Systemic Anti Cancer Treatment Protocol

Pazopanib in Renal Cell Cancer

PROTOCOL REF: MPHARPAZO
(Version No: 1.4)

The protocol has been temporarily amended – please see the Oral SACT Operational Changes during Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

Pazopanib is indicated for the first line treatment of advanced / metastatic renal cell carcinoma in patients

ECOG performance status of 0 or 1

Blueteq registration required

Dosage:

Drug	Dosage	Route	Frequency
Pazopanib	800mg	Oral	Once daily until disease progression or unacceptable toxicity

Supportive treatments:

Metoclopramide 10mg TDS as required

Extravasation risk:

Not applicable

Administration:

- Pazopanib should be taken without food, at least one hour before or two hours after a meal.
- Pazopanib film-coated tablets should be taken whole with water and not broken or crushed.

Drug Interactions

Pazopanib is metabolised by the cytochrome CYP3A4 pathway and therefore drugs that induce or inhibit this enzyme should be avoided where possible.

INDUCERS (lowers pazopanib levels):

Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone

INHIBITORS (increases pazopanib levels):

Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil

Warfarin and other anticoagulants – increased bleeding risk, therefore consider switch to LMWH

Fluconazole: Avoid concurrent use as associated with prolongation of the QT interval. Fluconazole is predicted to increase the exposure to pazopanib.

Concomitant use of pazopanib and simvastatin has been shown to increase the incidence of ALT elevations and should be undertaken with caution and close monitoring**.** Follow SPC guidelines for the management of hepatic events and discontinue Simvastatin if ALT levels elevate.

Investigations and Treatment Plan:

Cycle	Pre	C1		C2		C3		C4	Ongoing
Week		***1***	***3***	***5***	***7***	***9***	***11-12***	***13***	→
Clinical Assessment	X		X		X		X		Every 12 weeks
SACT Assessment	X	X		X		X		X	Every cycle
FBC	X		X	X	X	X		X	Every cycle
U&E & LFT	X		X	X	X	X		X	Every cycle
Thyroid function tests	X					X			Every 8 weeks
CT scan	X						X		Every 12 weeks
Informed Consent	X								
Blood pressure measurement	X	X	X	X	X	X	X	X	Every Cycle
PS recorded	X	X	X	X	X	X	X	X	Every Cycle
Toxicities documented	X	X	X	X	X	X	X	X	Every Cycle
Height recorded	X								
Weight recorded	X	X	X	X	X	X	X	X	Every cycle
Urine dipstick for protein									As clinically indicated
ECG	X								As clinically indicated

Dose Modifications and Toxicity Management:

Main Toxicities:

Hypertension, hepatic failure and increased transaminases, gastrointestinal disturbances such as diarrhoea, risk of QT prolongation, cardiac impairment, arterial thrombotic events (stroke, MI, TIA), myelosuppression, haemorrhage, GI perforation/ fistula, stomatitis, impaired wound healing, hypothyroidism, proteinuria, hair colour change, nausea, fatigue, anorexia, dysgeusia, PPE and rash. Please see 'Management of toxicities' table.

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets > 100 x 10^9/L

Caution advised in creatinine clearance <30ml/minAST < 3 x ULN (< 5 x ULN if liver metastates)
Bilirubin < 35 micromol/L
BP < 150/90

If ANC < 1.0 x 10^9/L or platelets less than 100 x 10^9 defer for one week

Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions.

The dose of pazopanib should not exceed 800 mg.

Non-haematological toxicities

Hepatic toxicity

Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring.

Serum liver tests should be monitored before initiation of treatment with pazopanib at weeks 3, 5, 7 and 9. These will be taken pre-treatment and according to the SPC. See 'investigation and treatment plan'. The HCA or nurse will provide the patient with an OCS form; this will allow the patient to be bled prior to clinic from various locations (i.e. Delamere or a District general hospital). The results are then reviewed by treatment /medical team before treatment review.

Liver test values	Dose modification
Transaminase elevation between 3 and 8 x ULN (and bilirubin < 2xULN)	Continue on pazopanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
Transaminase elevation of >8 x ULN (and bilirubin < 2xULN)	Interrupt pazopanib until transaminases return to Grade 1 or baseline. If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of pazopanib, if transaminase elevations > 3 x ULN recur, then permanently discontinued.
Transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN	Permanently discontinue pazopanib. Patients should be monitored until return to Grade 1 or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 x ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Management of toxicities	
Skin and tissue disorders	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 and limit peeling Patients should be advised that depigmentation of the hair or skin may also occur during treatment with pazopanib.
Gastrointestinal disorders	Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain are the most commonly reported gastrointestinal adverse reactions. **Diarrhoea:** <u>Grade 1 and 2</u> can be managed with supportive measures at home and with the use of anti-diarrhoea medication such as Loperamide 2mg after each stool if necessary. No treatment break or dose changes are required if the symptoms are well controlled.

	Grades 3 and 4 will need treatment interruption until improvement to Grade 1 or less. A step dose reduction is required. Advise the patient to avoid any exacerbating foods and to eat small high carbohydrate meals. Also to drink plenty of water and to record the daily stool frequency. Severe presentation may need admission if associated with any of the following: nausea/vomiting, cramping, fever, sepsis, neutropenia or dehydration. **Nausea:** Domperidone is usually satisfactory. Nausea often settles with habituation to the drug. Administration just before bedtime can help ameliorate this side-effect.
Hypertension	Hypertension is a known class effect of this drug and patients should be monitored closely and treated as appropriate. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice.There is no firm data on optimal management of hypertension induced by blockade of VEGF signalling and as such treatment according to national guidelines for essential hypertension is recommended. Thiazide diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers and dihydropyridine calcium channel antagonists (amlodipine and felodipine) are all reasonable first line agents depending on the patient's co-morbidities. Decision should not be based on single elevated BP reading and should be based on repeated evidence of elevation to eliminate possible contribution from 'white coat syndrome'. Patient should be advised to involve their GP for regular monitoring and if necessary treatment. Serial home BP monitoring can provide additional useful information. *Systolic 140-150 mmHg or Diastolic <90 mmHg:* -Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary. *Systolic 150-160mmHg or Diastolic 90-100mmgh:* -Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg.

	Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart): -Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Severe hypertension (>200mmHg systolic or >110mmHg diastolic)* Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled. Consider referral to cardiologist if refractory cases despite these steps. ****Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes.** NICE Clinical Guideline CG 127- Hypertension in adults diagnosis and management: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE
Cardiac disorders	Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmic or other medicinal products that may prolong QT interval and those with relevant pre-existing cardiac disease. When using pazopanib, base line and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within normal range is recommended. Increases in the QTc interval to over 500 msec have been observed, and therefore ECG at baseline is an important pre-treatment assessment. Repeat at 7 day interval in patients with borderline result, or as clinically indicated for other patients.
Thyroid dysfunction	Hypothyroidism has been observed to occur early as well as late during treatment with pazopanib; therefore TFTs require routine monitoring.

References:

http://www.medicines.org.uk/emc/medicine/23148/SPC/Votrient+200+mg+and+400+mg+film+coated+tablets/