Axitinib

Indication
Treatment of advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine

Regimen details
Axitinib 5mg orally twice daily

The dose can be adjusted up or down depending on toxicity (see dose adjustments below)

Cycle frequency
Continuous treatment, dispense monthly

Number of cycles
Until disease progression or unacceptable toxicity

Administration
If the patient vomits or misses a dose, no additional doses should be taken. The next prescribed dose should be taken at the usual time

Pre-medication
N/A

Emetogenicity
No routine antiemetics required

Additional supportive medication
N/A

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Blood pressure	Pre-treatment
Urine dip for proteinuria	Pre-treatment

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

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating axitinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm

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

FBC, U+E (including creatinine), LFT (including AST), TFTs (every 12 weeks), urinalysis (every 12 weeks), blood pressure, 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**
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 3 x ULN
Blood pressure	< 150/90

Dose modifications

Elderly
There are no specific dosage recommendations based on the age of the patient.

Renal impairment
No dose reductions necessary for mild-moderate renal impairment where the estimated GFR is above 15ml/min. There is no data on more severe renal impairment and caution is advised.

Hepatic impairment
For mild hepatic impairment (Child-Pugh A), no dose adjustment is necessary.
For Child-Pugh B, start at 2mg bd
There is no data available on severe hepatic impairment and use is not recommended

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

Dose increases
If after two consecutive weeks at 5mg bd with tolerable toxicity no greater than grade 2 (unless the patient's blood pressure is > 150/90 mmHg or the patient is receiving antihypertensive treatment) the dose can be increased to 7mg bd. The dose can further be increased to a maximum of 10mg bd.

Dose reductions
Axitinib dose can be reduced to 3mg bd and then to no less than 2mg bd

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 coadministration 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

References

Inlyta SPC - https://www.medicines.org.uk/emc/product/7948/smpc

THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, DESIGNATED LEAD CLINICIAN FOR KIDNEY CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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