Pazopanib

Indication
First line treatment of advanced or metastatic renal cell carcinoma and in cytokine pre-treated patients.

Regimen details
Pazopanib 800mg orally daily

Cycle frequency
Continuous treatment, dispense monthly

Number of cycles
Until disease progression

Administration
Pazopanib should be taken on an empty stomach, at least one hour before or two hours after a meal.
Tablets should be taken whole with water and not broken or crushed.
If a dose is missed or the patient vomits after taking their dose, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

Grapefruit and grapefruit juice should be avoided whilst taking pazopanib

Pre-medication
Nil

Emetogenicity
No routine antiemetics required

Additional supportive medication
Nil

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
TFTs	14 days
Urinalysis for proteinuria	14 days
Blood pressure	14 days

Blood pressure should be well controlled before commencing treatment

Pazopanib should be used with caution in patients with significant risk of haemorrhage

Pazopanib should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6

months. A treatment decision should be made based on the assessment of individual patient's benefit/risk

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysm and/or artery dissections. Before initiating pazopanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm

Pazopanib should be used with caution in patients at risk for GI perforation or fistula

Since vascular endothelial growth factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped 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. Pazopanib should be discontinued in patients with wound dehiscence

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST)
Repeat LFTs at weeks 3, 5, 7 9 and then monthly thereafter
Thyroid function every 12 weeks
Blood pressure weekly for the first cycle then every 4 weeks
Periodic urinalysis for proteinuria
ECG if patient has significant cardiac history

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 1.5 x ULN
AST	≤ 3 x ULN

Dose modifications

Hypertension

In the case of persistent hypertension, despite antihypertensive drug therapy, the dose of pazopanib may be reduced

- Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions
- Temporary suspension of pazopanib is recommended in patients who experience severe hypertension, despite antihypertensive drug therapy and dose reduction
- May be resumed once hypertension is appropriately controlled

Hepatic impairment (baseline values):

Mild impairment (normal bilirubin with raised ALT, or bilirubin up to 1.5x ULN regardless of ALT) – 800mg
Moderate impairment (bilirubin 1.5 – 3 x ULN, regardless of ALT) – 200mg
Severe impairment (bilirubin > 3 x ULN, regardless of ALT) – not recommended

Drug induced hepatotoxicity:

Liver test values	Dose modification
Transaminase elevation between 3 and 8 x ULN	Continue on pazopanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
Transaminase elevation of >8 x ULN	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 pazopanib should be 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

Other toxicities:

Withhold until resolved to ≤ grade 1 then resume with 200mg-400mg dose reduction

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
GI perforation
Teratogenicity
Cardiotoxicity
QT prolongation
Haemorrhage (rare)
Arterial/Venous thrombotic events
Reversible posterior leukoencephalopathy syndrome
Interstitial lung disease
Cardiac dysfunction/Heart failure
Aneurysm and/or artery dissections

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
Stomatitis and mucositis
Myelosuppression
PPE
Headache
Hypothyroidism
Thrombocytopenia
Proteinuria
Hypertension
Delayed wound healing

- **Other side effects**

Skin and hair changes
Taste disturbances
Fatigue
Raised LFTs

Significant drug interactions

– for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of pazopanib.

Simvastatin: avoid concomitant use – increases risk of elevation of transaminases.

Medicines that raise gastric pH: concomitant administration of esomeprazole decreases bioavailability of pazopanib. Co-administration of medicines that increase gastric pH should be avoided.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of pazopanib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, St John's Wort): avoid co-administration as these may reduce exposure to pazopanib.

Inhibitors and inducers of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP): avoid due to risk of altered exposure to pazopanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit or induce P-gp or BCRP should be considered.

Uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan): concomitant administration of pazopanib should be undertaken with caution as pazopanib is an inhibitor of UGT1A1.

Human organic anion transporting polypeptide (OATP1B1) substrates (e.g. rosuvastatin): concomitant administration of pazopanib should be undertaken with caution since pazopanib is an inhibitor of OATP1B1

Additional comments

References

Votrient SPC - https://www.medicines.org.uk/emc/product/7861/smpc

South West Clinical Network Clinical Network cancer protocols - http://www.swscn.org.uk/guidance-protocols/cancer-protocols/

THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, DESIGNATED LEAD CLINICIAN FOR KIDNEY CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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