Sunitinib (PNET)

Indication
Treatment of unresectable or metastatic neuroendocrine tumours of pancreatic origin with disease progression In the past 12 months in patients not previously treated with a tyrosine kinase inhibitor.

(NICE TA449)

ICD-10 codes
Codes with a prefix C25

Regimen details

Drug	Dose	Route
Sunitinib	37.5mg OD*	Oral

* The dose may be escalated to 50mg daily after 8 weeks if well tolerated.

Cycle frequency
Continuous

Number of cycles
Continued until disease progression or unacceptable toxicity.

Administration
Sunitinib is available as 12.5mg, 25mg, 37.5mg and 50mg capsules.
Sunitinib may be taken with or without food.
If a dose is missed or the patient vomits after taking their dose, the patient **should not** be given an additional dose. The patient should take the usual prescribed dose on the following day.

Grapefruit and grapefruit juice should be **avoided** whilst taking sunitinib.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (no routine antiemetics required)

Additional supportive medication
Loperamide if required.
Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment to minimise the risk of developing PPE.

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Blood pressure	Must be controlled before initiating sunitinib

Consider echocardiogram and ECG if patient has significant cardiac history.
Consider baseline urinalysis

Investigations – pre subsequent cycles

Patients should be reviewed 2-4 weeks after commencing sunitinib and prior to each cycle thereafter.

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Thyroid function	Every 12 weeks
Blood pressure	Weekly for first cycle then prior to each cycle

Consider periodic echocardiogram and ECG if patient has significant cardiac history.
Periodic urinalysis to monitor for proteinuria.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 30ml/min
AST/ALT	≤ 2.5 x ULN (or <5 x ULN if liver metastases)

Dose modifications

- ### Haematological toxicity

Toxicity	**Definition**	**Dose adjustment**
Neutropenia	Neutrophils 0.5-0.9 x 10^9/L	Delay until ≥ 1.0 x 10^9/L then continue at same dose (repeated occurrence – consider reducing dose by 12.5mg)
	Neutrophils <0.5 x 10^9/L	Delay until ≥ 1.0 x 10^9/L then reduce dose by 12.5mg
Thrombocytopenia	Platelets 25-49 x 10^9/L	Delay until ≥ 50 x 10^9/L then continue at same dose (repeated occurrence – consider reducing dose by 12.5mg)
	Platelets < 25 x 10^9/L	Delay until ≥ 50 x 10^9/L then reduce dose by 12.5mg

- ### Renal impairment

No starting dose adjustment is required when administering sunitinib to patients with renal impairment or with end-stage renal disease on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability.
Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

- **Hepatic impairment**

Sunitinib and its primary metabolite are mainly metabolised by the liver, however, no starting dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). There is no data available for patients with severe hepatic impairment (Child-Pugh Class C).
If patients develop significantly deranged LFTs or other signs or symptoms of hepatic failure during treatment, sunitinib should be discontinued.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Hypertension	Persistently >140/90mmHg despite standard antihypertensive medication.	Reduce dose in 12.5mg steps and continue to monitor. If persists discontinue treatment.
Diarrhoea	Grade 2	Withhold until ≤ grade 1 then continue at 100% dose
	Grade 3 and 4	Withhold until ≤ grade 1 then continue with 12.5mg dose reduction
Palmar-Plantar Erythrodysaesthesia (PPE)	Grade 1	100% dose with symptomatic treatment of PPE
	Grade 2	1st occurrence: withhold until ≤ grade 1 resume with 12.5mg dose reduction
		2nd occurrence: withhold until ≤ grade 1 resume with a further 12.5mg dose reduction
		3rd occurrence: discontinue
	Grade 3	1st occurrence: withhold until ≤ grade 1 resume with 12.5mg - 25mg dose reduction
		2nd occurrence: discontinue or withhold until ≤ grade 1 resume with 12.5mg - 25mg dose reduction
		3rd occurrence: discontinue
Stomatitis	Grade 1	100%
	Grade 2	Withhold until ≤ grade 1 and resume with 12.5mg dose reduction
	Grade 3	Withhold until ≤ grade 1 and resume 12.5mg - 25mg dose reduction
	Grade 4	Discontinue or withhold until ≤ grade 1 and resume with 12.5mg - 25mg dose reduction
Cardiotoxicity	LVEF < 50% (and > 20% below baseline) without evidence of CHF	Interrupt treatment and reduce dose by 12.5mg
	Evidence of CHF	Discontinue
Pancreatic function	Grade 4 elevations in lipase without evidence of pancreatitis	Omit until ≤ grade 3 resume at 100% dose
	Evidence of pancreatitis	Discontinue
Hypothyroidism	High TSH, normal T4	If symptomatic: thyroid replacement therapy If asymptomatic: monitor thyroid function prior to every cycle, no treatment required.
	High TSH, low T4	Thyroid replacement therapy

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cardiotoxicity
QT interval prolongation
Myelosuppression
Thyroid dysfunction
Proteinuria, nephrotic syndrome
Pancreatitis
Arterial thrombotic events
Haemorrhage
Impaired wound healing
Osteonecrosis of the jaw
Severe cutaneous reactions
Posterior reversible leukoencephalopathy syndrome (RPLS)

- **Frequently occurring side effects**

Diarrhoea, constipation
Nausea and vomiting
Stomatitis and mucositis
PPE
Myelosuppression
Epistaxis
Hypertension

- **Other side effects**

Skin and hair changes
Taste disturbances
Anorexia
Fatigue
Headache

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of sunitinib. If unable to avoid co-administration consider reducing the dose of sunitinib to 25mg daily.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of sunitinib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to sunitinib. If unable to avoid co-administration, the dose of sunitinib may need to be increased in 12.5mg steps up to a maximum of 62.5mg per day.

Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin or DOAC.

Additional comments

Patients with cardiac events in the previous 12 months were excluded from all sunitinib clinical studies. Patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib, especially patients with cardiac risk factors or history of coronary artery disease.

References

- National Institute for Health and Clinical Excellence (NICE TA449) accessed 26 May 2022 via www.nice.org.uk
- Summary of Product Characteristics – Sunitinib (Pfizer) accessed 26th May 2022 via www.medicines.org.uk
- Raymond, E. *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumours. N Engl J Med 2011; 364:501-513

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