

Chemotherapy Protocol

RENAL CELL

TIVOZANIB

Regimen

- Renal Cell - Tivozanib

Indication

- Patients with a confirmed histological diagnosis of renal cell carcinoma with a clear cell component that is locally advanced or metastatic where;
 - the patient is treatment naïve to systemic therapy and in particular has previously received neither any vascular endothelial growth factor (VEGF)-targeted systemic therapy nor mTOR pathway inhibitor-targeted treatment unless prior treatment with pazopanib or sunitinib has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of progression.
 - tivozanib is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment
 - a formal medical review as to whether treatment with tivozanib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
 - no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve
 - no prior treatment either with pazopanib or sunitinib unless such prior treatment has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression. Patients treated with tivozanib may switch to pazopanib or sunitinib where treatment has had to be stopped early under the same circumstances.
- WHO Performance status 0, 1

Toxicity

Drug	Adverse Effect
Tivozanib	Hypertension, dysphonia, fatigue, diarrhoea, decreased appetite, headache, hypertension, QT interval prolongation, dyspnoea, cough, abdominal pain, nausea, stomatitis, hand & foot syndrome, impaired wound healing, back pain, weight loss, posterior reversible encephalopathy syndrome

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBCs, LFTs and U&Es prior to each cycle
- Blood pressure weekly for the first 4 weeks then every 4 - 12 weeks
- Thyroid function tests at baseline then every 12 weeks.
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems or in the elderly. Repeat every 12 to 24 weeks as clinically indicated.
- Proteinuria before starting treatment and every 12 weeks thereafter.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

There is a correlation between overall survival and the cumulative dose exposure and it is therefore recommended that attempts be made to manage toxicity before a dose reduction is made.

The occurrence of undesirable effects may require temporary interruption and/or dose reduction of tivozanib therapy. In the pivotal study, the dose was reduced for grade 3 events and interrupted for grade 4 events.

When dose reduction is necessary, the tivozanib dose can be reduced to 890 microgram once daily with the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

Prior to cycle 1 the following criteria should be met;

Criteria	Eligible Level
Neutrophil	Greater than $1 \times 10^9/L$
Platelets	Greater than $100 \times 10^9/L$

Thereafter;

Neutrophils (x10⁹/L)	Dose Modifications
1 or greater	100%
less than 1	Delay until recovery to 1x10 ⁹ /L or greater. If recovery occurs within 7 days then continue with the last dose dose.
Platelets (x10⁹/L)	Dose Modifications
100 or greater	100%
Less than 100	Delay until recovery to 100x10 ⁹ /L or greater. If the recovery occurs within 7 days then continue with the last dose.

Hepatic Impairment

Tivozanib should be used with caution in patients with mild hepatic impairment with close monitoring of tolerability. No initial dose adjustment is necessary unless in response to toxicity.

In moderate hepatic impairment prescribe tivozanib 1340 micrograms once a day on alternate days, as they may be at an increased risk of adverse reactions due to increased exposure.

Tivozanib is not recommended in severe hepatic impairment.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment due to limited experience and in patients undergoing dialysis as there is no experience of tivozanib in this patient population.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Hypertension

Prior to starting treatment patients should be screened for hypertension. During treatment patients should be monitored for high blood pressure and controlled as appropriate with antihypertensives. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled.

The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes.

In the case of persistent hypertension despite use of antihypertensive therapy, the tivozanib dose should be reduced, or the treatment interrupted and re-initiated at a lower dose once the blood pressure is controlled. Discontinuation of treatment should be considered in cases

of persistent severe hypertension, posterior reversible encephalopathy syndrome, or other complications of hypertension.

Skin

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

Consideration of temporary interruption and/or reduction in treatment dose or, in severe or persistent cases, permanent discontinuation of treatment.

For precautionary reasons tivozanib should be discontinued prior to major surgical procedures. The decision to resume tivozanib should be made after an assessment of wound healing.

Proteinuria

Monitoring for proteinuria before initiation of, and periodically using a urine dipstick. Patients who show 2+ protein level on dipstick should have a 24 hour protein assessment.

For patients who develop NCI-CTC grade 2 (more than 1.0-3.4 g/24 hours) or grade 3 (greater than or equal to 3.5 g/24 hours) proteinuria, the dose of tivozanib has to be reduced or the treatment temporarily interrupted. If the patient develops NCI-CTC grade 4 proteinuria (nephrotic syndrome) tivozanib has to be discontinued. Risk factors for proteinuria include high blood pressure.

Thyroid dysfunction

Hypothyroidism has been observed to occur early as well as late during treatment with tivozanib. TFTs require routine monitoring.

QT Interval Prolongation

In clinical studies with tivozanib, QT/QTc interval prolongation has been reported. QT/QTc interval prolongation may lead to an increased risk for ventricular arrhythmias. It is recommended that tivozanib be used with caution in patients with a history of QT interval prolongation or other relevant pre-existing cardiac disease and those receiving other medications known to increase the QT interval. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range is recommended.

Regimen

28 day cycle until disease progression or unacceptable toxicity occurs (12 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Tivozanib	1340microgram once a day	1-21 inclusive followed by 7 days rest	Oral

Dose Information

- Tivozanib is available as 1340microgram and 890microgram capsules

Additional Therapy

- Mouthwashes according to local or national policy on the treatment of mucositis
- Loperamide 4mg oral after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

Administration Information

- Tivozanib is for oral administration. It may be taken with or without food.
- If a dose is missed the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to tivozanib.
- It must be made clear to all staff, including those in the community, that tivozanib should only be prescribed under the supervision of an oncologist.
- Tivozanib may interact with many other agents. Always check for drug interactions.

Coding (OPCS)

- Procurement – X71.5
- Delivery – X73.1

References

1. National Institute of Health and Clinical Excellence 2018. Technology Appraisal 512. Tivozanib for the treatment of advanced or metastatic renal cell carcinoma.

REGIMEN SUMMARY

Tivozanib

Day One

Take Home Medicines

1. Tivozanib 1340microgram once a day for 21 days (followed by a 7 day rest period)
oral
Administration Instructions
Oral chemotherapy
The usual dose is 1340microgram once a day for 21 days followed by a 7 day rest period (28 day cycle)

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	2018	None	Dr Deborah Wright Pharmacist	Dr Mathew Wheeler Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
 NHS Isle of Wight
 Portsmouth Hospitals NHS Trust
 Salisbury Hospitals NHS Foundation Trust
 University Hospital Southampton NHS Foundation Trust
 Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.