Sunitinib (renal)

Indication

First line treatment of patients with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

(NICE TA169)

ICD-10 codes

Codes with a prefix C64

Regimen details

Day	Drug	Dose	Route
1-28*	Sunitinib	50mg OD	PO

*Followed by 2 weeks rest (total cycle length 6 weeks). If the patient has tumour flare or worsening symptoms during the 2 week rest period continuous dosing at maximum dose 37.5mg OD may be considered (note this is an unlicensed dosing schedule).

Cycle frequency

Every 6 weeks (42 days) – '4 weeks on, 2 weeks off'.

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

ECG if patient has significant cardiac history.

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

Periodic urinalysis to monitor for proteinuria.
ECG if patient has significant cardiac history.

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 10-49 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 < 10 x 10^9/L	Delay until ≥ 50 x 10^9/L then reduce dose by 12.5mg

- **Renal impairment**

CrCl (ml/min)	**Sunitinib dose**
≥ 30	100%
< 30	No experience of use in patients with CrCl < 30ml/min – discuss with consultant and use with caution*

* Consultant decision. Patients with renal impairment were excluded from clinical trials, however small studies have suggested that sunitinib may be used in patients with severe renal impairment or end stage renal disease with close monitoring.

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 dosage adjustment is recommended in patients with mild to moderate hepatic impairment. There is no data available for patients with severe hepatic impairment.

Deteriorating organ function should be discussed with the consultant as this may be a sign of disease progression.

- **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**

Myelosuppression
Cardiotoxicity
QT interval prolongation
Thyroid dysfunction
Proteinuria, nephrotic syndrome
Pancreatitis

Arterial thrombotic events
Haemorrhage
Impaired wound healing

- **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.

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.

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

Additional comments

Nil

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 169 accessed 7 May 2014 via www.nice.org.uk
- Summary of Product Characteristics – Sunitinib (Pfizer) accessed 7 May 2014 via www.medicines.org.uk
- Study VEG108844, a Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARZ trial protocol, amendment number 2).

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