Axitinib (renal)

Indication
Treatment of advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor (UK licensed indication states sunitinib) or a cytokine.

(NICE TA333)

ICD-10 codes
Codes with a prefix C64

Regimen details

Day	Drug	Dose	Route
1-28	Axitinib	5mg BD	PO

Patients who tolerate axitinib starting dose of 5 mg BD with no adverse reactions for two consecutive weeks may have their dose increased to 7 mg BD (unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment). Subsequently patients who tolerate axitinib dose of 7 mg BD (using the criteria above) may have their dose increased to a maximum of 10 mg BD.

Note: in some patients it may be appropriate to increase the dose to 6mg BD before increasing to 7mg BD.

Cycle frequency
Continuously

Number of cycles
Continued until disease progression or unacceptable toxicity.

Administration
Axitinib is available as 1mg, 3mg, 5mg and 7 mg tablets.

Axitinib should be taken orally twice daily approximately 12 hours apart with or without food. Axitinib tablets should be swallowed whole with a glass of water.

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 next prescribed dose at the usual time.

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

Pre-medication
Nil

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

Additional supportive medication
Loperamide if required.
Mouthwashes if required.

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 axitinib
Urinalysis (to assess for proteinuria)	Baseline

ECG/ECHO if patient has significant cardiac history. Axitinib should be used in caution in patients who are at risk of, or have history of, thrombotic events. Axitinib has not been studied in patients who had an arterial embolic or thrombotic event within the previous 12 months, or venous embolic or thrombotic event within the previous 6 months.

Existing hypertension should be well controlled before starting treatment.

Axitinib should not be used in patients with untreated brain metastases or recent active gastrointestinal bleeding.

Investigations – pre subsequent cycles

Patients should be reviewed 2 weeks after commencing axitinib 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	3 monthly
Blood pressure	Weekly for the first cycle then prior to each cycle
Urinalysis (to assess for proteinuria)	3 monthly

ECG/ECHO as clinically indicated.

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	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	≥ 60mL/min
Bilirubin	< 1.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L or platelets < 100 x 10^9/L discuss with consultant.
If bleeding requiring medical intervention occurs, interrupt axitinib until resolved.

- **Renal impairment**

Patients with renal impairment were excluded from clinical trials and there is no experience of use in patients with CrCl < 60ml/min – discuss with consultant and use with caution.

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.

- **Hepatic impairment**

Bilirubin (x ULN)	**Axitinib dose**
< 1.5	100%
1.5-3	2mg BD
> 3	Discontinue

There is no data available for axitinib in 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**

If a dose reduction is required, the dose should be reduced to 3mg BD and subsequently if required, to 2mg BD.

Hypertension

Blood pressure should be well controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy.

- If persistent hypertension, despite use of anti-hypertensive treatment – reduce axitinib dose.
- If severe hypertension, temporarily interrupt axitinib and restart at a lower dose once normotensive.
- If severe or persistent arterial hypertension and symptoms suggestive of posterior reversible encephalopathy syndrome (headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances), a diagnostic brain MRI should be performed. Temporarily interrupt or permanently withdraw treatment.

Thyroid dysfunction

Thyroid function should be monitored prior to treatment and throughout treatment.
Manage with standard medical intervention and axitinib may continue at the same dose.

Proteinuria

If moderate to severe (≥ +2 on urine dipstick) reduce the dose or withhold axitinib until resolved.

Dysphonia

Consider dose reduction if severe or troublesome.

Skin toxicity (PPE)

If ≥ grade 3, interrupt treatment until ≤ grade 1. Resume at reduced dose.
Patients should be advised to use regular moisturiser and to keep the skin cool.

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

- **Serious side effects**

Myelosuppression
Thyroid dysfunction, hypothyroidism
Proteinuria, nephrotic syndrome
GI perforation
Arterial/venous thrombotic events
Haemorrhage
Posterior reversible encephalopathy syndrome (PRES)
Hepatic changes

- **Frequently occurring side effects**

Dizziness
Hypertension
Diarrhoea, constipation
Nausea and vomiting
Dysphonia
Reduced appetite
Stomatitis and mucositis
Dysgeusia
PPE

- **Other side effects**

Anorexia
Fatigue
Headache

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

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, erythromycin, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of axitinib. If co-administration is unavoidable consider reducing axitinib dose.

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

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to axitinib. If co-administration unavoidable, consider gradual dose increases with close monitoring and reduce dose back to previous level on discontinuation of the enzyme inducer.

Strong inhibitors of CYP1A2 and CYP2C19 (e.g. ciprofloxacin and other fluoroquinolones, fluvoxamine, moclobemide, verapamil, chloramphenicol and some herbal teas such as peppermint and camomile): use with caution, effect not been studied but potential risk of increased axitinib plasma concentrations.

The risk of decreased axitinib plasma concentrations should be considered when administering axitinib to smokers (CYP1A2 induction).

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

Antacids: avoid concomitant administration with potent antacids (proton pump inhibitors, histamine H2 antagonists). Give 2 hours before or 2 hours after axitinib.

Additional comments

Adequate contraception methods to be applied during and up to 1 week after the therapy.

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 333 accessed 20 Jan 2016 via www.nice.org.uk
- Summary of Product Characteristics – Axitinib (Pfizer) accessed 20 Jan 2016 via www.medicines.org.uk
- Rini et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial (2011); Lancet 378:1931-193

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