Systemic Anti Cancer Treatment Protocol

LENVATINIB (Lenvima)
Hepatocellular Carcinoma

PROTOCOL REF: MPHALEHCGA
(Version No: 1.0)

Approved for use in:

First line systemic therapy for the treatment of Child-Pugh A locally advanced or metastatic hepatocellular carcinoma (HCC), ECOG performance status 0 or 1

Or

Patients (meeting the criteria above) who have had to discontinue sorafenib within 3 months of starting sorafenib solely because of toxicity (i.e. there was sorafenib toxicity that could not be managed by dose delay or dose modification) and there has been no disease progression whilst on sorafenib

Patients will require registration with NHS England via the Blueteq website (https://www.blueteq-secure.co.uk/Trust/default.htm)

Dosage:

Patients with an actual body weight of **≥ 60kg**

Drug	Dosage	Route	Frequency
Lenvatinib	12mg	Oral	Once Daily continuously (supplied every 28 days)

Patients with an actual body weight of **< 60kg**

Drug	Dosage	Route	Frequency
Lenvatinib	8mg	Oral	Once Daily continuously (supplied every 28 days)

Dose adjustments are based only on toxicities observed and **not on body weight changes during treatment**. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Supportive treatments:

Domperidone 10mg up to three times a day when required

Loperamide 2mg when required (max.16mg in 24 hours)

Extravasation risk:

N/A

Administration:

- Lenvatinib is available as 4mg capsules
- Lenvatinib should be administered at the same time once daily, with or without food
- For patients with swallowing difficulty, Lenvatinib capsules must not be opened but may be dissolved using the following instructions;

  Pour a tablespoon of water or apple juice into a small glass and put the capsules into the liquid without breaking or crushing them. Leave for at least 10 minutes then stir for at least 3 minutes to dissolve the capsule shells. Drink the mixture. After drinking, add the same amount of water or apple juice, swirl and swallow.

- If a patient misses a dose and it cannot be taken within 12 hours; then that dose should be skipped and the next dose taken at the usual time of administration.

Drug Interactions

No interaction was shown between lenvatinib and midazolam (a sensitive CYP3A and Pgp substrate, commonly used to check for CYP3A activity) therefore no drug-drug interactions are expected between lenvatinib and other CYP3A4/Pgp substrates.

Lenvatinib can prolong QT interval therefore caution should be used when using in combination with other QT prolonging drugs such as amiodarone, ciprofloxacin, citalopram, erythromycin, fluoxetine, fluconazole and ondansetron.

Main Toxicities:

- Diarrhoea
- Nausea and vomiting
- Abdominal pains
- Mucositis
- Dyspepsia
- Dry mouth
- Constipation
- Decreased appetite/weight
- Taste disturbance
- Dysphonia
- Headache
- Dizziness
- Myalgia
- Fatigue
- Insomnia
- Rash
- Palmar-Plantar (PPE)
- Alopecia
- Cardiac disorders
- Haemorrhage
- Hypertension
- Hypercholesterolaemia
- Urinary tract infections
- Renal impairment
- Proteinuria
- Hypothyroidism
- Increased bilirubin
- Increase in transaminases
- Hypokalaemia
- Hypocalcaemia
- Hypomagnesaemia
- Neutropenia
- Thrombocytopenia

Investigations and Treatment Plan:

	Pre	C1 D1	C1 D8	C1 D15	C2 D1	C2 D15	C3 D1	Ongoing
Medical Assessment	X				X		X	Then alternate cycles once stable
Nursing Assessment	X	X		X	X	X	X	Two-weekly for first 2 cycles then every cycle
FBC	X			X	X	X	X	Two-weekly for first 2 cycles then every cycle
U&E & LFT	X			X	X	X	X	Two-weekly for first 2 cycles then every cycle
Magnesium	X			X	X	X	X	Two-weekly for first 2 cycles then every cycle
Fasting lipids and cholesterol	X							Every 12 weeks
CT scan	X							Every 12 weeks
TFTs & TSH	X							Every 12 weeks

AFP	X				X		X	Every 4 weeks
Blood Pressure	X	X	X*	X	X	X	X	Monitor after 1 week of treatment*, then every 2 weeks for the first two cycles, then every 4 weeks
Urine Dipstick for protein	X			X		X		Then every 12 weeks (unless clinically indicated)
Informed Consent	X							
PS recorded	X	X		X	X	X	X	Every cycle
Toxicities documented	X	X		X	X	X	X	Every cycle
Weight recorded	X	X		X	X	X	X	Every cycle

*****Blood pressure check on C1 day 8 to be arranged either with GP surgery or for patient to attend chemotherapy clinic

Dose Modifications and Toxicity Management:

Haematological Toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L*****

Discuss with consultant if:-

ANC ≤ 0.99 x 10^9/L	Platelets ≤ 49 x 10^9/L*****

*****Patients may have longstanding thrombocytopenia which is likely attributed to hypersplenism secondary to portal hypertension rather than being treatment-related. Review of the platelet trend over a period of time is therefore recommended to fully assess

Non-haematological Toxicity

Hypertension

- Blood pressure (BP) should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib.
- Usually occurs early on in the course of treatment therefore BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter.

Blood pressure (BP) level	Recommended action
Systolic BP ≥140 mmHg up to <160 mmHg **OR** Diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving **OR** Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg **OR** Diastolic BP ≥100 mmHg (despite optimal antihypertensive therapy)	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, 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.

Proteinuria

- Usually occurs early on in the course of treatment therefore urine protein should be monitored regularly.
- If urine dipstick proteinuria ≥2+ is detected, withhold treatment and obtain a 24-hour urine protein.
- Treatment can be restarted once urine protein resolves to < 2g/24hrs.
- Lenvatinib should be discontinued in the event of nephrotic syndrome and not to be resumed.

Dose modifications for persistent or intolerable Grade 2 or 3 toxicities

Adverse Reaction	Modification	Adjusted Dose (≥60 kg BW)	Adjusted Dose (<60 kg BW)
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	8 mg Once Daily	4 mg Once Daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	4 mg Once Daily	4 mg on Alternate Days
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline	4 mg on Alternate Days	Discontinue

Hepatic impairment

No dose adjustments are required for patients with mild hepatic impairment (Child-Pugh A). There was limited data on the safety of lenvatinib in patients with (Child-Pugh B) hepatic impairment therefore caution is advised as patients may be more susceptible to toxicities. There is no data in patients with severe hepatic impairment (Child Pugh C) and is not recommended for use in these patients.

Renal impairment

No dose adjustments are required for patients with mild or moderate renal impairment. The manufacturer does not provide advice on dose modifications for severe renal impairment due to lack of data therefore is not recommended.

References:

NHS England, *National Cancer Drugs Fund List.* Available from: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/ [Accessed on 28/11/2018]

Summary of Product Characteristics - Lenvima 4mg hard capsules. Available from: https://www.medicines.org.uk/emc/product/6840/smpc [Accessed on 28/11/2018]

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial (REFLECT trial) Kudo M, Finn RS, Qin S *et al*. The Lancet 2018; 391: 1163-1173