REGIMEN TITLE: Axitinib in Renal cell carcinoma

Indication: An option for 2nd line treatment in advanced renal cell carcinoma with progression after previous TKI (tyrosine kinase inhibitor) or cytokine therapy

LCNDG criteria to be met:
- An assessment of potential need for co-administration with inhibitors or inducers of CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19 and uridine diphosphate-glucuronosyltransferase (UGT) 1A1, will be undertaken in the patient and doses adjusted accordingly
- No severe renal impairment
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (unless due to longstanding physical disability) without significant co-morbidity
- Patient able to tolerate and comply with oral dosage forms

Notes: Axitinib should be used with caution in patients who are at risk of, or who have a history of, arterial or venous embolic and thrombotic events (including transient ischaemic attack, myocardial infarction, cerebrovascular accident, retinal artery or vein occlusion/ thrombosis, pulmonary embolism or deep vein thrombosis). 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.

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

Existing hypertension should be well controlled before starting treatment.

Treatment with axitinib should be stopped at least 24 hours prior to elective surgery.

Regimen details: Axitinib  5mg  PO Twice daily

Continuous therapy.

Dose escalation
If the starting dose of 5mg twice daily is well tolerated for at least 2 consecutive weeks, i.e.
- No adverse effects > grade 2 (CTCAE v.3.0) and
- Blood pressure < 150/90mmHg and
- No antihypertensives are required

Then Axitinib dose may be increased to 7mg  PO Twice daily.

According the same criteria, subsequently the dose may be increased to Axitinib 10mg  PO Twice daily if appropriate.

*See dose modifications section for dose reductions and monitoring

Administration: Available as 1mg and 5mg film-coated tablets (56 tablet packs)
Take tablets with or without food, approximately 12 hours apart.
Swallow whole with a glass of water.
Frequency: Prescribed in 4 week cycles - continued until disease progression or unacceptable toxicity

Anti-emetics: Mildly emetogenic

Supportive medication: Diarrhoea can be managed with loperamide – 2mg PRN (max. 16mg/day). Mouthwashes according to local mouth care guidance if needed.

Regular investigations:
- LFTs (incl. AST, ALT) *Prior each cycle
- FBC, Hb/haematocrit *Prior each cycle
- U&Es *Prior each cycle
- Blood pressure *Prior each cycle
- MUGA/ECHO Baseline in pre-existing cardiac disease, repeat if cardiac toxicity suspicion
- ECG Baseline and periodic monitoring, as above
- Thyroid function Alternate cycles, monitor for symptoms/signs of thyroid dysfunction.
- Urinalysis (proteinuria) Baseline & periodically when required

* Mid-cycle assessment is recommended during the first cycle

Comments: To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

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

Toxicities: Arterial/venous embolic and thrombotic events, haemorrhage, GI perforation/fistula, posterior reversible encephalopathy syndrome (PRES), hypertension, proteinuria, hepatic changes, hypothyroidism, diarrhoea, constipation, dysphonia, nausea, decreased appetite and weight, PPE, rash, headache, dysgeusia, stomatitis, fatigue

Precautions and Dose Modifications

Haematological toxicity

Baseline levels
- Neutrophils $\geq 1.5 \times 10^9/L$
- Platelets $\geq 100 \times 10^9/L$ 100% dose

Discuss lower than normal haematological findings and treatment doses with consultant.

Non-Haematological Toxicity

When dose reduction of Axitinib is necessary due to any toxicity, the axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily.
Hypertension

Blood pressure should be well controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In the case of persistent hypertension, despite use of antihypertensive medicinal products, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib and restart at a lower dose once the patient is normotensive. If axitinib is interrupted, patients receiving antihypertensive medicinal products should be monitored for hypotension.

In case of 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 magnetic resonance image (MRI) should be considered. Temporarily interrupt or permanently withdraw treatment.

Elevation of haemoglobin or haematocrit

Increases in haemoglobin or haematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib. An increase in red blood cell mass may increase the risk of embolic and thrombotic events.

Haemorrhage

Interrupt treatment temporarily in case of any bleeding requiring medical intervention.

Proteinuria

For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment. In studies the treatment has been interrupted in proteinuria ≥ 2g/24hr.

Hand-feet symptoms

Encourage regular use of moisturizers to hand and feet regularly. Advise minimizing activities that put pressure on feet or hands, as usually the pressure point areas are affected. Keeping skin cool is beneficial, avoiding extreme heat (such as strong sunlight or hot baths). Support use of non-deodorant, non-fragrance products. Consider products with anti-itch additions in pruritus, and exfoliating urea containing products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Non-steroidal anti-inflammatory creams and analgesia may help but a 1-2 week dose interruption may be necessary for painful symptoms.

Renal Impairment

No dose adjustment is required. Discuss with consultant if CrCl <15ml/min
**Hepatic Impairment**

Axitinib is contra-indicated in severe hepatic impairment.

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Dose</th>
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<tbody>
<tr>
<td>&lt;1.5 x ULN</td>
<td>Give 100%</td>
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<tr>
<td>1.5-3 x ULN</td>
<td>Reduce dose from 5mg BD to 2mg BD</td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>Discontinue</td>
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**Drug interactions: Avoid axitinib in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.**

Concurrent use of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates, dexamethasone, St John’s Wort) can decrease axitinib plasma concentration and reduce efficacy. **If co-administration is unavoidable, consider increasing axitinib dose gradually. If axitinib dose is increased, careful clinical monitoring is indicated.**

**If co-administration with an enzyme inducer is stopped, reduce the axitinib dose immediately back to previous level.**

Concurrent use of CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, grape fruit juice) can increase axitinib plasma concentration and increase toxicity. **If co-administration is unavoidable, consider reducing axitinib dose.**

The effect of strong inhibitors of CYP1A2 and CYP2C19 has not been studied. Caution should be exercised due to the risk of increased axitinib plasma concentrations in patients taking strong inhibitors of these isozymes (ciprofloxacin and other fluoroquinolones, fluvoxamine, moclobemide, verapamil, chloramphenicol and some herbal teas such as peppermint and chamomile)

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

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

**References:**

www.medicines.org.uk
www.micromedex.com
Rini et al. (2011); Lancet 378:1931-1939
Pfizer MI enquiry, Jan 2013