

Chemotherapy Protocol

RENAL CELL CANCER

CABOZANTINIB

Regimen

- Renal Cell – Cabozantinib (60mg-tablets)

Indication

- Cabozantinib is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

Toxicity

| Drug | Adverse Effect |
|--------------|--|
| Cabozantinib | Hypertension, diarrhoea, osteonecrosis, QT interval prolongation, perforations, fistulas, intra-abdominal abscesses, Posterior reversible encephalopathy syndrome, palmer-plantar erythrodyesthesia, hypothyroidism, proteinuria |

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

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one of treatment. This should include magnesium, potassium, calcium and phosphate. Abnormal levels should be corrected.
- Thyroid function tests at baseline and 2, 4, 8 and 12 weeks and then every 12 weeks thereafter
- ECG at baseline and 2, 4, 8 and 12 weeks and then every 12 weeks thereafter
- Blood pressure prior to each cycle. Existing hypertension should be well controlled prior to starting treatment
- Urine dipstick for protein prior to every cycle.

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.

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

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. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

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

In general neutrophils should be greater than $1.5 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$ prior to each cycle. Discuss lower than normal haematological findings and treatment doses with consultant.

Hepatic Impairment

| Drug | Dose (% of original dose) |
|--------------|---|
| Cabozantinib | Dose reductions should be considered when grade 2 elevated ALT, AST or bilirubin for longer than 1 week occurs. For grade 3 and above then treatment should be withheld until resolved to baseline levels and then restart treatment at lower dose |

Renal Impairment

| Drug | Dose (% of original dose) |
|--------------|------------------------------|
| Cabozantinib | No information available |

Other

Dose interruptions are required for management of NCI-CTC grade 3 or greater toxicities or intolerable grade 2 toxicities. Treatment may be resumed with a reduced dose according to the table below only after the toxicity has improved to NCI-CTC grade 1 toxicity. Toxicity is more commonly observed in patients aged 75 years or older.

| Cabozantinib Dose Level | Dose |
|--------------------------------|------|
| 1 st dose reduction | 40mg |
| 2 nd dose reduction | 20mg |

QT interval change

Cabozantinib should be used with caution in patients with a history of QT prolongation, patients who are taking anti-arrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. ECG QTc interval should not be greater than 480 msec. Serum calcitonin level should be greater than or equal to 500pg/ml.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a syndrome of subcortical vasogenic oedema diagnosed by a MRI of the brain. PRES has been observed in patients receiving cabozantinib. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status. Discontinue cabozantinib if PRES is diagnosed.

Perforations, Fistulas and Intraabdominal Abscesses

Serious and sometimes fatal perforations, fistulas and intraabdominal abscesses have been observed with cabozantinib. Treatment should be discontinued in patients who experience a GI perforation or a GI or non-GI fistula.

Osteonecrosis of the Jaw

Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy. Patients should be advised regarding oral hygiene practice. For invasive dental procedures, cabozantinib treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

Diarrhoea

Administration of loperamide is recommended at the first sign of diarrhoea. If it is not controlled with loperamide alone, additional agents can be added but if combination therapy is not controlling the diarrhoea to tolerable levels then a dose reduction is recommended. Stop treatment in for NCI-CTC grade 3 diarrhoea. Re-start with a reduced dose once diarrhoea has subsided.

Hypertension

Blood pressure should be well controlled prior to initiating cabozantinib.

Patients should be monitored for hypertension. If the blood pressure exceeds 150/100 mmHg then instigate treatment, either by increasing the dose of existing anti-hypertensives, adding additional agents or commencing therapy. In the case of persistent hypertension (blood pressure greater than 150/100mmHg), despite use of anti- hypertensive medicinal products, consider cabozantinib dose reduction. For patients who develop severe hypertension despite dose reduction and antihypertensives, cabozantinib should be discontinued.

Palmer- Plantar Erythrodesia

Encourage regular use of moisturizers to hand and feet regularly. Advise minimizing activities that put pressure on feet or hands, as usually the pressure point areas are affected. Keeping skin cool is beneficial, avoiding extreme heat (such as strong sunlight or hot baths). Support use of non-deodorant, non-fragrance products. Consider products with anti-itch additions in pruritus, and exfoliating urea containing products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Non-steroidal anti-inflammatory creams and analgesia may help but a 1-2 week dose interruption may be necessary for painful symptom.

Proteinuria

Monitor urinary protein prior to each cycle. Discontinue cabozantinib in patients who develop nephrotic syndrome.

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in ARIA)

| Drug | Dose | Days | Administration |
|--------------|------|------------|----------------|
| Cabozantinib | 60mg | 1-28 incl. | Oral |

Dose Information

- The cabozantinib brand (Cabometyx) is licensed for the treatment of renal cell cancer.
- Cabometyx (cabozantinib) tablets and Cometriq (cabozantinib) capsules are not bioequivalent and should not be used interchangeably. If a patient must switch from cabozantinib capsules to cabozantinib tablets, the patient should continue at a Cabometyx dose not to exceed 60 mg or the current Cometriq dose (whichever is lower).
- Cabozantinib tablets are available as 20mg, 40mg and 60mg tablets

Administration Information

- Cabozantinib tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking the tablets.
- If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

Additional Therapy

- Antiemetics

- metoclopramide 10mg three times a day when required oral

Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that this is a course of oral chemotherapy that must be prescribed by specialist oncology professionals.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.
- Cabozantinib is associated with many drug interactions. Always check before prescribing.

Coding

- Procurement – X71.5
- Delivery – X73.1

References

1. National Institute for Health and Clinical Excellence. Technology Appraisal 463. Cabozantinib for previously treated advanced renal cell carcinoma. August 2017 DOH: London.

REGIMEN SUMMARY

Cabozantinib (60mg-tablets)

Day One

Take Home Medicines

1. Cabozantinib 60mg once a day for 28 days oral
Administration Instructions

Oral chemotherapy.

Cabometyx (cabozantinib) tablets and Cometriq (cabozantinib) capsules are not bioequivalent and should not be used interchangeably. If a patient must switch from cabozantinib capsules to cabozantinib tablets, the patient should continue at a Cabometyx dose not to exceed 60 mg or the current Cometriq dose (whichever is lower).

Cabozantinib tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking the tablets.

If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

Available as 60mg, 40mg and 20mg tablets, please ensure dose modifications occur in multiples of these strengths.

DOCUMENT CONTROL

| Version | Date | Amendment | Written By | Approved By |
|---------|---------------|-----------|---------------------------------|--|
| 1 | December 2017 | None | Dr Deborah Wright Pharmacist | Dr Mathew Wheater Consultant 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.