Lenvatinib (Thyroid Cancer)

Indication

First line tyrosine kinase inhibitor (TKI) option for the treatment of progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hurthle cell) in patients whose disease no longer responds to radioactive iodine.

No previous treatment with other TKI (eg. Sorafenib) unless TKI stopped within 3 months of starting it because of toxicity that cannot be managed by dose delay or modification and in the absence of disease progression.

(NICE TA535)

ICD-10 codes

Codes with a prefix C73

Regimen details

Day	Drug	Dose	Route
1-28	Lenvatinib	24mg OD	Oral

Cycle frequency

Continuously until disease progression or unacceptable toxicity.

Number of cycles

As above

Administration

Lenvatinib is available as 10mg and 4mg capsules. Note the **Lenvima®** brand is the only product licensed for thyroid carcinoma.The dose should be taken at about the same time, once daily, with or without food. The capsules should be swallowed whole.

For patients who cannot swallow the capsules, these can be added to a tablespoon of water or apple juice to produce a suspension. The capsules must not be broken or crushed but must be left to dissolve for 10 minutes, and stirred for at least 3 minutes to dissolve the capsule shells. Once the suspension has been swallowed the same amount of water must be added to the glass, swirled to collect any residue then swallowed.

If a dose is missed and it cannot be taken within 12 hours, that dose should be skipped and the next dose taken at the usual time.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential (though nausea is common)

Additional supportive medication

Patients should be supplied with metoclopramide and loperamide on commencing treatment.

Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment and to avoid activities that put pressure on hands and feet to minimise the risk of developing palmar plantar erythema.

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Blood pressure*	14 days
Urinalysis for proteinuria	14 days
ECG for QTc interval**	14 days

* Blood pressure should be well controlled (defined as BP ≤ 140/90) prior to commencing treatment and if patients are known to be hypertensive, they should be on a stable dose of antihypertensive for at least 1 week prior to treatment with lenvatinib.
** Review concomitant medications that may also lead to QTc prolongation. Electrolyte abnormalities, such as hypokalaemia, hypocalcaemia or hypomagnesaemia must be corrected prior to commencing treatment.
** Consider echocardiogram if concerns about cardiac status.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Every 2 weeks for first month then monthly
U+E (including creatinine)	Every 2 weeks for first month then monthly
LFTs	Every 2 weeks for first two months then monthly
Ca	Every 2 weeks for first month then monthly
Mg	Every 2 weeks for first month then monthly
Thyroid function	Every three months
Blood pressure*	After 1 week, then every 2 weeks for first two months, then monthly
Urinalysis for proteinuria	Every 2 weeks for first two months, then monthly
ECG for QTc interval	Every 2 weeks for first month then periodically as indicated

* Hypertension may develop within a week of commencing TKIs. Patients should be encouraged to monitor their blood pressure at home regularly, ideally daily.

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)	≥ 30ml/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 1.5 x ULN
QTc	<500ms

Dose modifications

Mild to moderate adverse reactions (eg. Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management. Severe (eg. Grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement of the reaction to Grade 0-1 or baseline. Treatment should be discontinued in case of life-threatening reactions (Grade 4).
If dose reductions are required, the dose should be reduced as per table below:

Dose level	Lenvatinib dose
Full dose	24 mg OD
1st dose reduction	20 mg OD
2nd dose reduction	14 mg OD
3rd dose reduction	10 mg OD

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L or platelets < 100 x 10^9/L, discuss with consultant.

- **Renal impairment**

No specific dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (<30ml/min), the recommended starting dose is 14mg OD.

- **Hepatic impairment**

No specific dose adjustment is required in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment (Child-Pugh C) the recommended starting dose is 14mg OD.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Hypertension Hypertension should be managed aggressively and pro-actively to minimise dose interruptions and reductions. Antihypertensives should be started as soon as elevated BP is confirmed. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. Examples of appropriate anti-hypertensives include • Step 1 ACE inhibitor (eg. Ramipril - start at 2.5mg then increasing to 5mg) • Step 2 Adding calcium channel blocker (eg. Amlodipine - start at 5mg then increasing to 10mg) and/or diuretics if required. • Step 3 If BP not controlled on a combination of antihypertensives, refer for cardiology opinion.	Systolic blood pressure (SBP) ≥ 140 mmHg up to < 160 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg up to < 100 mmHg	Continue lenvatinib and initiate antihypertensive therapy OR Continue lenvatinib and increase the dose of current antihypertensive or initiate additional antihypertensive therapy
	SBP ≥ 160 mmHg or DBP ≥ 100 mmHg despite optimal antihypertensives	Withhold lenvatinib When SBP ≤ 150 mmHg, DBP ≤ 95mmHg and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose
	Life threatening consequences (malignant hypertension, neurological deficit or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management

Toxicity	Definition	Dose adjustment
Proteinuria	Grade 1 Urinalysis: 1+ protein Urinary protein ≥ ULN - < 1.0g/24h Urine protein/creatinine ratio < 100mg/mmol (or urine albumin/creatinine ratio <70 mg/mmol)	Continue lenvatinib
	Grade 2 Urinalysis: 2+ protein Urinary protein 1.0 - < 3.5g/24h Urine protein/creatinine ratio 100 – 300 mg/mmol (or urine albumin/creatinine ratio 70-250 mg/mol)	If >2+ proteinuria is documented a more formal measurement by either 24 hour urine collection or urine protein/creatinine ratio should be undertaken. If ≥ 2g/24h, stop lenvatinib and resume at reduced dose when <2g/24h
	Grade 3 Urinalysis: 3+ protein Urinary protein > 3.5g/24h Urine protein/creatinine ratio >300mg/mmol (or urine albumin/creatinine ratio >250mg/mmol)	Withhold lenvatinib. Then as per Grade 2. In case of chronic persistent proteinuria, discontinue and refer to nephrologist
	Grade 4 Nephrotic syndrome	Discontinue
Diarrhoea	Grade 1 - 2	Continue lenvatinib with supportive measures such as loperamide
	Grade 3	Withhold lenvatinib and resume at reduced dose once resolves to ≤ 1
	Grade 4	Discontinue
Skin toxicity, including palmar plantar erythema	Grade 1-2	Continue lenvatinib. Patients should be advised to use regular emollients eg udderly smooth or urea containing moisturisers such as eucerin and to keep skin cool.
	≥ Grade 3	Withhold lenvatinib and resume at reduced dose once resolves to ≤ 1
QTc interval prolongation	>500ms	Withhold lenvatinib and resume at reduced dose when <480ms
Renal impairment or failure, or Hepatoxicity	Grade 3	Withhold lenvatinib and resume at reduced dose once resolves to ≤ 1
	Grade 4	Discontinue
Cardiac dysfunction, GI perforation or fistula, Haemorrhage	Grade 3	Withhold lenvatinib and resume at reduced dose once resolves to ≤ 1
	Grade 4	Discontinue
Non-GI fistula	Grade 4	Discontinue
Posterior reversible encephalopathy syndrome (PRES)	Any grade	Discontinue
Arterial thromboembolism	Any grade	Discontinue

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

- **Serious side effects**

Myelosuppression
Electrolyte abnormalities (hypocalcaemia, hypomagnesaemia, hypokalaemia)
Proteinuria, nephrotic syndrome
Renal failure and impairment
Hepatic changes
Cardiac failure
GI perforation or fistula
Non GI fistula
Arterial thromboembolism
Haemorrhage
Aneurysm and artery dissections
Thyroid dysfunction
Posterior reversible encephalopathy syndrome (PRES)
QTc interval prolongation
Wound healing complications

- **Frequently occurring side effects**

Hypertension
Proteinuria
Diarrhoea
Anorexia
Weight loss
Fatigue
Nausea
Vomiting
Stomatitis
Dysphonia
Headache
Palmar Plantar Erythema
Rash
Peripheral oedema
Joint and muscle ache

- **Other side effects**

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

As lenvatinib may prolong the QT interval avoid, concomitant use with other medications which can lead to QT prolongation (including amiodarone, quinidine, sotalol, chloroquine, clarithromycin). Use with caution in patients taking medications which may cause electrolyte disturbances such as hypokalaemia, hypocalcaemia, hypomagnesaemia.

Additional comments

Adequate contraception methods to be applied during and up to four weeks after finishing treatment. Unknown if lenvatinib reduces effectiveness of hormonal contraceptives therefore women using oral hormonal contraceptives should add a barrier method.

References

- NICE Technology Appraisal Guidance 535 – Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine, Accessed 12 August 2021 via www.nice.org.uk
- Summary of Product Characteristics Lenvatinib (Lenvima) . Accessed 18 August 2021 via https://www.medicines.org
- Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621-630
- Reed N, Glen H, Gerrard G et al Expert consensus on the management of adverse events during treatment with lenvatinib for thyroid cancer. Clin Oncol 2020, 32 (5): e145-e153

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