Chemotherapy Protocol

THYROID CANCER

LENVATINIB

Regimen

- Thyroid – Lenvatinib

Indication

- The treatment of differentiated thyroid cancer after radioactive iodine where all the following criteria are met:

  - the patient has a confirmed histological diagnosis of differentiated thyroid carcinoma (papillary or follicular or Hurthle cell type)

  - the patient has either metastatic disease or inoperable locally advanced disease

  - the disease is refractory to radioactive iodine

  - the disease is progressive and is either symptomatic or imminently likely to become symptomatic

  - the patient is treatment naïve to both lenvatinib and sorafenib unless either:

  a) previously enrolled in the company's lenvatinib compassionate access scheme and all other NHS England treatment criteria are fulfilled ie if treated with previous sorafenib, lenvatinib will only be accepted for NHS funding if the patient was intolerant of sorafenib according to the conditions set out in b) below or

  b) the patient has had to discontinue sorafenib within 3 months of starting sorafenib because of toxicity (ie there is sorafenib toxicity which cannot be managed by dose delay or dose modification) and there has been no disease progression whilst on sorafenib

  Note: Sequential use of lenvatinib and then sorafenib is only funded if the patient has to discontinue lenvatinib because of intolerance within 3 months of its start and if the disease has not progressed whilst the patient is on lenvatinib. The use of lenvatinib after disease progression on or after sorafenib is not funded and vice versa.

  - 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

  - no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)

- WHO Performance status 0, 1, 2

- 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 chemotherapy that if a third dose reduction is necessary treatment should be stopped.

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

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80mg/L).

Hepatic Impairment

Child Pugh Class	Lenvatinib Dose
A	No dose adjustment
B	No dose adjustment
C	14mg once a day

Further dose reductions may be required based on tolerability

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

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Lenvatinib	less than 30ml/min	14mg once a day

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

Dose level	Daily dose (lenvatinib)
Recommended daily dose	24mg once a day
First dose reduction	20mg once a day
Second dose reduction	14mg once a day
Third dose reduction	10mg once a day

Cardiac

Hypertension is commonly reported in association with lenvatinib and may be severe. Median time to onset is 35 days in renal cell patients patients receiving combination treatment. Blood pressure should be well controlled prior to starting treatment. Early detection and management of hypertension are important during treatment.

Blood Pressure	Recommended Action (lenvatinib)
Systolic blood pressure greater than or equal to140mmHg 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 ≥160 mmHg or diastolic blood pressure greater than or equal to100 mmHg despite optimal antihypertensive therapy	Withhold lenvatinib until the systolic blood pressure is less than or equal to150mmHg and diastolic blood pressure is les 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 in10% 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

If proteinuria occurs at a level greater than 2g/24 hours interrupt treatment 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	24mg 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 H_2 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 lenvantinib.
- It must be made clear to all staff, including those in the community, that lenvantinib 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.

Coding (OPCS)

- Procurement – X
- Delivery – X

References
1. Schlumberger M, Tahara M, Wirth HJ et al. Lenvatinib versus placebo in radioiodine refractory thyroid cancer. N Engl J Med 2015; 372 (7): 621-630.

REGIMEN SUMMARY

Lenvatinib

Day 1

Take Home Medicines

1. Lenvatinib 24mg 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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	August	Dose adjustment table updated	Dr Deborah Wright Pharmacist	Dr Jenny Marshall Consultant Clinical Oncologist
1	May 2018	None	Dr Deborah Wright Pharmacist	Dr Jenny Marshall Consultant Clinical 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.