Keywords

Somatostatin analogs · Interferon-α · Everolimus · Sunitinib · Tolerability · Toxicity · Dose adjustment · Drug interaction · Patient information

Abstract

Systemic therapies established in the management of patients with neuroendocrine tumors (NETs) include somatostatin analogs and interferon-α, also referred to as biotherapy. Recent randomized controlled studies have extended the knowledge on the frequency of side effects associated with biotherapy. More recently, novel targeted drugs, such as the mammalian target of rapamycin inhibitor everolimus and the multiple tyrosine kinase inhibitor sunitinib, have been introduced in the management of NETs. Although targeted drugs are generally well tolerated, with most adverse events being of mild to moderate severity and manageable, novel targeted drugs exhibit a distinct adverse event profile that warrants guidance for appropriate diagnostic and therapeutic management. This is particularly important given

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Introduction

Recently updated ENETS consensus guidelines provide a comprehensive overview on the use of systemic therapies and their indications in neuroendocrine tumors (NETs) [1] while standards of care (SOC) guidelines give advice on how to safely use drugs. Systemic therapies established in the management of patients with NETs include somatostatin analogs (SSAs), interferon (IFN)-α, also referred to as biotherapy, and novel targeted agents such as the mammalian target of rapamycin inhibitor everolimus and the tyrosine kinase inhibitor sunitinib. Other novel targeted agents evaluated in phase 2 trials (e.g., bevacizumab, axitinib, or pazopanib) remain investigational (pending further validation in phase 3 studies and subsequent licensing) and will not be covered by these guidelines. SOC guidelines for systemic chemotherapy will be covered in a separate chapter [2].

Established systemic therapies are presented separately by drug class covering a brief summary of the indication, administration and dosing schedule, adverse events (AEs), actions and dose adjustments for AEs, monitoring of AEs, evaluation of treatment effect, patient information, drug interactions, and information on pregnancy. The severity of AEs is indicated by Common Terminology Criteria for Adverse Events [3].

Somatostatin Analogs

Indication

SSAs are indicated to treat symptoms related to peptide hypersecretion in functionally active NETs; this includes distinct clinical syndromes such as carcinoid syndrome, and syndromes related to duodenal NETs or pancreatic NETs (pNETs) (e.g., VIPoma, glucagonoma, or gastrinoma) and, more rarely, parathyroid hormone-related peptide-secreting tumors. Malignant somatostatin receptor-2-positive insulinoma may respond to an SSA; however, it should be used with caution since hypoglycemia may worsen due to decreased secretion of glucagon [4].

Further, SSAs are indicated to inhibit tumor growth in NETs [5, 6]. In this respect, octreotide LAR is registered for midgut NET and NET of unknown primary, and lanreotide autogel is registered for intestinal and pNET and NET of unknown primary. In general, somatostatin receptor status should be positive on somatostatin receptor imaging if an SSA is going to be used with antiproliferative intent [7].

Administration and Dosing Schedule

Octreotide and lanreotide are registered drugs for NETs in Europe. Octreotide is available as a short-acting subcutaneous (s.c.) formulation and as long-acting intramuscular injection (octreotide LAR 10, 20, and 30 mg). Lanreotide, available only as long-acting formulations (30, 60, 90, and 120 mg), is administered by deep s.c. injection.

The optimal antiproliferative doses have not been investigated; however, based on placebo-controlled phase 3 trials, octreotide LAR 30 mg/month and lanreotide 120 mg/month, respectively, are recommended. Although lower doses may be used for control of hormonal symptoms, knowledge of the antiproliferative effect at the evaluated doses makes these doses preferable in these patients.

The starting dose of octreotide LAR, according to the summary of product characteristics (SPC), is 20 mg for symptom control (with 2-week overlap for patients established on s.c. octreotide) and 30 mg as an antiproliferative agent. Depending on the severity of symptoms and spread of the disease, some patients with functioning NETs may need 30 mg octreotide LAR. For lanreotide, the SPC gives a starting dose range of 60–120 mg/month. Tolerability to an SSA may be tested with s.c. doses of octreotide (50–100 μg b.i.d. or t.i.d., with escalation over 3–4 days, up to 600 μg/day) in patients considered to be sensitive to side effects. In general, SSA treatment is maintained for as long as the patient is benefitting.

In cases of refractory carcinoid syndrome or uncontrollable specific symptoms (e.g., diarrhea) related to functionally active pNET, SSA doses may be increased to above-label doses by shortening the injection interval from 4-weekly to 3- or even 2-weekly if clinically required [8]. Alternatively, if an immediate effect is required, “rescue” octreotide 100–200 μg s.c. may be used on an as-re-
required basis. In addition, if other drugs (e.g., IFN) or treatments (e.g., locoregional therapies) are considered unfeasible, octreotide s.c. may be used on a regular schedule (e.g., 100–200 μg b.i.d. or t.i.d.).

In patients with carcinoid syndrome, a continuous intravenous infusion of octreotide (50–100 μg/h) is required before surgery or any scheduled interventional therapies, continuing for 24–48 h depending on the type of surgery and extent of tumor burden. The infusion should start preferably 12 h prior to surgery. For more details, see the chapter on perioperative management [9].

Above-label dosages of SSA are not only used for improved syndrome control but also for tumor growth control in slowly growing tumors although not approved in this indication. Octreotide at a dose of 60 mg (2 injections with 30 mg every 4 weeks) has been explored in the NETTER-1 trial [10]; however, more frequently 30 mg is used every 3 or even every 2 weeks. Lanreotide 120 mg every 2 weeks for antiproliferative purpose is under evaluation in a clinical trial (NCT02651987; www.clinicaltrials.gov). A higher than standard dose of either octreotide or lanreotide can be considered outside of clinical trials in selected cases, with radiological progression within a long time frame (2–3 years) or low tumor burden or any other setting where alternative treatment options such as everolimus or peptide receptor radionuclide therapy in intestinal NET, and chemotherapy or targeted agents in pNET seem not appropriate or feasible.

Adverse Events

SSAs are generally well tolerated [11]; in the phase 3 trials, discontinuation due to treatment-related AEs was reported in only 1% of patients with enteropancreatic NETs with lanreotide [6] and in 12% of patients with midgut NETs with octreotide LAR [5].

The most frequent AEs are gastrointestinal disorders including abdominal discomfort or pain, nausea, flatulence, and diarrhea. In general, these AEs resolve within 2–3 weeks on treatment. To reduce gastrointestinal AEs, dose escalation of SSA may be instituted as described previously. Transient hypoglycemia, usually not clinically significant, may occur and can be avoided by regular food intake. Bradycardia, a very rare AE, has been reported after s.c. injection of octreotide or when given as an intravenous bolus in larger doses [12–15], it should be considered if other causes have been ruled out.

SSAs modestly suppress thyroid-stimulating hormone (TSH) secretion, but in general do not cause clinically evident hypothyroidism requiring thyroid hormone replacement [16].

AEs occurring with long-term use of SSAs include diarrhea/steatorrhea due to pancreatic enzyme insufficiency; sludge in the gallbladder or gallstones; hyperglycemia, hypocalcaemia, and vitamin B₁² deficiency. Deficiency of one or more fat soluble vitamins has been described in more than 70% and multiple deficiencies in 38% of patients with long-term SSA use for ≥18 months. These included deficiencies for vitamin A, D, E, K, and E in erythrocytes in 6, 28, 15, 63, and 58% of the patients [17]. Subcutaneous nodules at the site of depot injections are not uncommon. Hair loss is reported in few patients.

Actions and Dose Adjustments of SSA for AEs

In general, dose reductions, to 10–20 mg octreotide LAR/month or 60–90 mg lanreotide autogel/month for AEs, are rarely needed.

Pancreatic enzyme insufficiency is a common AE during treatment with SSAs [18]; if diarrhea/loose stools occur, determination of fecal elastase to establish the diagnosis of pancreatic enzyme insufficiency is recommended as well as substitution with pancreatic enzymes, if confirmed. Other causes of diarrhea related to surgery (e.g., bacterial overgrowth, short bowel syndrome, or bile acid loss) or more general causes of diarrhea (e.g., lactose intolerance) should be considered and excluded. Use of cholestyramine in cases of bile acid loss or loperamide, if no specific reason for diarrhea can be identified, is recommended.

Gallstones have been reported in 10% of the patients with lanreotide autogel and in 14% of those with octreotide LAR in the CLARINET and PROMID trials, respectively [5, 6]. If symptomatic, the gallbladder should be removed. In cases of planned surgery for primary tumor or metastases, or abdominal surgery unrelated to NET, a prophylactic cholecystectomy can be considered.

Hyperglycemia occurred in 5% of patients with 120 mg lanreotide autogel/month in the CLARINET study, and was reported in 5% of patients with carcinoid syndrome when treated with 40 mg/month octreotide LAR (2% of grade 3–4) [19]. Patients with impaired glucose tolerance or diabetes mellitus should be monitored closely when SSA therapy is initiated; initiation or adjustment of antidiabetic therapy might be necessary.

Vitamin B₁₂ deficiency may occur with SSA therapy [20] and should be substituted. Similarly, in cases of vitamin D deficiency or deficiency of other fat soluble vitamins substitution is recommended.

Thyroid hormone replacement is indicated with the occurrence of hypothyroidism.
In ≤1% of patients, severe and/or durable SSA-related diarrhea, or increased diarrhea and/or flushing in carcinoid syndrome due to paradoxical release of mediators, or exacerbation of hypoglycemia in metastatic insulinoma may occur [21]. In such cases, SSA should be stopped and an alternative treatment considered.

**Monitoring of AEs**

Before starting an SSA, the following investigations should be performed:
- Physical examination with determination of blood pressure and heart rate
- Laboratory: blood cell count, transaminases, bilirubin, blood glucose, HbA1c, electrolytes (including calcium), creatinine, TSH, vitamin D and vitamin B12
- Electrocardiogram (ECG)
- Ultrasound of the gallbladder

During follow-up, the following investigations are advised:
- Physical examination with determination of blood pressure and heart rate
- Laboratory: blood cell count, transaminases, bilirubin, blood glucose, HbA1c (if hyperglycemia develops), electrolytes (including calcium), creatinine at 1 month and 3-monthly thereafter; vitamin B12, fat-soluble vitamins and TSH should be monitored annually
- Fecal elastase if steatorrhea occurs
- ECG if clinically indicated (bradycardia, signs of chronic heart failure); in patients with carcinoid heart disease, ECG and echocardiography should be regularly performed (every 3–12 months depending on the severity)
- Ultrasound of the gallbladder if clinically indicated

**Evaluation of the Treatment Effect**

**Biochemical Control**

Before starting therapy, the following biomarkers should be measured:
- Chromogranin A (CgA); neuron-specific enolase (NSE) may be considered in grade 2 NET if CgA is normal.
- 5-Hydroxyindole acetic acid (5-HIAA) in blood or 24-h urine (collection on acetic acid or hydrochloric acid, depending on local laboratory requirements) in patients with (suspected) carcinoid syndrome.
- Additional tumor markers, if indicated, depending on the type of tumor (e.g., gastrin, vasoactive intestinal polypeptide [VIP], glucagon, or insulin).

At follow-up, biomarkers elevated at baseline should be remeasured at 3 months, then in parallel to imaging (see below), if specific symptoms increase or new symptoms appear, or in case of clinical suspicion of progressive disease.

**Tumor Response**

Before treatment and during follow-up, the following investigations are recommended:
- Cross-sectional imaging, either CT or MRI of the liver and abdomen every 3–6 months depending on tumor grade and primary tumor origin (e.g., 6-monthly in grade 1 small intestinal NET, and every 3 months in grade 2 pNET); the interval can be prolonged to 1 year if the disease is stable after 3–5 years.
- Somatostatin receptor imaging (if not previously available or older than 1 year); either an octreoscan or 68Ga-SR-PET/CT to assess somatostatin receptor status and for whole-body staging [7]. Repeat somatostatin receptor imaging after 12–24 months according to ENETS guidelines [22].
- CT of the thorax if somatostatin receptor imaging revealed thoracic lesions; then every 3–12 months depending on tumor grade and growth rate.

**Patient Information**

- Patients with carcinoid syndrome should receive information on dietary restrictions (to avoid food that elevates serotonin in blood) before biochemical assessment of 5-HIAA in blood or 24-h urine. This is particularly important if the diagnosis of carcinoid syndrome needs to be established in patients with mild symptoms suspicious of carcinoid syndrome. Drugs that can interfere with 5-HIAA determination and are not necessarily needed should be avoided.
- Certain foods (with a high or moderate amount of amines; very spicy foods; or high-fat meals) and alcoholic beverages may induce flushing and/or diarrhea, and thus should be avoided.

**Drug Interactions**

- The bioavailability of bromocriptine, quinidine, or terfenadine may be increased by octreotide or lanreotide.
- Cyclosporin: reduction of serum cyclosporine levels have been recorded that may increase the risk of transplant rejection.
- Patients receiving insulin, oral antidiabetic agents, β-blockers (e.g., propranolol, bisoprolol, carvedilol, or atenolol), calcium channel blockers, or agents to control fluid and electrolyte balance may require dose adjustments of these treatments while on SSA.
Precise information on drug interactions can be retrieved from the US Food and Drug Administration (FDA) [23].

**Pregnancy and Lactation**

Data concerning the use of SSA in pregnancy are very limited. Pregnancy has been reported in women while on octreotide or lanreotide; based on these case reports and animal studies, SSAs seem not to be teratogenic or genotoxic [24, 25]. However, octreotide does cross the placenta, and data are too limited to fully assess the human fetal risk [25]. Therefore, the use of SSA should only be considered if the assumed benefits far outweigh potential risks following multidisciplinary discussion between the oncologist, endocrinologist, and gynecologist.

There are no data on the excretion of SSA into human milk, but animal studies have shown excretion of octreotide into breast milk, so it is preferable that patients do not breast-feed while on SSA treatment or this should be done with great caution [25].

**Interferon**

**Indication**

IFN-α 2b is registered in Europe for the treatment of NETs associated with carcinoid syndrome; it is also used for functionally active pNETs (e.g., VIPoma, glucagonoma, or insulinoma) to improve symptoms related to hypersecretion of amines and peptides. In general, it is used as an add-on therapy to SSA in refractory carcinoid syndrome or if SSAs are not the preferred choice (e.g., negative somatostatin receptor status) or not tolerated. Uncontrolled and prospective randomized trials have shown activity of IFN similar to that of SSA in gastroenteropancreatic NETs [26–28]. A recent large controlled trial in advanced “carcinoids” supported its antiproliferative activity [29]. However, IFN is not registered as an antiproliferative agent, but may be considered as an option, particularly in patients with non-pNET [1].

**Administration and Dosing Schedule**

The most frequently used recombinant IFN preparations have been IFN-α2b and IFN-α2a, which differ from each other by a single amino acid residue. More recently, pegylated (PEG) forms of IFN are in clinical use. Standard IFN-α is administered s.c. thrice weekly; PEG IFN-α once weekly. According to the SPC (http://www.ema.europa.eu/ema/) and ENETS guidelines, the standard dose of IFN-α2b (IntronA®) is 3–5 MU 3 times a week [1]. A starting dose of 3 MU 3 times a week is recommended with titration of the dose according to tolerability. The standard dose of IFN-α2a (Roferon®) is 3–4.5 MU 3 times a week. For safety reasons, the white blood cell count should not be lower than 3 × 10⁹/L.

PEG-IFN-α2b (PEG-Intron™), at a dose of 0.5 μg/kg, has been used in NETs [30, 31]; starting at 50 μg/week s.c., the dose is increased in 4-weekly intervals up to 150 μg/week (depending on weight and tolerability). Dose increase to 150 μg/week is very rarely necessary.

IFN-α should be interrupted 3–4 weeks before surgery, peptide receptor radionuclide therapy or transarterial embolization/transarterial chemoembolization and for at least 2–4 weeks thereafter (in exceptional cases, it may not be feasible to interrupt IFN due to severe carcinoid syndrome, especially in patients with a high tumor burden).

**Contraindication**

IFN should not be used in patients with severe autoimmune diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus [SLE]); if psychiatric disorders (e.g., depression or psychosis) are present or previously reported; in patients with severe renal or hepatic insufficiency or epilepsy; or after organ transplantation.

Caution is advised in elderly patients (>70 years) because of the frequency of impaired hepatic, renal, bone marrow, or cardiac function; concomitant diseases; or other drug therapy.

**Adverse Events**

In comparison to SSA, IFN needs to be interrupted more frequently for AEs [26–28]. These include:

- Fever and flu-like symptoms (chills, malaise, headache, myalgia, tachycardia) are common (affecting approx. 90% of patients) during therapy with standard IFN-α; occurring mostly within 1–2 h after injection.

- Fatigue or weight loss occurs in about 50% of patients (26% of grade 3–4).

- Myelosuppression leading to dose-dependent leukopenia (7% of grade 3–4), lymphopenia, anemia (30%), and thrombocytopenia (20%).

- Autoimmune disorders occur in up to 20% of patients, most frequently hyperthyroidism (Basedow disease) or Hashimoto disease; others include vasculitis, Raynaud phenomenon, rheumatoid arthritis and SLE.

- Psychiatric side effects, especially depression.

- Reversible hair loss.

- Polyneuropathy (rarely).
– Mild hepatotoxicity (elevation of transaminases) in 30% of patients; fatal hepatotoxicity has been reported, but is extremely rare.
– Elevated triglyceride levels.

AEs of grade 3–4 are less frequently reported with PEG-IFN-α2b (fatigue 25%, myalgia <10%, headache 0%) [30, 31], compared to conventional IFN-α2b.

**Actions and Dose Adjustments of IFN for AEs**

If standard IFN therapy is not tolerated, PEG-IFN may be used instead unless serious AEs occurred, such as psychiatric disorders including depression, or serious autoimmune diseases.

– Flu-like symptoms: may be attenuated by premedication with paracetamol (1,000 mg orally or rectally) or aspirin/NSAIDs.

– For grade 2–3 fatigue or weight loss, reduce dose or stop treatment.

– Reduce IFN dose if leukocytes drop below $3 \times 10^9/L$.

– Autoimmune hyperthyroidism may be transient but may also require thyrostatic drugs (e.g., a thioamide). If tachycardia is present, β-blockers may be used. Hashimoto disease requires thyroid hormone substitution.

Discontinuation of IFN is required under the following conditions:

– Psychiatric disorders

– Severe bone marrow depression

– Severe weight loss (grade 3)

– Severe hepatic disease; discontinue IFN for any patient developing signs or symptoms of liver failure

– Autoimmune disease, such as SLE, rheumatoid arthritis

**Monitoring of AEs**

Patients should be seen regularly by a physician every 4–6 weeks initially for assessment of the general condition, performance status (PS) and body weight.

Before starting IFN, the following investigations should be performed:

– Laboratory: blood cell count, transaminases, bilirubin, albumin, prothrombin time, blood glucose, electrolytes including calcium, creatinine, thyroid function tests (according to local practice), triglycerides

– ECG

  In the follow-up, the following investigations are recommended:

– Laboratory: blood cell count, transaminases, bilirubin, blood glucose, electrolytes including calcium, creatinine, triglycerides at 1 month and 3-monthly thereafter; vitamin B₁₂ and TSH once a year

– ECG if clinically indicated (tachycardia, arrhythmia)

**Evaluation of Treatment Effect**

**Biochemical Control**

Before starting therapy, the following biomarkers should be measured:

– CgA; NSE may be considered in grade 2 NET.

– 5-HIAA in blood or 24-h urine (collection on acetic acid or hydrochloric acid, depending on local laboratory requirements) in patients with (suspected) carcinoid syndrome.

– Additional tumor markers, if indicated, depending on the type of tumor (e.g., gastrin, VIP, glucagon, or insulin).

At follow-up, biomarkers elevated at baseline should be remeasured at 3 months; then in parallel to imaging (see below); if specific symptoms increase or new symptoms occur; or in case of clinical suspicion of progressive disease.

**Tumor Response**

Before treatment and during follow-up, the following investigations are recommended:

– Cross-sectional imaging, either CT or MRI of the liver and abdomen every 3–6 months depending on tumor grade and primary tumor origin (e.g., 6-monthly in grade 1 small intestinal NET, and every 3 months in grade 2 pNET); the interval can be prolonged to 1 year if the disease is stable after 3–5 years.

– CT of the thorax if somatostatin receptor imaging revealed thoracic lesions; then every 3–12 months depending on tumor grade and growth rate.

**Patient Information**

– Patients should be informed that the most common AE is flu-like symptoms (fever, headache, fatigue, anorexia, and nausea or vomiting); these usually decrease in severity as treatment continues; symptoms may be minimized by bedtime doses and premedication with paracetamol.

– In case of suspected infections, patients should be advised to see their physician to determine white blood cell count and infective markers (C-reactive protein/pro-calcitonin).

– Patients should be informed that IFN may cause drowsiness or dizziness and that depressed mood may occur, even after long-term use, and requires prompt consultation.

– Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with IFN and, therefore, it is recommended that they avoid driving or operating machinery.
IFN should be stopped 3–4 weeks prior to surgery and after surgery depending on comorbidities/complications to decrease perioperative risk of infections.

**Drug Interactions**

There are multiple drug interactions with IFN-α 2b and IFN-α 2a; please refer to the product’s SPC. Selected drug interactions include:

- Inhibition by IFN of the hepatic enzymes CYP1A2 and CYP2C19.
- Ribavirin: concurrent treatment may increase the risk of hemolytic anemia.
- Theophylline: IFN may inhibit hepatic metabolism of theophylline, therefore monitor for increased levels/effects.
- Zidovudine: IFN may decrease zidovudine metabolism; the neutropenic effects of zidovudine and IFN may be synergistic and require monitoring.

Precise information on drug interactions can be retrieved from the US Food and Drug Administration (FDA) [23].

**Pregnancy and Lactation**

Contraceptive measures are recommended during therapy. Pregnanies have been described with IFN therapy [32]. Although no congenital malformations have been reported in a series of 27 infants, intrauterine growth retardation was present in 22%. As for lactation, the effect is undetermined; discontinue breast-feeding or the drug.

**Targeted Therapy**

This section focuses on novel targeted drugs, everolimus and sunitinib, which are registered for use in advanced NETs; therapy should be in the hands of experienced clinicians. In fact, several physicians may be involved in the management of AEs, including the primary physicians. Awareness of potential side effects and instruction of the patient may help to optimize therapy management. The aim of these SOC guidelines is to provide guidance for diagnosis and management of AEs.

**Everolimus**

**Indication**

Everolimus is an inhibitor of the mammalian target of rapamycin, an intracellular protein kinase downstream of the phosphatidylinositol 3-kinase/Akt pathway involved in key components of tumorigenesis, including cell growth, proliferation, and angiogenesis.

Everolimus is registered for therapy of advanced, progressive pNETs and for advanced, progressive grade 1/grade 2 nonfunctional NETs of gastrointestinal or lung origin [33, 34]. Everolimus may improve symptoms from NET-related endocrine hypersecretion; particularly in patients with metastatic insulinomas [35].

**Administration and Dosing Schedule**

The recommended dose of everolimus is 10 mg/day as a continuous oral treatment. Prescribers should refer to the SPC from the European Medicines Agency (EMA) for updated prescribing information (http://www.ema.europa.eu/ema/). Side effects may lead to treatment discontinuation in 17–25% of patients and to dose reductions in 60% of patients to 5 mg/day or even 5 mg every other day. Treatment interruption is advised if grade 3–4 treatment-related AEs develop, until recovery to grade <1. Then treatment may be reinitiated generally with dose adjustments as indicated below.

Hepatic impairment will increase the exposure to everolimus and requires dose reduction to 7.5 mg daily in patients with mild hepatic impairment (Child-Pugh class A) and 5 mg daily in patients with moderate hepatic impairment (Child-Pugh class B). The dose may be further decreased by one dose level if not well tolerated.

Interruption of everolimus should be considered at least 2 weeks, preferably 3–4 weeks, prior to surgical interventions and thereafter to minimize potential immunosuppressive effects and increased infection risk.

**Adverse Events**

Although generally well tolerated, with most AEs of mild to moderate severity and manageable, everolimus exhibits a distinct AE profile. Frequencies of AEs are extracted from RADIANT-2 and RADIANT-3 trial data [33, 36]; the most relevant toxicities include:

- Stomatitis: oral ulceration (inflammation of the mucous membranes of the oral cavity, inner surface of the lips or tongue) represents the most common AE reported in >60% of patients (7–9% of grade 3–4). It usually occurs within the first 8 weeks of treatment, with decreasing prevalence thereafter; mucosal lesions usually resolve within 10–14 days of treatment discontinuation.
- Skin rash (featuring papulopustular or maculopapular eruptions which may be pruritic) is a common AE; reported in 29–49% of patients, it is mostly mild to moderate in severity. Impaired wound healing may occur.
- Diarrhea occurs in 30% of patients and is mostly mild to moderate (grade 3–4 in 3–7% of patients).
- Myelotoxicity: anemia or thrombocytopenia occurs in less than 20% of the patients, and is rarely (∼5%) grade 3–4.
- Infections occur in around 20% of the patients and may range from a simple cold to pneumonia or opportunistic infections including invasive fungal infections (e.g., aspergillosis or candidiasis). Although most infections in the trials were mild, some were severe (2–7%) and culminated in respiratory failure and sepsis and were occasionally fatal [37]. There is a risk of reactivation of latent hepatitis B virus infection.
- Noninfectious pneumonitis occurs in 12–17% of patients and is characterized by noninfectious lung infiltrates and negative blood and bronchoalveolar lavage bacterial tests. Typical findings are ground-glass attenuation and focal consolidation, mainly in the lower lobes on CT or chest X-ray. Clinical symptoms such as dyspnea or cough are typical, but may be absent.
- Metabolic abnormalities include hyperglycemia, hyperlipidemia and hypophosphatemia. Hyperglycemia of any grade was reported in 12% of patients with everolimus and octreotide LAR in RADIANT-2, and was in a similar range (13%) in pNET in RADIANT-3; grade 3–4 hyperglycemia occurred in 5%. Raised triglyceride and cholesterol levels were reported in 39 and 66%, respectively. Hypophosphatemia (which may cause muscle weakness) occurred in 40% of pNET patients, 10% of which were grade 3–4.
- Renal function: mild reversible creatinine elevation has been reported in around 20% of patients with pNET (RADIANT-3); 1% were graded 3–4.
- Asthenia or fatigue is reported in one-third of treated patients, although it is generally mild to moderate (only in 1–2% it is of grade 3–4).
- Peripheral edema occur in 13–20% of the patients, but are very rarely severe (≤1% grade 3–4).

Actions and Dose Adjustments of Everolimus for AEs [38]

- Stomatitis
  - Stomatitis is mostly of grade 1–2; early intervention to prevent worsening is important. Spicy and salty foods should be avoided. Regular preventive oral rinses with isotonic saline, or alcohol- and peroxide-free mouthwash or sage tea are recommended. The use of dexamethasone mouth rinse may be considered to prevent stomatitis in potentially susceptible patients, based on the findings of the SWISH trial in postmenopausal women with breast cancer receiving everolimus and exemestane. The study demonstrated a lower incidence of stomatitis (2.4% grade ≥2 stomatitis at 8 weeks), compared with 33% in a historical control) when concomitant dexamethasone mouth was used [39].
  - Grade 1 (minimal symptoms; normal diet): continue everolimus, use oral mouth wash solutions.
  - Grade 2 (symptomatic, but patient is able to eat adequately): continue therapy if possible, or interrupt, until grade ≤1; use topical therapies including corticosteroids.
  - Grade 3 (insufficient oral fluid and food intake): interrupt therapy until recovered to grade ≤1, thereafter continue with 5 mg daily.
  - Grade 4 (parenteral nutrition required): terminate everolimus.
- Skin rash; in general, skin lesions resolve spontaneously during treatment
  - Grade 1–2 localized skin rash can be treated with topical cortisone creams and moisturizers.
  - For grade 3–4 skin lesions and generalized rash, interruption of everolimus and low-dose corticosteroids (e.g., prednisone 10–25 mg/day orally) can be considered until grade ≤1.
- Noninfectious pneumonitis
  - Grade 1 (asymptomatic radiographic findings only): observation, low-dose CT of the chest after 4–6 weeks recommended.
  - Grade 2 (symptomatic, but no impairment of daily activity); interrupt everolimus until grade ≤1, then reinitiate treatment at 5 mg daily.
  - Grade 3 (impairment of daily activity; oxygen required): interrupt everolimus until recovery to grade ≤1; then resume at one dose level lower, if grade 3 pneumonitis recurs after reexposure at a lower dose (e.g., 5 mg/day), discontinue everolimus.
  - Grade 4 (mechanical ventilation required, life-threatening): terminate everolimus.
- Infections
  - For all infections of grade 2–3, prompt treatment with appropriate antibiotic, antifungal, or antiviral drugs is required, with interruption of everolimus therapy. After recovery, reexposure at a lower dose is feasible. If grade 4 infections occur, everolimus should be discontinued.
  - Hyperglycemia diabetes (hyperglycemia grade ≥2) should be treated according to EASD and ADA guidelines
    - Grade 1–2: blood glucose <250 mg/dL; continue everolimus, start antidiabetic drugs if glucose >160 mg/dL (grade 2); monitoring of glucose by the patient.
• Grade 3: blood glucose >250–500 mg/dL; interrupt everolimus, until hyperglycemia resolves, and then restart therapy generally at reduced doses (5 mg/day), although dose titration up to 10 mg/day may be considered if hyperglycemia is adequately controlled.
• Grade 4: blood glucose >500 mg/dL, discontinue everolimus.
  – Hyperlipidemia, hypertriglyceridemia and hypercholesterolemia should be treated according to standard guidelines [40]
    • If triglyceride levels are ≥500 mg/dL, use fibrates.
    • If statins are used, be aware of potential interactions of statins with CYP3A4 enzymes.
  – Hypophosphatemia; weekly to monthly monitoring of serum phosphate depending on the severity
    • Grade 1–2: should be managed with diet and oral phosphate (1,000–2,000 mg/day divided in 4 doses) depending on the severity of phosphate depletion.
    • Grades 3 and 4: severe hypophosphatemia (<2 mg/dL and <1 mg/dL, respectively) can lead to respiratory and heart failure; and requires hospitalization for intravenous phosphate therapy. Everolimus therapy should be interrupted.
  – Creatinine elevation
    • Grade 1–2: avoid nephrotoxic drugs; adjust antihypertensive medication.
    • Grade 3–4: interrupt everolimus; after normalization of creatinine in grade 3 events everolimus can be restarted at a lower dose.

In general, discontinuation of therapy is recommended for grade 4 AEs according to the CTC [3], but there may be few exceptions, depending on the circumstance, in which clinical judgement can be used and it might be considered to restart therapy with dose reduction.

Monitoring of AEs
Patients should be reviewed every 4 weeks while on treatment; with long-term therapy (>2 year) and good tolerability clinical follow-up can be reduced to 3-monthly.
Before starting everolimus, the following investigations should be done:
  – Thorough physical investigation and assessment of comorbidities (e.g., diabetes, cardiovascular or lung disease, and infections).
  – Preexisting infections should be treated appropriately and should have fully resolved before starting treatment with everolimus.
  – Laboratory: blood cell count, blood glucose, electrolytes, calcium, serum phosphate, creatinine, transaminases, cholesterol and triglycerides (in general, lipid levels should be normalized before initiating everolimus therapy).
  – Antibody status for HBV and HCV should be determined. In case of positive serology, PCR for HCV RNA and HBV DNA, respectively, should be determined.
  – If clinically indicated, rule out tuberculosis by IFN-γ test (e.g. Quantiferon® or Mantoux reaction test).
  – At baseline, a (low-dose) CT scan may be considered optionally for reference purposes of a later possible pneumonitis.
During treatment, the following investigations are recommended:
  – Assessment of the general condition, PS, and weight every 4 weeks.
  – Laboratory parameters should be measured regularly after 2 weeks, and thereafter at least on a monthly basis (more frequently if needed) for 3 months: blood cell count, blood glucose, electrolytes, calcium, serum phosphate, creatinine, cholesterol, and triglycerides. With long-term treatment, particularly if no abnormal findings, laboratory evaluations may be prolonged to 2- to 3-month intervals.
  – For patients with a history of HCV, routine HCV RNA monitoring is mandatory; and HBV DNA for a history of hepatitis B.
  – Physicians should be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, initiate appropriate treatment promptly and consider interruption or discontinuation of everolimus.

Evaluation of Treatment Effect

  – Biochemical markers: CgA or NSE (if elevated prior to therapy); specific biomarkers (depending on functionality).
  – Tumor follow-up: conventional imaging, either CT or MRI (whatever method depicts tumor lesions most accurately) every 3 months. With long-term therapy and stable disease, the staging interval may be prolonged to 6-monthly. Although RECIST evaluation has limitations in NET response assessment, these criteria are still considered the reference method [41].

Patient Information
The patient should be advised
  – that stomatitis is a frequent, but mostly transient and mild event.
  – that infections may occur with everolimus therapy, and that oral corticosteroids should not be given while treatment with everolimus is ongoing.
that live vaccines need to be avoided.

– that an interruption of everolimus for at least 2 weeks, preferably 3–4 weeks prior to scheduled surgery or any other intervention as well as 2–4 weeks thereafter is needed.

– not to drink grapefruit juice due to its impact on metabolism of everolimus.

– that contraception in females and males is required during therapy.

Drug Interactions

Everolimus is a substrate of cytochrome P450 (CYP3A4), and interacts with p-glycoprotein (pGP); thus a number of drugs may change the blood level of everolimus. Inhibitors of CYP3A4 and pGP that are commonly in use include ketoconazole, erythromycin, verapamil, diltiazem, cimetidine, fluconazole, and cyclosporine. Antifungal systemic therapy may increase serum concentrations of everolimus and everolimus should be adjusted (or serum levels monitored closely for elevation). Before starting everolimus, careful consideration of concomitant medication is needed to rule out potential interactions [23].

Pregnancy and Lactation

Pregnancies while on everolimus-based immunosuppression in kidney transplant patients have been reported [42]. In animal studies, toxic effects have been seen; men and women should adhere to contraceptive methods and women should not perform breastfeeding while taking everolimus.

Sunitinib

Indication

Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, KIT, and RET. It is licensed for patients with progressive, unresectable, locally advanced or metastatic, well-differentiated pNET based on a placebo-controlled trial [43]; trials are ongoing to evaluate the efficacy of sunitinib in non-pNET.

Administration and Dosing Schedule

The recommended dosing regimen of sunitinib is 37.5 mg orally once daily as continuous therapy; note that this dosing schedule differs from that used for gastrointestinal stromal tumors and advanced renal cell cancer (50 mg daily for 4 weeks followed by 2 weeks off therapy [“4/2 schedule”]). Prescribers should refer to the SPC for updated prescribing information (http://www.ema.europa.eu/ema/). The dose may be reduced to 25 mg/day or 12.5 mg/day depending on tolerability.

Due to the mechanism of action, sunitinib should be interrupted for 3–4 weeks prior to, and at least 2 weeks after surgical interventions due to potential bleeding risk and impact on wound-healing.

Adverse Events

The most frequent AEs reported in the phase 3 pNET trial were diarrhea, nausea, asthenia, vomiting, and fatigue; these were mainly grade 1–2. The commonest grade 3–4 toxicities were neutropenia, hypertension, diarrhea, asthenia, and fatigue. Discontinuation due to AEs occurred in 15% of patients; and 31% of patients required at least one dose reduction [43, 44].

Hypertension of any grade occurred in 26% of patients (grade 3–4 in 10%); it is an on-target AE associated with VEGF-1 inhibition.

– Neutropenia occurred in 29% of patients overall; only 12% were of grade 3–4 and there were no reported cases of febrile neutropenia in the phase 3 study. It is usually short-lived and may be due to neutrophil margination (vs. true neutropenia) as neutrophil levels have been reported as returning to normal within 24 h of corticosteroid administration.

– Gastrointestinal toxicity: the commonest AE was diarrhea (59%) although only 5% were of grade 3–4. Typical onset is approximately 3 weeks into treatment and rarely starts beyond 6 months. Other causes (pancreatic duct obstruction or SSA-induced) need to be considered. Dose modification of sunitinib is rarely necessary. Nausea (occurring in 45% of patients) and vomiting (34%) were generally mild or moderate in severity and grade 3–4 events were rare; other causes (such as duodenal obstruction, electrolyte imbalance, etc.) should be considered and treated. Dysgeusia may occur.

– Fatigue and asthenia occur in about 1/3 of patients (but grade 3–4 in only 5%). Fatigue usually develops during the first month of treatment, with the highest incidence frequently noted after 2–3 months. Other causes (such as hypothyroidism, anemia, malignancy itself, depression, electrolyte imbalance, and dehydration) need to be considered and treated.

– Dermatologic AEs occurred frequently in the phase 3 pNET trial including hair and skin depigmentation (29% of patients), hand-foot syndrome (HFS; 23%), rash (18%), and dry skin (15%). Grade 3–4 HFS (6% of patients) is painful and may be debilitating; it particu-
larly affects high-pressure ("wear and tear") areas of the hands and feet [45].

- Oral toxicity, stomatitis, and mucositis: although this is frequently reported (48%), only 6% are severe (grade 3–4); it often occurs during the first month of treatment (peak severity occurs during the second and third months) and appears to stem from functional irritation of the mucosa [46].

- Thyroid dysfunction: hypothyroidism occurred in 7% of all cases, all of grade 1–2 severity; the exact mechanisms are not known. Longer duration of sunitinib treatment appears to increase the incidence of all-grade hypothyroidism [47].

- Cardiovascular events: according to the SPC, sunitinib may 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). Sunitinib should be used with caution in patients with a history of QT interval prolongation, those taking antiarrhythmics, or those with relevant preexisting cardiac disease, bradycardia, or electrolyte disturbances. Note that patients with QTc intervals of >450 ms for males or >470 ms for females were excluded from the pivotal study.

- Thromboembolic events were not reported in patients treated with sunitinib in the phase 3 pNET trial.

Dose Adjustments for AEs

- Hypertension: this is usually manageable and allows continued sunitinib therapy.
  - Grade 1–2 (blood pressure elevated but <160/100): use vasodilatory antihypertensive drugs (e.g., ACE inhibitors or angiotensin II receptor antagonists in preference to calcium channel blockers, diuretics or β-blockers. Avoid CYP4503A4 inhibitors such as diltiazem and verapamil (calcium channel blockers); this is not an issue with the dihydropyridine class of calcium channel blockers. Use caution with β-blockers and calcium channel blockers that cause PR elongation.
  - Grade 3 (blood pressure ≥160/100): interrupt sunitinib until hypertension is under control, resume at same dose initially but may need to reduce dose if grade 3 hypertension recurs.
  - Grade 4 (life-threatening; e.g., malignant hypertension, neurological deficit, hypertensive crisis): discontinue sunitinib.

- Neutropenia: no dose adjustments are required for grade 1–2 neutropenia.

- Interruption of sunitinib is recommended for grade 3–4 events; in case of grade 3 events, reintroduction of sunitinib at a reduced dose once neutropenia has improved to grade ≤2.

- In grade 4 events, discontinuation of therapy is recommended; however, if lasting <1 week and without any clinical symptoms/sequelae reintroduction of sunitinib at a lower dose can be considered in selected cases.

- For prolonged neutropenia, the use of growth factors may be considered in line with NCCN guidelines [48].

- Gastrointestinal toxicity.
  - Diarrhea: oral hydration and anti diarrheals usually suffice for grades 1–2; interruption of sunitinib is recommended for grades 3–4, with reintroduction of sunitinib at the same dose (grade 3) or at a reduced dose (grade 4) once diarrhea has improved to grade ≤1. A dose reduction may be preferred following grade 3 diarrhea on an individual patient basis.

- Nausea/vomiting: antiemetic agents should be used early. Proton pump inhibitors will protect the gastric mucosa but should not be given within 2 h of sunitinib as they may interfere with its absorption and metabolism. Ondansetron and related drugs are not recommended since they may interfere with sunitinib metabolism through the CYP3A4 pathway. Dose adjustments of sunitinib are seldom necessary.

- Fatigue: exclude secondary cause(s); interruption of sunitinib is recommended for grade 3 fatigue, with reintroduction of sunitinib at a reduced dose once fatigue has improved to grade ≤1.

- Dermatological AEs rarely require dose reduction; interruption of sunitinib is recommended for grades 3–4, with reintroduction of sunitinib at a reduced dose once the AE (usually HFS) has improved to grade ≤1.

- For oral toxicity, stomatitis, and mucositis symptoms are via dietary modification and oral care, dose adjustments/interruptions for oral toxicity are seldom necessary.

- Thyroid dysfunction: regular surveillance of thyroid function is recommended (initially 12-weekly and symptom-directed). Overt hypothyroidism should be treated with thyroid hormone replacement therapy according to local guidelines. Asymptomatic subclinical hypothyroidism should be monitored and treated if hypothyroidism becomes overt; sunitinib dose modifications are generally not required.
Cardiovascular events: periodic monitoring (ECG and electrolytes) should be considered and additional monitoring for signs and symptoms of congestive heart failure employed. The dose of sunitinib should be interrupted and/or reduced in patients without clinical evidence of congestive heart failure but with an ejection fraction <50% and >20% below baseline.

Thromboembolic events have been treated successfully in other settings with low-molecular-weight heparin for 3–6 months without bleeding complications. Continued sunitinib is at the physician’s discretion; interruption should be considered for patients in cardiopulmonary compromise with later reintroduction at the same dose level. Oral antivitamin K should be avoided as it interacts with both sunitinib and heparin. Asymptomatic pulmonary emboli should be treated on an individual patient basis, balancing potential risks and benefits.

In general, discontinuation of therapy is recommended for any grade 4 AEs according to the CTC [3], but there may be few exceptions, depending on the circumstance, in which clinical judgement can be used and it might be considered to restart therapy with dose reduction (see above).

Monitoring of AEs

Patients should be reviewed every 4 weeks while on treatment; with long-term therapy (>2 year) and good tolerability, clinical follow-up can be reduced to 3-monthly.

Before starting sunitinib, the following investigations should be done:

- Thorough physical investigation (including baseline blood pressure and heart rate) and assessment of comorbidities (e.g., hypertension, history of bleeding, etc.).
- Laboratory: blood cell count, blood glucose, electrolytes, calcium, serum phosphate, creatinine, transaminases and thyroid hormones.
- ECG (and estimation of left ventricular ejection fraction for patients with a cardiac history).

During treatment the following investigations are recommended:

- Assessment of the general condition, PS, and weight every 4 weeks.
- Laboratory parameters should be measured regularly after 2 weeks, and thereafter at least on a monthly basis (more frequently if needed) within the first 3 months: blood cell count, blood glucose, electrolytes, calcium, serum phosphate, and creatinine; the frequency of these tests may be reduced thereafter depending on the stability of the patient.
- Thyroid functions tests 12-weekly.

ECG and left ventricular ejection fraction as clinically indicated.

Evaluation of Treatment Effect

- Biochemical markers: CgA or NSE (if elevated prior to therapy); specific biomarkers (depending on functionality).
- Tumor follow-up: conventional imaging, either CT or MRI (whatever method depicts tumor lesions most accurately) every 3 months. With long-term therapy and stable disease, the staging interval may be prolonged to 6-monthly. Although RECIST evaluation has limitations in NET response assessment, these criteria are still considered the reference method [41].

Patient information

The patients should:

- be informed that hair may go gray, and that this reverses after stopping sunitinib.
- be informed that a discoloration of the skin may occur and that dysgeusia is common.
- be advised that blood pressure may increase and require treatment.
- know that bleeding may occur, requiring immediate attention.
- keep well hydrated, avoiding foods which may exacerbate diarrhea in individual patients (e.g., caffeine, lactose-containing foods, fatty or high-fiber foods and fruits [except pectin-containing fruit, e.g., apples and bananas]). These will vary from patient to patient.
- know that grapefruit juice and Hypericum perforatum should not be taken while on sunitinib treatment.
- be encouraged to take care of their hands and feet from the onset of treatment, including the use of moisturizing and urea-based creams; avoid rubbing (e.g., ill-fitting shoes), manicure/pedicure, etc.
- know that skin toxicity may be reduced by avoiding hot showers, reducing sun exposure, and wearing loose-fitting clothing and comfortable shoes.

Drug Interactions

In accordance with prescribing information for sunitinib, patients should try to avoid taking strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, itraconazole, erythromycin, clarithromycin, etc.) and should not drink grapefruit juice. If no alternative is available, a dose reduction of sunitinib should be considered where sunitinib is coadministered with these medications.

Similarly, patients should try to avoid taking CYP3A4 inducers (e.g., rifampicin, dexamethasone, phenytoin,
Pregnancy and Lactation

Studies in animals have shown fetal malformations with sunitinib; it should not be used during pregnancy or in men/women not using effective contraception.

As for lactation, it is not known whether sunitinib or its primary active metabolite is excreted in human milk; however, because of the potential for serious adverse reactions in breastfeeding infants, women should not breastfeed while taking sunitinib.

Appendix

Antibes Consensus Conference Participants

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References


