Lenvatinib & everolimus

Indication
Advanced renal cell carcinoma (RCC) after one prior vascular endothelial growth factor (VEGF)-targeted therapy

Regimen details
Lenvatinib (Kisplyx) 18mg orally daily
Everolimus 5mg orally daily

Cycle frequency
Continuous treatment, dispense monthly

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food. The capsules can be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Alternatively, the lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed.

Everolimus tablets should be taken whole, with or without food at the same time each day

Avoid grapefruit or grapefruit juice

Pre-medication
None

Emetogenicity
Minimal (supply metoclopramide prn)

Additional supportive medication
Supply loperamide with first cycle

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Fasting glucose	14 days
Lipids	14 days
TFTs	14 days

Blood pressure	14 days
Urinalysis for proteinuria	14 days
ECG	14 days
Calcium	14 days
Magnesium	14 days

Blood pressure must be well controlled before starting treatment with lenvatinib

Electrolyte disturbances must be corrected before starting treatment with lenvatinib

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

Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of lenvatinib following a major surgical procedure. Therefore, the decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Investigations –pre subsequent cycles

Investigation	**Frequency**
FBC	Every 2 weeks for the first 2 months then every 4 weeks
U&Es	Every 2 weeks for the first 2 months then every 4 weeks
LFTs	Every 2 weeks for the first 2 months then every 4 weeks
Calcium	Every 4 weeks
Magnesium	Every 4 weeks
Fasting glucose	Every 6-8 weeks then as clinically indicated
Lipids	Every 6-8 weeks then as clinically indicated
TFTs	Every 6-8 weeks then as clinically indicated
Blood pressure	After week 1 then every 2 weeks for the first 2 months then every 4 weeks

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	≥ 75 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ ULN
AST	< ULN

Dose modifications

Lenvatinib dose modifications

Dose level	**Daily dose**	**Number of capsules**
Recommended daily dose	18 mg orally once daily	One 10 mg capsule plus two 4 mg capsules
First dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Second dose reduction	10 mg orally once daily	One 10 mg capsule
Third dose reduction	8 mg orally once daily	Two 4 mg capsules

The dose of everolimus may be reduced to alternate days or 2.5mg OD. Dose modifications lower than this are not recommended

Haematological toxicity

Toxicity	Definition	Dose adjustment
Neutropenia	Neutrophils 0.5 – 1.0 x 10^9/L	1st occurrence: Delay until ≥ 1.0 x 10^9/L then continue both drugs at same dose 2nd occurrence: Delay until ≥ 1.0 x 10^9/L then continue with reduced dose of everolimus 3rd occurrence: Discontinue everolimus
	Neutrophils < 0.5 x 10^9/L	1st occurrence: Delay until ≥ 1.0 x 10^9/L then continue with reduced dose of everolimus 2nd occurrence: Discontinue everolimus
Febrile neutropenia	Grade 3	Delay until neutrophils ≥1.25 x 10^9/L and no fever then continue with reduced dose everolimus
	Grade 4	Discontinue everolimus
Thrombocytopenia	Platelets 50-75 x 10^9/L	1st occurrence: Delay until recovery then continue at same dose 2nd occurrence: Delay until recovery then continue with reduced dose of everolimus 3rd occurrence: Discontinue everolimus
	Platelets 25-49 x 10^9/L	1st occurrence: Delay until recovery then continue reduced dose everolimus 2nd occurrence: Discontinue everolimus

Renal impairment

No adjustment of starting dose for either agent is required on the basis of renal function in patients with mild or moderate renal impairment.

In patients with severe renal impairment (CrCl < 30mL/min), the recommended starting dose is 10 mg OD lenvatinib with 5 mg OD of everolimus. Further dose adjustments may be necessary based on individual tolerability. Treatment is not recommended in patients with end-stage renal disease.

Cases of renal failure have been reported in patients receiving everolimus. Renal function should be monitored.

Patients with acute renal failure should stop treatment until the cause has been investigated and treated

Hepatic impairment

Degree of hepatic impairment	Everolimus dose	Lenvatinib dose
Mild (Child Pugh A)	5mg daily	18mg daily
Moderate (Child Pugh B)	5mg daily	18mg daily
Severe (Child Pugh C)	Not recommended – if used, dose must not exceed 2.5mg daily	Not recommended – if used, 10mg daily

Other toxicities

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

*Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Venous thromboembolism
Impaired wound healing
Teratogenicity
Hepatotoxicity
Infertility (males)
ARDS

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
Hyperlipidaemia
Hyperglycaemia
Hypertension
Hypothyroidism
Oedema
Myelosuppression
Rash
Pneumonitis (patients should report any new or worsening respiratory symptoms)
Stomatitis/Mucositis

- **Other side effects**

Taste disturbances
Fatigue
Headache
Insomnia
Weight loss

Significant drug interactions

– for full details consult product literature/ reference texts

Everolimus:

Potent CYP3A4 and PgP inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration - may increase plasma concentrations of everolimus. Risk of toxicity

Moderate CYP3A4 and PgP inhibitors (e.g. erythromycin, imatinib, ciclosporin, verapamil, diltiazem, grapefruit juice): co administration with caution and close monitoring/consider dose reduction of everolimus

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

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, dexamethasone, St Johns Wort): avoid co-administration - may reduce exposure to everolimus. Risk of therapeutic failure

ACE inhibitors: caution, increased risk of angioedema

Lenvatinib:

As lenvatinib may prolong the QT interval avoid concomitant use of other medications which can lead to QT prolongation (including amiodarone, quinidine, sotolol, chloroquine, clarithromycin).

Use with caution in patients taking medications which may cause electrolyte disturbances

Oral contraceptives: it is not known if lenvatinib may reduce the effectiveness of hormonal contraceptives and so women should also use a barrier method.

Agents acting on the renin-angiotensin aldosterone system: use with caution due to potentially higher risk for acute

renal failure

Additional comments

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take everolimus.

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method

References

Kisplyx SPC - https://www.medicines.org.uk/emc/product/7881/smpc

Afinitor SPC - https://www.medicines.org.uk/emc/product/6658/smpc

South West Clinical Network Cancer Protocols - http://www.swscn.org.uk/guidance-protocols/cancer-protocols/

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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