Systemic Anti-Cancer Treatment Protocol

Sunitinib in Renal Cell Carcinoma

PROTOCOL REF: MPHARSUNI
(Version No: 1.3)

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:

Sunitinib is indicated for the first line treatment of advanced / metastatic renal cell carcinoma in patients with favourable risk (MSKCC or IMDC) and have an ECOG performance status of 0 or 1.

Blueteq registration required

Dosage:

Drug	Dosage	Route	Frequency
Sunitinib	50mg	oral	Once daily for 4 weeks followed by 2 weeks rest, until disease progression or unacceptable toxicity

Alternatively, Sunitinib can be given once daily for 2 weeks followed by 1 week rest **OR** at a lower dose in a continuous dosing regimen.

Supportive treatments:

Metoclopramide 10mg TDS as required

Loperamide 2mg prn

Extravasation risk:

Not applicable

Administration:

Sunitinib 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.

Patients should be advised to take their sunitinib at night as this may mitigate some of the immediate toxicities.

Drug Interactions

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

INDUCERS (lowers sunitinib levels): Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone

INHIBITORS (increases sunitinib levels): Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil

Caution should be exercised when using intravenous bisphosphonates either simultaneously or sequentially with Sunitinib.

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

Main Toxicities:

Fatigue, diarrhoea, nausea, anorexia, hypertension, a yellow skin discoloration, hand-foot skin reaction, altered taste, constipation and stomatitis

Investigations and Treatment Plan:

	Pre	C1	C1	C2	C3	C4	Ongoing
Week		**1**	**3**	**7**	**13**	**19**	→
Clinical Assessment	X	X	X	X	X	X	Every 12 weeks
SACT assessment (including PS and toxicities)	X	X		X	X	X	Every cycle
FBC	X		X	X	X	X	Every cycle
U&E & LFT	X		X	X	X	X	Every Cycle
Thyroid function tests	X				X		Every 12 weeks
CT scan	X				X		Every three cycles
Informed Consent	X						First cycle only
Blood pressure measurement	X	X	X	X	X	X	Every Assessment
Height recorded	X						
Weight recorded	X	X	X	X	X	X	Every cycle
Urine dipstick for protein							As clinically indicated
ECG							As clinically indicated

<u>Assessment visits</u>

Review around week 3 during the first cycle, thereafter, the patient can be seen every 6-12 weeks as per schedule above.

Dose Modifications and Toxicity Management

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.

Haematological toxicity

Proceed on day 1 if:-

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

Creatinine < 200 micromol/L

AST < 3 x ULN (< 5 x ULN if liver metastates)

Bilirubin < 35 micromol/L

BP < 150/90

If ANC < 1.0 x 10^9/L defer for one week

If ANC > 1.0 but < 1.5 x 10^9/L discuss with consultant oncologist whether to defer or continue.

Dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability.

Non-haematological toxicity

Sunitinib	
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.
Gastrointestinal disorders	Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain are the most commonly reported gastrointestinal adverse reactions. **Diarrhoea:** Grade 1 and 2 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 required if symptom well controlled. <u>Grades 3 and 4</u> will need treatment interruption until improvement to Grade 1 or less. 1 step dose reduction is required when restarted. 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. Also to drink plenty of water and to record their 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 of Sunitinib just before bedtime can help ameliorate this side-effect.
Hypertension	Patients should be screened for hypertension and controlled as appropriate. The 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. <u>*Systolic 140-150 mmHg or Diastolic <90 mmHg:*</u> -Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary. <u>*Systolic 150-160mmHg or Diastolic 90-100mmgh:*</u> -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. <u>*Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):*</u> -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. The aim is to achieve a blood pressure below 140/90 Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes. Refer patients with refractory hypertension to cardiology. 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	Cardiovascular events, including heart failure, cardiomyopathy, and myocardial disorders, some of which were fatal, have been reported in patients treated with sunitinib. The administration of sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction < 50% and > 20% below baseline. Prolongation of QT interval and Torsade de pointes have been observed in sunitinib-exposed patients. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Therefore, a baseline ECG in important pre-treatment and a repeat is necessary at the 7 day interval for patients with a 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 sunitinib.

	Therefore, TFTs require routine monitoring every three months

Please refer to the TKI toxicity decision aid for advice regarding side effects associated to sunitinib.

References:

Electronic medicines compendium. *Sutent 50mg capsule.* Available from: https://www.medicines.org.uk/emc/product/7966/smpc [accessed on: 15/10/2018]

Guidelines for the Management of Urological Cancer. Mersey and Cheshire Cancer Network Kidney Cancer Treatment Guidelines.
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