PAZOPANIB

First line use in advanced renal cell carcinoma for patients with PS 0 or 1; NICE approved 2011
Patients intolerant to first line sunitinib may be switched to first line pazopanib

Drug/Dosage: **Pazopanib** initiate at 800mg po once daily as continuous therapy

The daily dose may be reduced in 200mg steps, if problems with tolerability. The daily dose may not be increased above 800mg, as funding has not been approved for this.

Administration: Pazopanib is available as 200mg and 400mg tablets. The daily dose should be taken once daily at least one hour before, or two hours after, any food.
Grapefruit and grapefruit juice should be avoided while on pazopanib.

Frequency: Clinical review every 4 weeks, with an extra review for toxicity two weeks after starting. Continue until disease progression or unacceptable adverse events.

Main Toxicities: diarrhoea; hypertension; haemorrhage (rare); myelosuppression; fatigue; hair and skin colour changes; mucositis; hypothyroidism; headache; anorexia; increased transaminases; palmar-plantar erythema

Anti- emetics: mildly emetogenic (avoid domperidone)

Regular:	FBC	every 4 weeks for at least 4 months, then may be reduced to every 8 – 12 weeks in patients with stable disease
Investigations:	LFTs	baseline, at weeks 2 and 4, then every 4 weeks for at least 4 months
	U&Es	every 4 weeks for at least 4 months
	Ca^{2+} and Mg^{2+}	baseline, then periodically as indicated (see Cardiac Toxicity)
	Blood pressure	weekly for 1st cycle (ideally via GP, with patient making a record of the readings for the next oncology appointment), then every 4 weeks
	ECG	baseline and periodically, only if patient has relevant cardiac history (e.g. on anti-arrhythmics, history of QT prolongation).
	Thyroid function	baseline, then every 3 months

Comments: Patients should be advised to apply moisturiser to their hands and feet regularly throughout treatment, and to minimise activities that put pressure on feet or hands if they start to develop sore hands or feet. Recommended moisturisers are Udderly Smooth or urea-containing moisturisers e.g. Eucerin.

Also, ensure patient has a supply of metoclopramide, loperamide and Difflam mouthwash, for management of symptoms as required.

Wound healing: Pazopanib may adversely affect the wound healing process.
Stop pazopanib at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing.

Interactions: Elimination of pazopanib is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. dexamethasone, phenytoin, St Johns wort) with pazopanib should be avoided, as this may increase the risk of therapeutic failure. Continuing with the enzyme inducer while increasing the pazopanib dose above 800mg daily is not an option, as there is no funding for this.

Reason for Update: reduced frequency of FBC in stable patients	Approved by Consultant: Dr A Michael
Version: 6	Approved by Lead Chemotherapy Nurse: Sara Wills-Percy
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Prepared by: S Taylor	Checked by: C Tucker

Co-administration of pazopanib with enzyme inhibitors (eg itraconazole, erythromycin, clarithromycin, grapefruit juice) should also be avoided. If this is not possible, the dose of pazopanib may need to be reduced according to tolerability.

Co-administration with PPIs or H_2 antagonists should be avoided, as a raised pH reduces absorption of pazopanib. If a PPI is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI. If the H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hrs before or at least 10 hrs after a dose of an H2-receptor antagonist. Pazopanib should be administered at least 1 hr before or 2 hrs after administration of short-acting antacid.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations.

Dose Modifications

Cardiac Toxicity: If hypertension develops, it should be treated (usually by GP) and monitored closely until stabilised. If the patient develops persistent hypertension despite intensifying anti-hypertensive therapy, the dose of pazopanib should be reduced. In severe persistent hypertension, the patient may require a break from pazopanib treatment until blood pressure is brought under control. In this case, re-introduce pazopanib with care.
QT prolongation and Torsades de Pointes have been reported. Pazopanib should be used with caution in patients with any relevant cardiac history, or those taking anti-arrhythmics or other medicines that prolong QT. Ensure electrolytes are maintained within the normal range.

Skin Toxicity: Hand-foot syndrome is less common than with sunitinib. However if there is ulceration, or if pain relief is required, it may require a 1-2 week break in treatment until resolved to Grade ≤ 1. The patient should be advised to moisturise their hands and feet regularly, and to keep them cool. The patient may also be advised to take care to minimise excessive periods of pressure on their feet.

Hypothyroidism: Manage according to standard medical practice. Pazopanib treatment may continue.

Hepatotoxicity: *After pazopanib treatment started:*

Liver function	Management
ALT / AST elevation to 3 - 8 x ULN	Continue treatment, but with once weekly LFT monitoring until resolved to ≤ Grade 1
ALT / AST elevation to > 8 x ULN	Interrupt pazopanib until it resolves to ≤ Grade 1. Consider the risk-benefit of re-challenge, but if the decision is taken to re-start pazopanib, then it should be re-introduced at a reduced dose of 400mg daily and LFTs should be monitored weekly for 8 weeks. If transaminases rise to > 3 x ULN after re-introduction, discontinue pazopanib. (Fatalities have occurred).
ALT / AST elevation to > 3 x ULN **and** bilirubin elevation to > 2 x ULN	Permanently discontinue pazopanib

N.B. Mild, 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 may continue treatment with once weekly LFT monitoring until resolved to ≤ Grade 1.

Hepatic Impairment: *Before pazopanib started:*

Liver function	Pazopanib starting dose
Bilirubin ≤ 1.5 x ULN, regardless of ALT *or* Bilirubin < ULN and any degree of raised ALT	800mg od
Bilirubin >1.5 – 3 x ULN, with any ALT value	200mg od
Bilirubin > 3 x ULN	Pazopanib contra-indicated

Renal Impairment: No dose adjustment is required in patients with CrCl > 30ml/min. Pazopanib and its metabolites have low renal excretion. However, caution is advised in patients with CrCl < 30ml/min as there is no data in these patients - discuss with Consultant.

References: Sternberg, CN et al; JCO 2010; 28: 1061 - 1068