. The efficacy of telotristat ethyl in diarrhea reduction in this setting has been documented in two double-blind pivotal phase 3 trials, TELESTAR and TELECAST, and the clinical benefit was maintained over the longer term in open-label extension studies [28-31]. These trials were not powered to assess other carcinoid syndrome symptoms and the reported reductions in abdominal pain and flushing were not statistically significant. The influence of telotristat ethyl on carcinoid heart disease and mesenteric fibrosis development and progression remains to be studied. The safety profile is very favorable, with very few side effects, but data from long-term follow-up trials, such as TELEPATH (NCT02026063), need to be awaited. Among the adverse events of special interest (depression related, elevated hepatic enzymes, GI symptoms), slightly higher rates of nausea, constipation and depression were reported in the treatment arms when compared to the placebo arms [27,32]. Despite initial concern about the potential impact of long-term serotonin synthesis inhibition, no depression-related serious adverse events have been reported.

Everolimus

The PI3K/AKT/mTOR signaling pathway plays a pivotal role in recognition of stress signals and regulation of cell survival, proliferation and apoptosis, and it is deregulated in several human malignancies, including NETs. Everolimus is a rapamycin analog that inhibits the multiprotein complex mTOR complex 1 (mTORC1). Oral everolimus at a daily dose of 10 mg achieves peak concentration after 1-2 h and reaches a steady state condition within 7 days. The drug has been extensively studied in NET treatment, either alone or in combination. Everolimus is considered a valid treatment option in NETs based on two phase 3 registry trials. The RADIANT-3 trial conducted by Yao *et al*, in unresectable or metastatic, well-differentiated (G1-G2) progressive pNETs, showed a significantly longer median progression-free survival (PFS) for everolimus compared to placebo (11.4 vs. 5.4 months; hazard ratio [HR] 0.34, P<0.0001) [33]. Quite similarly, RADIANT-4, a large placebo-controlled study that used everolimus monotherapy to treat unresectable or metastatic well-differentiated (G1-G2) non-functional GI or lung NETs, demonstrated a statistically significant median PFS benefit for everolimus in this population (11 vs. 3.9 months; HR 0.48, P<0.00001) [34]. This drug seems to induce tumor stabilization rather than regression, as conventional tumor response rates per Response Evaluation Criteria In Solid Tumors (RECIST) are rarely noted (<5% of patients). It is common practice to combine everolimus with SSAs, especially in functional NETs. However, superiority of the combination over everolimus monotherapy in terms of antiproliferative effect has never been clearly demonstrated.

Class effects of mTOR inhibitors include epithelial-cutaneous toxicity (i.e., stomatitis and rash), interstitial lung

Table 1 Recommendations for clinical management of interferon (IFN)-α toxicity

General description/incidence (%)	Preventive measures	Treatment
Flu-like symptoms (not available) • headaches, myalgia, fever, nausea, diarrhea • onset 3-5 h after subcutaneous administration • incidence decreases after 4 weeks of therapy	• premedication with antipyretics and analgesics • education on maintaining adequate hydration • administration in the evening (sleep through most of these symptoms)	• paracetamol up to 4 g/day, starting 30 min before • antiemetics can reduce nausea, benzodiazepines in refractory cases, corticosteroids to be avoided (counteractive to IFN-α as an immunosuppressant) • loperamide or similar agents for diarrhea
Anorexia (not available)	• patient education on ideal body weight, optimal calorie-dense diet and maintaining adequate hydration • smaller, more frequent meals, high protein supplement	• consider treatment interruption in severe cases
Hepatotoxicity (30%) • rule out other causes/underlying conditions	• avoid hepatotoxic agents	• grade 3/4: interrupt until recovery to ≤grade 1/2 • stepwise dose reduction on reinitiation
Thyroid dysfunction (8-20%) • hyperthyroidism followed by hypothyroidism (auto-immune pattern; thyroid antibodies often detectable)		• beta-blockers, thyroid inhibitors or thyroxine replacement therapy per standard guidelines • IFN-α dose interruption or adjustment exceptional
Fatigue (not available) • rule out other causes (thyroid dysfunction, psychological/emotional distress, anemia, etc.)	• ensure a consistent sleep cycle - maintain activity levels during the day - avoid excessive caffeine and alcohol - adequate fluid and nutritional intake	• in analogue to cancer-related fatigue guidelines • cognitive and behavioral sleep therapy
Hematologic toxicity Anemia (25%) Thrombocytopenia (10-20%) Leukopenia (40-60%)		• thrombocytopenia <50×10^9/L: 50% dose reduction • thrombocytopenia <25×10^9/L: discontinue therapy • neutropenia <0.75×10^9/L: 50% dose reduction • neutropenia <0.5×10^9/L: discontinue therapy
Hypertriglyceridemia (not available)	• limit dietary intake of saturated fat, cholesterol, simple sugars and alcohol, stimulate intake of soluble fiber and plant sterols • reduce weight and increase physical activity in overweight patients	• treat dyslipidemia according to standard guidelines • prompt initiation of fibrates if triglycerides >500 mg/dL (acute pancreatitis risk)
Neuropsychiatric (not available) • depression, sleeplessness, irritability, concentration difficulty, anxiety	• educate patients and caregivers to report symptoms • psychiatric advice in advance in case of psychiatric disorder history	• zolpidem/zoplicone 1st choice for sleeplessness • selective serotonin reuptake inhibitor 1st choice for depression; refer to psychiatrist; cognitive therapy • psychostimulants/anxiolytics as indicated • treat ≥4 weeks after IFN cessation (3 months in PEG) • dose modification or interruption in severe cases
Cutaneous (not available) • local reactions injection site, xerosis cuti, sicca symptoms, pruritus, alopecia		• urea-containing emollients • artificial tears/saliva • estriol crème/lubricants

PEG, pegylated

disease (non-infectious pneumonia), metabolic disturbances and immune suppression. Other common side effects are nausea, diarrhea, fatigue and peripheral edema [33-35]. About 5-7% of patients experience grade 3-4 toxicity. Most class-effect adverse events are manageable and resolve without the need for treatment discontinuation. According to the everolimus prescribing information, a number of parameters should be measured at baseline and followed during treatment (Table 2) [36]. Clinical guidance on toxicity management

Table 2 Follow-up recommendations under everolimus therapy

At baseline and periodically thereafter
• physical examination • urine dipstick for proteinuria • complete blood count with differential • blood chemistry including creatinine, electrolytes, liver function • blood cholesterol and triglycerides • blood glucose*

* weekly during the first month of treatment in high risk patients

Table 3 Recommendations for clinical management of everolimus toxicity

General description/incidence (%)	Preventive measures	Treatment

Stomatitis (62-64%)
• mTOR-inhibitor associated stomatitis (mIAS) differs from chemotherapy/radiation induced stomatitis
• "aphthous-like"; well circumscribed single or multiple ovoid-shaped ulcerations typically on non-keratinized mucosa. Painful, long-lasting and more functionally limiting than their small size (<0.5 cm) would suggest
• lesions typically present within first treatment cycle
• most common dose limiting toxicity
• specific pathophysiology largely unknown
	• patient education on prompt symptom reporting
	• basic oral hygiene and dental examinations
	• avoid epithelial injury
	  - avoiding spicy, acidic, salty, crunchy food
	  - avoiding alcohol- or peroxide containing mouthwash
	  - brushing with soft toothbrush
	  - frequent bland rinses with sterile water or saline
	• sodium bicarbonate rinses and antiseptic mouthwashes lack benefit or have produced inconsistent results
		• evaluate for bacterial, viral or fungal infections
		• topical and systemic pain control (non-opioid analgesics often insufficient)
		• topical or intralesional corticosteroids
		  - e.g,. dexamethasone 0.5 mg/5mL oral solution
		  - e.g., prednisolone 15 mg/5mL oral solution
		• systemic corticosteroids for severe persisting mIAS
		  - e.g., prednisone 5 mg bid
		• grade 2/3: dose interruption until recovery to≤grade 1
		  - grade 2: reinitiate at same dose, unless recurrent
		  - grade 3: reinitiate at lower dose
		• grade 4: permanent everolimus discontinuation

Pneumonitis (8-17%)
• inconsistent definition and reporting in literature
• often asymptomatic or mildly symptomatic (cough, dyspnea, hypoxia, pleural effusion)
• potentially life-threatening (respiratory insufficiency)
• non-specific clinical, radiological, pathological features
• wide range of onset over several months
• diagnostic work-up (high-resolution computed tomography, pulmonary function test, often broncho-alveolar lavation) to differentiate from infectious (incl. opportunistic) or other cardiopulmonary events
	• patient education on prompt symptom reporting
	• everolimus should not be used in severe pre-existent pulmonary disease
		• grade 1: watchful waiting
		• grade 2:
		  - consider dose interruption until recovery to ≤grade 1
		  - reinitiate at lower dose
		  - discontinue if recovery takes>4 weeks
		• grade 3:
		  - dose interruption until recovery to ≤ grade 1
		  - reinitiate at lower dose, unless recurrent
		• grade 4: permanent everolimus discontinuation
		• systemic corticosteroids to be considered for ≥ grade 2
		  - e.g., prednisone 40 mg q.d.; dose temper over several weeks; add pneumocystis prophylaxis during treatment

Rash (27-49%)
• dermatitis presents as maculopapular or papulopustular eruptions, usually on upper trunk, face, scalp, neck and sometimes extremities
• starting within the first month of treatment
	• prevent skin irritation and dryness
	  - avoid detergents, disinfectants, soap
	  - avoid hot showers and excessive sun exposure
	  - use pH-neutral, fragrance-free skin care products
	  - topical application of (urea-based) moisturizers.
		• majority resolves without therapeutic interventions
		• grade 1/2: topical corticosteroids and moisturizer
		  - consider dose interruption until recovery to ≤grade 1
		  - reinitiate at same dose, unless recurrent
		• grade 3: topical and/or systemic corticosteroids
		  - dose interruption until recovery to ≤grade 1
		  - reinitiate at lower dose, discontinue if grade 3 recurs
		• grade 4: permanent everolimus discontinuation

(Contd...)

Table 3 (*Continued*)

General description/incidence (%)	Preventive measures	Treatment

Metabolic events
Hyperglycemia (10-15%)
Dyslipidemia (not available)
	• everolimus should not be used in uncontrolled diabetes
	• optimization of lipidemic control (serum cholesterol <300 mg/dL and fasting triglycerides ≤2.5×upper limit
	• limit dietary intake of saturated fat, cholesterol, simple sugars and alcohol, stimulate intake of soluble fiber and plant sterols
	• reduce weight and increase physical activity in overweight patients
		• treat hyperglycemia according to standard guidelines
		• treat dyslipidemia according to standard guidelines
		• grade 1/2: no dose adjustments
		• grade 3:
		  - dose interruption until recovery to ≤grade 1
		  - reinitiate at lower dose
		• grade 4: permanent everolimus discontinuation
		• prompt initiation of fibrates if triglycerides >500 mg/dL (acute pancreatitis risk)

Infections (20-29%)
• localized and systemic infections (bacterial, viral, candidiasis, invasive fungal infections)
	• screening for tuberculosis and hepatitis B virus status in high prevalence areas	• prompt diagnosis and treatment (antibiotic, antifungal or antiviral treatment as appropriate)
		• grade 2/3: dose interruption until recovery to ≤grade 1
		  - grade 2: reinitiate at same dose, unless recurrent
		  - grade 3: reinitiate lower dose
		  discontinue if grade 3 recurs
		• grade 4: permanent everolimus discontinuation

Hematologic toxicity Anemia (15-17%) Thrombocytopenia (13-14%)		• grade 2/3: dose interruption until recovery to ≤grade 1 - grade 2: reinitiate at same dose, unless recurrent - grade 3: reinitiate lower dose discontinue if grade 3 recurs
Neutropenia (not available)		• grade 4: permanent everolimus discontinuation • grade 3: dose interruption until recovery to ≤grade 1 reinitiate at same dose, unless recurrent • grade 4: dose interruption until recovery to ≤grade 1 reinitiate lower dose discontinue if grade 3/4 recurs

is summarized in Table 3 [33-41]. Dose reduction usually involves a switch to a daily dose of 5 mg. In their meta-analysis, Ravaud *et al* found a convincing correlation between a higher everolimus exposure and improved tumor size reduction on the one hand, but an increased risk of ≥ grade 3 pulmonary, stomatitis and metabolic events on the other [42]. Caution is warranted when prescribing systemic corticosteroids for treatment of everolimus-associated adverse events, in view of the additional immunosuppressive effect and the possible interaction with CYP3A4, which can lead to reduced everolimus efficacy.

Sunitinib

Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor (MTKI) that blocks, among others, the vascular endothelial growth factor receptor, platelet-derived growth factor receptor and c-KIT receptor. It has gained approval for the treatment of unresectable or metastatic, well-differentiated, progressive pNETs, based on the phase III trial by Raymond *et al*, which demonstrated a robust median PFS benefit of continuous daily dosing (CCD) with sunitinib 37.5 mg/day over placebo [43,44]. Similarly to everolimus treatment, objective

responses according to RECIST are exceptional under sunitinib treatment. The CCD administration schedule differs from its use in advanced renal cell carcinoma (RCC) and imatinib-resistant GI stromal tumors, in which intermittent dosing at 50 mg/day, 4 weeks on and 2 weeks off, is used. A meta-analysis of sunitinib data in solid tumor trials has shown a clear association between higher sunitinib exposure and improvement of outcome parameters [45]. These findings stress the importance of maintaining dose intensity and avoiding unnecessary dose reductions or delays by early and adequate toxicity prevention and management. Most common adverse events are grade 1-2 and include fatigue, palmar-plantar erythrodysesthesia (hand-foot syndrome; HFS), hypertension, GI symptoms and hypothyroidism. Grade 3-4 toxicity occurs in 5% of cases, with neutropenia (12%) and hypertension (10%) as most frequent events; however, there have been no reports of febrile neutropenia so far [44]. MTKI-associated HFS has certain distinct clinical and histopathological features, likely due to different pathophysiology, differentiating this entity from chemotherapy-induced (e.g. fluoropyrimidines) HFS [46]. Typical hair color changes and skin depigmentation are quite harmless and occur in 29% of treated patients [44]. Some adverse events have been studied as surrogate biomarkers of sunitinib efficacy in RCC treatment; however, their impact on pNET management remains to be clarified [47]. According to the sunitinib prescribing information, a number of parameters should be measured at baseline and followed during treatment (Table 4) [48]. Clinical guidance on toxicity management is summarized in Table 5 [43,44,49]. Dose adjustments should be made in 12.5 mg increments and in some cases an intermittent dosing schedule (e.g. 2 weeks on/1 week off) might be appropriate [48].

PRRT

PRRT is a novel form of targeted systemic radiotherapy delivering radionucleotides to tumor cells expressing high levels of SSTRs. This strategy involves a SSA carrier molecule (octreotide or octreotate) attached to a radionucleotide by a chelator, of which DOTA (tetraazacyclododecane-tetraacetic acid) and DTPA (diethylenetriamine-pentaacetic acid) are the most commonly used. Frequently used radionucleotides include yttrium-90 (^{90}Y-dotatoc) and lutetium-177 (^{177}Lu-dotatate). Both ^{90}Y and ^{177}Lu are beta-emitters; they differ in maximum energy level (2.27 MeV versus 0.49 MeV), tissue penetration depth (11 mm versus 2 mm) and half-life (2.67 days versus 6.68 days) [50]. As a gamma-ray emitter, ^{177}Lu can also

be used for dosimetry and to monitor tumor response. Dose-limiting toxicities are imposed by bone marrow and kidney irradiation. Therefore, the cumulative dose of radiolabelled SSA is fractionated in sequential cycles (usually 4-5), delivered systemically every 6-9 weeks.

Over the last 25 years, the antitumor effect of PRRT had been shown only in non-randomized early-phase studies, with quite similar efficacy for ^{90}Y and ^{177}Lu and disease control rates of 68-94% [51]. NETTER-1 is the first randomized phase III trial clearly demonstrating superiority of ^{177}Lu-dotatate over high-dose octreotide LAR in octreoscan-positive midgut NETs, progressive on standard dose SSA [52]. After a median follow up of 14 months, a 79% reduction in the risk of progression or death was seen in the PRRT arm (P<0.0001; HR 0.21; 95% confidence interval 0.13-0.33). Median PFS was not reached in the investigational arm versus 8.4 months in the control arm. The overall response rate was 18% for ^{177}Lu-dotatate versus 3% for high-dose octreotide LAR. PRRT is the only NET therapy with a distinct predictive biomarker, namely the baseline SSTR expression density (Krenning score). pNETs appear to respond better, but relapse earlier [53]. Large lesions, high hepatic tumor burden, fluorodeoxyglucose avidity and high Ki-67 are negative predictive factors [51,54,55]. The role of PRRT combinations with radiosensitizing cytotoxic agents or targeted agents, such as everolimus, remains to be further investigated in large randomized trials, as do treatment combinations of both radionucleotides aiming to take advantage of their different penetration ranges in targeting a variety of lesion types (large versus small size, heterogeneous SSRT expression, etc.).

Careful patient selection, appropriate timing of therapy, dose optimization and rigorous monitoring are mandatory to minimize the risk of short- and long-term toxicity, summarized in Table 6 [50,51,56-58]. ^{177}Lu-dotatate has a more favorable toxicity profile, particularly concerning renal and hematological adverse events. Risk factors for increased toxicity after PRRT include the number of prior therapies, exposure to chemotherapy with alkylating agents, radiation-based therapy, age >65 years, impaired renal function, depleted myeloid reserve and poor performance status [58]. Normal age-adjusted renal function is mandatory for ^{90}Y-labelled peptides. Mild renal impairment can be tolerated for ^{177}Lu-labeled peptides; however, glomerular filtration rate and tubular extraction rate should be at least 60% of mean age-adjusted normal values [59]. White blood cell count should be >3000/μL, with absolute neutrophil count >1000/μL, platelets >75,000/μL for ^{177}Lu and >90.000/μL for ^{90}Y, and red blood cell count >3 × 10^6/μL [59].

Concluding remarks

The therapeutic armamentarium for the treatment of GEPNETs has expanded significantly over the last two decades. However, the ideal sequencing strategy remains controversial. As patients live longer and remain active for a longer period of time, the optimal treatment toxicity management is of

Table 4 Follow-up recommendations under sunitinib therapy [48]

At baseline, at day 15 of therapy and monthly thereafter
• physical examination including blood pressure and heart rate • urine dipstick for proteinuria • complete blood count with differential • blood chemistry including creatinine, electrolytes, liver function

At baseline and three-monthly thereafter
• Thyroid stimulating hormone, T3, and T4

Table 5 Recommendations for clinical management of sunitinib toxicity

General description/incidence (%)	Preventive measures	Treatment
Fatigue (32%)/Asthenia (34%) • rule out other causes (thyroid dysfunction, psychological/emotional distress, anemia, etc.) • typically after 1 month; peak after 2 to 3 months	• ensure a consistent sleep cycle - maintain activity levels during the day - avoid excessive caffeine and alcohol - adequate fluid and nutritional intake	• dose reductions do not have tremendous impact • grade 3/4: interrupt until recovery to ≤grade 1/2 • consider intermittent dosing 2 weeks on/1 week off
Hand-foot syndrome (23%) • typically occurs within first 2 to 4 weeks	• focus on prevention and patient education • inspection of palms and soles; treat pre-existent calluses or hyperkeratotic areas • avoid exposure to hot water, constrictive footwear or excessive skin friction. • use of cotton gloves and socks • daily application of moisturizing cream from day 1	• topic antiseptic or antibiotic treatment as indicated • keratolytics such as urea 20-40% or salicylic acid 6% for hyperkeratotic areas • topic or systemic analgesics • grade 3/4: interrupt until recovery to ≤grade 1/2 - grade 3: reinitiate at same dose, unless recurrent - grade 4: reinitiate at lower dose or discontinue
Hypertension (26%) • class effect of anti-angiogenics	• actively screen for hypertension (may include home monitoring)	• treat as appropriate per standard guidelines - angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers - dihydropyridine calcium channel blockers • grade 3/4: interrupt until recovery to ≤grade 1/2 - grade 3: reinitiate at same dose, unless recurrent - grade 4: reinitiate at lower dose or discontinue
Hypothyroidism (7%) • may be proceeded by an episode of hyperthyroidism		• thyroxine replacement therapy per standard guidelines • sunitinib dose interruption or adjustment exceptional
Diarrhea (59%) • rule out other causes (disease related, pancreatic insufficiency, infection, drugs, etc.) • sunitinib diarrhea typically resolves a few days after discontinuation	• avoid caffeine, high lactose-containing, fatty or high fibre foods and fruits (except pectin-containing fruit) • maintain adequate hydration	• oral or intravenous (re)hydration as indicated • oral anti-diarrheals (e.g., loperamide) • grade 3/4: interrupt until recovery to ≤grade 1/2 - grade 3: reinitiate at same dose, unless recurrent - grade 4: reinitiate at lower dose or discontinue
Hematologic toxicity Thrombocytopenia (17%) Neutropenia (29%)		• grade 3/4: interrupt until recovery to ≤grade 2 - grade 3: reinitiate at same dose, unless recurrent - grade 4: reinitiate at lower dose or discontinue
Nausea (45%)/vomiting (34%) • rule out other causes than sunitinib		• early treatment with alizapride/metoclopramide • caution with CYP3A4 interaction (e.g., ondansetron)
Stomatitis (22%)	• identical to table 3 (everolimus associated stomatitis)	• dose reductions rarely necessary for isolated oral mucositis, may be considered for multiple toxicities • grade 3/4: interrupt until recovery to ≤grade 1/2 - grade 3: reinitiate at same dose, unless recurrent - grade 4: reinitiate at lower dose or discontinue

paramount importance. Although clinical trials mainly focus on grade 3-4 toxicity, even persisting grade 2 toxicity becomes more of an issue, impacting quality of life and compliance in this setting of long-term treatment. Nonetheless, prospective data on optimal adverse event management are lacking and recommendations are largely based on expert opinion and drug prescribing information. When interpreting the available evidence in the literature, one should pay attention to the version of the Common Terminology Criteria for Adverse Events used, as historically used versions might differ substantially from current ones and may lead to under- or over-reporting.

Little is known about the exact magnitude of the impact of dose interruptions and/or modifications of these drugs in the GEPNET indication. The predictive significance of adverse event occurrence for treatment outcome has been demonstrated for epidermal growth factor receptor inhibitor-related skin toxicity in metastatic colorectal cancer and certain MTKI-related toxicity in advanced RCC. However, this information is lacking in the setting of NET treatment and needs to be systematically addressed in future clinical trials, as does the need for toxicity-related biomarkers in general.

Table 6 Recommendations for clinical management of peptide receptor radionucleotide therapy (PRRT) toxicit

General description	Preventive measures	Treatment
Acute toxicity		
Nausea/vomiting • usually mild and self-limiting • primarily attributable to the concomitant amino acid infusion given for nephroprotective purposes		• treatment with standard anti-emetic therapy
Carcinoid crisis (<1%) • due to massive release of metabolically active amines		• octreotide 0.5 mg subcutaneous, t.i.d. • adrenergic drugs should be avoided in case of shock • octreotide up to 1 mg intravenous in case of shock
Hematologic toxicity • due to bone marrow irradiation • usually mild and self-limiting • occurring typically 4-6 weeks after administration • lymphopenia most frequent		
Hepatotoxicity • due to hepatocyte irradiation (radiation-induced liver disease) • theoretically risk is increased in high liver burden, although not well documented		
Long-term toxicity		
Renal toxicity • radionucleotides are reabsorbed in the proximal tubules and accumulate in the renal interstitium, causing inflammation and fibrosis leading to irreversible kidney injury • coadministration of positively charged amino acids competitively inhibits proximal tubular radiopeptide reabsorption and recirculation in the kidney and decreases radioactive uptake in the kidneys by 40%	• use of appropriate dosimetry • 25 g lysine and 25 g arginine diluted in 2L saline solution, started 30-60 min before PRRT and maintained over 4 h • consider dose reduction in case of pre-existing nephrotoxic factors (uncontrolled diabetes, hypertension, old age, single kidney, etc.)	• overall a mild loss of renal function over time occurs of 7.3%/year for yttrium-90 (^{90}Y) and 3.8%/year for lutetium-177 (^{177}Lu). • incidence grade 3/4 renal toxicity in ^{90}Y: 3-9% • incidence grade 4 renal toxicity in ^{177}Lu: <0.4% • end-stage renal failure after PRRT is extremely rare
Leukemia/myelodysplastic syndrome • occurring in <2%, typically 5-10 years after therapy		

Finally, we want to stress the critical role of patient and treating physician in maintaining adequate dose intensity in GEPNET medical treatment. The diversity and complexity of NET management today requires the support of a dedicated multidisciplinary team, e.g., including an oncologist, gastroenterologist, dermatologist, cardiologist, psychologist, nutritional expert, and oncology nurses.

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