Systemic Anti Cancer Treatment Protocol

CABOZANTINIB

PROCEDURE REF: MPHACABOZ
(Version No: 1.0)

Approved for use in:

Adult patients with progressive, unresectable locally advanced, or metastatic medullary thyroid cancer.

Dosage:

Drug	Daily dosage	Route	Schedule
Cabozantinib capsules	140mg	Oral	Daily, until disease progression.

The majority of patients will require one or more dose adjustments due to toxicity and therefore patients should be closely monitored during the first 8 weeks of therapy.

Supportive Treatments:

Domperidone 10mg three times a day
Loperamide 2mg prn as indicated

Administration/directions:

The capsules should be swallowed whole and not opened. And should be taken on an empty stomach – patients should not eat anything for at least one hour before and two hours after taking cabozantinib.

If a dose is missed, it should not be taken if it is less than 12 hours before the next dose would be due. Concomitant administration with proton pump inhibitors should be avoided as cabozantinib demonstrates pH dependent solubility.

Cabozantinib is a CYP3A4 substrate and P-glycoprotein inhibitor

Concomitant administration of digoxin, posaconazole, dabigatran, ketoconazole, itraconazole, erythromycin, clarithromycin, grapefruit juice, dexamethasone, phenytoin, carbamazepine, rifampicin should be avoided.

Cabozantinib's effect on contraceptive steroids is unknown and their effectiveness cannot be guaranteed.

Main Toxicities:

Cabozantinib	
Hypertension	All patients should be monitored, and treated with standard anti-hypertensives as required. If hypertension persists despite appropriate therapy then cabozantinib dose should be reduced
Osteonecrosis	For invasive dental procedures, cabozantinib should be held at least 28 days prior to scheduled surgery, if possible.
Perforations, fistulas, intra-abdominal abscesses. **Wound complications** **Haemorrhage**	Serious GI perforations and fistulas have been observed. Patients at risk should be evaluated carefully before commencing therapy. Treatment should be stopped at least 28 days prior to surgery Patients with involvement of the trachea or bronchi by tumour or history of haemoptysis prior to treatment should be carefully evaluated before commencing therapy
Thromboembolic events	Venous and arterial thromboembolisms have been observed with cabozantinib. Discontinue in patients who develop an acute MI or clinically significant arterial complications.
Dermatological	PPE syndrome has been observed. Hair colour changes, rash, dry skin, acne, abnormal hair growth, skin hypopigmentation, skin exfoliation and alopecia occur commonly
Proteinuria	Monitor regularly during treatment. Discontinue cabozantinib in patients who develop nephrotic syndrome
Cardiovascular	Use in caution in patients with history of QT interval prolongation, patients taking antiarrhythmics or relevant pre-existing cardiac disease or electrolyte disturbances. Periodic monitoring should be considered.
Metabolism and nutrition disorders	Decreased appetite, hypocalcaemia, hypophosphataemia, hyperbilirubinemia, hypoalbumenia and dehydration.
GI disorders	Diarrhoea, nausea, stomatitis, constipation, vomiting, abdominal pain, dysphagia, dyspepsia
Additional side effects	Immunosuppression, fatigue and muscle spasms are also common side effects. Seizures, headaches and confusion may be signs of a serious but uncommon side effect of RPLS (reversible posterior leukoencephalopathy syndrome)

Investigations:

	Pre	C1	C2	C3	Ongoing
Medical Assessment	X	X	X	X	Every Cycle
Nursing Assessment		X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs	X	X	X	X	Every cycle
Calcium	X	X	X	X	Every cycle
Magnesium	X	X	X	X	Every cycle
Thyroid function	X	X	X	X	Every cycle
CT scan	X				As clinically indicated
Informed Consent	X				
Blood glucose	X				Repeat if clinically indicated
Blood pressure measurement	X	X	X	X	Every cycle
Baseline ECG	X				Repeat if clinically indicated
Urine dipstick for protein	X	X	X	X	Every cycle
Baseline oral examination	X				Any extensive dental work to be completed prior to commencing
PS recorded	X	X	X	X	
Toxicities documented	X	X	X	X	
Weight recorded	X	X	X	X	Every cycle

Review thromboembolic risk and consider prophylactic anticoagulants in those at significant risk
Review all other medications for potential drug-drug interactions

Toxicity Management/ Dose Modifications:

Dose interruptions are required for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities.

Cabozantinib dose level	New Dose
1st dose reduction	100mg
2nd dose reduction	60mg

Cabozantinib

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.
Stomatitis	Good oral hygiene is important to minimise the risk of stomatitis. Oral rinsing after meals is recommended If stomatitis interferes with adequate nutrition then dose reduction is recommended.
Dermatological	The patients should be advised to avoid hot water and to wear gloves when performing housework. Use simple moisturising creams to keep the skin moist. For persistent grade 2 PPE or grade 3, then treatment should be interrupted until severity decreases to grade 0 or 1.
Hypertension	If BP exceeds 150/100 mmHg then instigate treatment, either by increasing the dose of existing anti-hypertensives, adding additional agents or commencing therapy. If optimal treatment does not result in BP < 150/100 then cabozantinib should be dose reduced. If BP exceeds 160/110 mmHg, consider dose reducing the cabozantinib at the same time as instigate treatment for the hypertension.
Proteinuria	Monitor regularly during treatment. Discontinue cabozantinib in patients who develop nephrotic syndrome
Osteonecrosis	Cabozantinib should be discontinued in patients who experience osteonecrosis of the jaw

Hepatic impairment	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	Data in this population are not yet available.

References:

Cometriq hard capsules, Summary of Product Characteristics, Swedish Orphan Biovitrum. 21/03/14. Available from www.medicines.org.uk/emc/medicine. Last updated 17/09/2014.

COMET1 clinical trial protocol: XL184-307