Pazopanib (renal)

Indication

First line treatment of patients with advanced renal cell carcinoma (RCC) who have not received prior cytokine therapy **and** have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (WHO performance status of 0 or 1). Patients intolerant to first line sunitinib treatment.

(NICE TA215)

ICD-10 codes

Codes with a prefix C64

Regimen details

Drug	Dose	Route
Pazopanib	800mg* OD	PO

* any dose modifications should be made in 200mg steps

Cycle frequency

Once daily until disease progression or unacceptable toxicity.

Number of cycles

As above

Administration

Pazopanib is available as 200mg and 400mg tablets.
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

This regimen has mild emetic potential (no routine antiemetics required)

Additional supportive medication

Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment to minimise the risk of developing PPE.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Blood pressure	Must be controlled before initiating pazopanib

Urinalysis to monitor for proteinuria

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Every 4 weeks for the first 4 months
U+E (including creatinine)	Every 4 weeks for the first 4 months
LFTs	Every 2 weeks for the first month then every 4 weeks for the next 4 months
Calcium	Periodic monitoring
Magnesium	Periodic monitoring
Thyroid function	Every 12 weeks
Blood pressure	Weekly for first cycle then every 4 weeks

Periodic urinalysis to monitor 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**
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	≥ 30ml/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 1.5 x ULN

Dose modifications

- **Haematological toxicity**

Not recommended if significant risk of haemorrhage. Haemorrhage has been reported as a rare complication of pazopanib treatment.

Myelosuppression may require dose reduction (in steps of 200mg) and/or 1-2 week breaks in treatment until resolved to ≤ grade 2.

- **Renal impairment**

CrCl (ml/min)	**Pazopanib dose**
≥ 30	100%
< 30	No experience of use in patients with CrCl < 30ml/min – discuss with consultant and use with caution*

* Pharmacokinetic studies suggest that renal impairment is unlikely to have a clinically relevant effect on pazopanib metabolism and clearance.

- **Hepatic impairment**

On treatment initiation:

Bilirubin (x ULN)	**Pazopanib dose**
≤1.5	800mg – monitor LFTs
1.5-3	200mg – monitor LFTs
>3	Contra-indicated

During treatment:

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Pazopanib dose**
≤2	and	≤3	100%
≤2	or	3-8	Continue and monitor transaminases weekly until ≤3 x ULN
≤2	or	>8	Withhold until transaminases ≤3 x ULN If benefit deemed to outweigh risk of hepatotoxicity reintroduce at reduced dose and monitor LFTs weekly for 8 weeks. If subsequent transaminases >3 x ULN discontinue treatment.
>2	and	>3	Perform bilirubin fractionation. If direct (conjugated) bilirubin >35% of total discontinue pazopanib.*

* If bilirubin is raised without elevation of transaminases bilirubin fractionation should be performed. If bilirubin is <35% direct (conjugated) continue with pazopanib, if bilirubin is >35% direct (conjugated) further evaluation for the underlying cause of cholestatis should be performed.

- **Other toxicities**

Toxicity	**Definition**	**Dose adjustment**
Hypertension	Persistently >140/90mmHg despite standard antihypertensive medication.	Reduce dose in 200mg steps and continue to monitor. If persists discontinue treatment.
Diarrhoea	Grade 2	Withhold until ≤ grade 1 then continue at 100% dose
	Grade 3 and 4	Withhold until ≤ grade 1 then continue with 200mg dose reduction
Palmar-Plantar Erythrodysaesthesia (PPE)	Grade 1	100% dose with symptomatic treatment of PPE
	Grade 2	1st occurrence: withhold until ≤ grade 1 resume with 200mg dose reduction
		2nd occurrence: withhold until ≤ grade 1 resume with a further 200mg dose reduction
		3rd occurrence: discontinue
	Grade 3	1st occurrence: withhold until ≤ grade 1 resume with 200mg-400mg dose reduction
		2nd occurrence: discontinue or withhold until ≤ grade 1 resume with 200mg-400mg dose reduction
		3rd occurrence: discontinue
Stomatitis	Grade 1	100% dose
	Grade 2	Withhold until ≤ grade 1 and resume with 200mg dose reduction
	Grade 3	Withhold until ≤ grade 1 and resume with 200mg-400mg dose reduction
	Grade 4	Discontinue or withhold until ≤ grade 1 and 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 thrombotic events
Reversible posterior leukoencephalopathy syndrome

- **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 Johns 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

Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment to minimise the risk of developing PPE.

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 215 accessed 2 Apr 2014 via www.nice.org.uk
- Summary of Product Characteristics Pazopanib accessed 2 Apr 2014 via www.medicines.org.uk
- Study VEG108844, a Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARZ trial protocol, amendment number 2).

Written/reviewed by: Dr M Beresford (Consultant Oncologist, Royal United Hospital, Bath), Dr S Hilman (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

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