

Chemotherapy Protocol
HEPATOCELLULAR CANCER
LENVATINIB (59kg or less)

Regimen

- Hepatocellular – Lenvatinib

Indication

- Lenvatinib is indicated where either;
 - the patient has a confirmed histological diagnosis of hepatocellular carcinoma (HCC)
 - or a biopsy is deemed to be very high risk or technically not feasible and the criteria below are also all met;
 - a. the decision not to biopsy has been made and documented by a specialist HCC multi-disciplinary team meeting.
 - b. the tumour meets the non-invasive diagnostic criteria of HCC*
 - c. data is submitted as part of the ongoing 'Systemic Therapy Audit, previously known as the Sorafenib Audit 2'.

It is expected that this second option will only apply in exceptional circumstances and it should be noted that audit of non-biopsy rates will be reviewed regularly.

*EASL-EORTC Clinical Practice Guidelines: Management, Journal of Hepatology (2012); 56:908-943. Noninvasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1cm in diameter, a more conservative approach with 2 techniques is recommended in suboptimal settings.

- the patient has either metastatic disease or locally advanced disease that is ineligible for or failed surgical or loco-regional therapies
- the patient has not received any previous systemic therapy for hepatocellular carcinoma or the patient has had to discontinue sorafenib within three months of starting sorafenib and solely because of toxicity (i.e. there was sorafenib toxicity which could not be managed by dose delay or dose modification) and there has been no disease progression whilst on sorafenib
- the patient had Child Pugh function class A
- lenvatinib will be prescribed as monotherapy
- a formal medical review as to whether treatment with lenvatinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
- lenvatinib will be continued until loss of efficacy, unacceptable toxicity of the patient chooses to stop treatment

- WHO Performance status 0, 1
- Palliative intent

Toxicity

Drug	Adverse Effect
Lenvatinib	Hypertension, renal failure, hepatotoxicity, cardiac impairment, QT interval prolongation, posterior reversible encephalopathy syndrome, haemorrhage, GI perforation or fistula, thyroid abnormalities

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, U&Es and LFTs every 28 days
- Blood glucose levels at baseline and after 28 days of treatment. Thereafter every 4-8 weeks
- Triglycerides at baseline then every 8 weeks
- Proteinuria less than 1g/24 hours, with proteinuria measured prior to each cycle
- Thyroid function every 28 days
- Blood pressure should be monitored at baseline, after one week of lenvatinib then every two weeks for the first two months and then every 28 days thereafter.
- ECG as clinically indicated

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well. The toxicities below should be read in conjunction with the relevant Summary of Product Characteristics (www.medicines.org.uk).

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for SACT that if a third dose reduction is necessary treatment should be stopped.

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.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing cycle 1 the following criteria must be met.

Criteria	Eligible Level
Neutrophils	Equal to or more than $1 \times 10^9/L$
Platelets	Equal to or more than $50 \times 10^9/L$

HCC 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 regorafenib toxicity.

Hepatic Impairment

Child Pugh Class	Lenvatinib Dose
A	No dose adjustment
B	Use with caution, may be more susceptible to toxicity
C	Not recommended

Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (less than 1%) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary. If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted

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. Further dose reductions may be required based on tolerability.

Renal impairment and renal failure have been reported in patients treated with lenvatinib. The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or

discontinuation may be necessary. If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of lenvatinib is adjusted as in the table below

Adverse Reaction	Modification	Adjusted Dose (59kg or below)	Adjusted Dose (60kg or above)
First occurrence	Interrupt until resolved to NCI-CTC grade 0-1	4mg once a day	8mg once a day
Second occurrence (same or new reaction)	Interrupt until resolved to NCI-CTC grade 0-1	4mg on alternate days	4mg once a day
Third occurrence (same or new reaction)	Interrupt until resolved to NCI-CTC grade 0-1	Discontinue	4mg on alternate days

Cardiac

Hypertension is commonly reported in association with lenvatinib and may be severe. Blood pressure should be well controlled prior to starting treatment. Early detection and management of hypertension are important during treatment. Hypertension tends to develop early in treatment. Blood pressure should be monitored at baseline, one week later and then every two weeks for the first eight weeks of treatment and four weekly thereafter.

Blood Pressure	Recommended Action (lenvatinib)
Systolic blood pressure greater than or equal to 140mmHg and up to 160mmHg or diastolic blood pressure greater than or equal to 90mmHg up to 100mmHg	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 \geq 160 mmHg or diastolic blood pressure greater than or equal to 100 mmHg despite optimal antihypertensive therapy	Withhold lenvatinib until the systolic blood pressure is less than or equal to 150mmHg and diastolic blood pressure is less than or equal to 95mmHg and the patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose level
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management

Decreases in left ventricular ejection fraction (LVEF) were seen in 10% of RCC patients receiving combination treatment. Patients should be monitored for signs and symptoms as dose modification may be required. Arterial thromboembolic events were reported as well,

including fatal cases. Lenvatinib should be discontinued if such an arterial thromboembolic event occurs. Use lenvatinib with caution in patients who are at increased risk of cardiac events.

QT prolongation has been reported and may lead to severe ventricular arrhythmias, including Torsades de pointes. Lenvatinib is not recommended in patients with congenital long QT syndrome or those with risk factors for prolonged QT. Lenvatinib should be stopped when the QT interval is longer than 500ms. Treatment may be resumed at a reduced dose level when the interval is 480ms or less. Electrolyte abnormalities should be corrected prior to starting treatment.

[Endocrine](#)

Lenvatinib impairs exogenous thyroid suppression. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

[Proteinuria](#)

Proteinuria usually develops early in treatment. If proteinuria occurs at a level greater than or equal to 2+ or 2g/24 hours interrupt treatment, obtain a 24 hour urine protein, until it is less than this, then dose reduce down a level and resume treatment. Lenvatinib should be stopped if nephrotic syndrome occurs.

[Regimen](#)

28 day cycle continued as long as clinical benefit is observed or until unacceptable toxicity occurs (6 cycles will be set in Aria)

Drug	Dose	Days	Administration
Lenvatinib	8mg once a day	1-28 incl.	Oral

[Dose Information](#)

- Lenvatinib is available as 10mg and 4mg hard capsules.

[Administration Information](#)

- Lenvatinib should be taken at the same time of day each day consistently with or without food. Capsules should be swallowed whole. If a dose is missed and cannot be taken within twelve hours then it should be missed and the next dose taken at the appropriate time.

[Additional Therapy](#)

- Routine anti-emetics are not required.
- Mouthwashes according to local or national policy on the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to lenvatinib.
- It must be made clear to all staff, including those in the community, that lenvatinib should only be prescribed under the supervision of an oncologist.
- Lenvatinib interact with many other agents. Always check for drug interactions.
- There are several brands of lenvatinib. Please dispense the correct brand.

References

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

REGIMEN SUMMARY

Lenvatinib (59kg or less)

Day 1

Take Home Medicines

1. **Warning – Check Dose and Weight**

Administration Instructions

The starting dose of lenvatinib varies depending on the body weight. The dose does not need to be changed in relation to weight changes during treatment. Dose changes should only occur in relation to toxicity.

2. **Lenvatinib 8mg once a day oral**

Administration Instructions

Oral chemotherapy.

Please supply an original pack per 28 day cycle. There are several brands of lenvatinib. Please ensure the product you dispense is appropriate for the indication (hepatocellular carcinoma)

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	April 2020	None	Dr Deborah Wright Pharmacist	Dr Alaaeldin Shablak Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information.