Axitinib and avelumab

Indication
First line treatment of advanced renal cell carcinoma (RCC)

Regimen details
Axitinib 5mg bd continuously (see dose modifications below)

Day	Drug	Fluid	Route	Time
1 & 15	Avelumab 800mg	250ml Sodium chloride 0.9%	IV	60 mins

Cycle frequency
Every 28 days

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Administer the drug solution using a volumetric pump through an intravenous line containing a sterile non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2micrometer)

Patients should be monitored for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria.

For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued

For Grade 1 infusion-related reactions, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 infusion-related reactions, the infusion should be temporary discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate.

In case of recurrence of Grade 1 or Grade 2 infusion-related reaction, the patient may continue to receive avelumab under close monitoring, after appropriate infusion rate modification and premedication with paracetamol and antihistamine

Pre-medication
Give chlorphenamine IV 10mg and paracetamol 1000mg orally prior to the first 4 infusions

Emetogenicity
Minimal

Additional supportive medication
None

Extravasation
Neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Blood pressure	14 days
ECG	Baseline
Calcium	14 days
Glucose	14 days
Thyroid function tests	14 days
Serum samples for HIV, hep C antibody and HBs Ag if risk factors	14 days
Pregancy test (if applicable)	14 days
Cortisol	14 days
Follicle stimulating hormone	14 days
Luteinizing hormone	14 days
Testosterone	14 days

Blood pressure must be well controlled before initiating treatment with axitinib. The use of vascular endothelial growth factor (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

Temporary interruption of axitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume axitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-related adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), blood pressure, TFTs

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	≥ 15 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Dose modifications

If the starting dose of axitinib 5mg twice daily is well tolerated for at least 2 consecutive weeks

- No adverse effects > grade 2
- Blood pressure < 150/90mmHg
- Not receiving anti-hypertensive treatment

Then the axitinib dose may be increased to 7mg twice daily.

Subsequently, using the same criteria, patients who tolerate an axitinib dose of 7 mg twice daily may have their dose increased to a maximum of 10 mg twice daily.

Axitinib dose may be reduced to 3 mg twice daily and further to 2 mg twice daily if not tolerated.

Renal impairment

No dose adjustment is required. Virtually no data are available regarding axitinib treatment in patients with a creatinine clearance of < 15 mL/min.

Hepatic impairment

No dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (e.g. the starting dose should be reduced from 5 mg twice daily to 2 mg twice daily). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population

Immune Related Adverse Events (IRAEs)

Immunotherapy toxicities should be aggressively managed as they can cause permanent and life-threatening complications.
Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.
Refer to network guidelines for management of IRAEs

Adverse effects –

for full details consult product literature/ reference texts

Immune related adverse effects
Diarrhoea
Nausea
Infusion reactions
Hypertension
Fatigue
Weight loss
Rash

Significant drug interactions

– for full details consult product literature/ reference texts

Avelumab is primarily metabolised through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic drug-drug interactions with other medicinal products.

Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, phenobarbital and St. John's wort) may decrease axitinib plasma concentrations.

Additional comments

Axitinib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take axitinib

References

Avelumab with axitinib for untreated advanced renal cell carcinoma NICE TA 645: https://www.nice.org.uk/guidance/ta645

Avelumab SPC Accessed 12/3/2024: https://www.medicines.org.uk/emc/product/8453

Axitinib SPC Accessed 12/3/2024: 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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