SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Sunitinib

Gastrointestinal stromal tumours (GIST)

PROTOCOL REF:
(Version No. __1.2__)

Approved for use in:

GIST: Unresectable and/or metatstatic malignant gastrointestinal stromal tumours if:

- Imatinib treatment has failed because of resistance or intolerance

  AND

- The drug cost for the first treatment cycle will be met by the manufacturer through patient access scheme.

Dosage:

Drug	Dose	Route	Frequency
Sunitinib capsules	**50mg**	Oral	Once daily for 4 weeks followed by 2 weeks rest
Alternative unlicensed dose*			
Sunitinib capsules	**37.5mg**	Oral	Once daily **continuous**

*continuous unlicensed dosing may be considered in patients thought to be at increased risk of side effects. Supported by UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST) 2017.

Continued every 6 weeks (or 4 weeks unlicensed dose) until disease progression or unacceptable toxicity.

Supplied as 50mg or 25mg and 12.5mg x 28 capsules

Administration / Counselling Points:

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.

Sunitinib can cause hypertension. Patients will require regular blood pressure monitoring during treatment. Serial home BP monitoring can provide additional useful information.

Patients should be counselled on unlicensed use in Solitary Fibrous Tumour.

During treatment, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Emetogenic risk:

Minimal to low risk

Supportive treatments:

Not routinely required

Extravasation risk:

Not applicable

Dosing in renal and hepatic impairment:

Renal	No dose adjustment required.

Hepatic	Sunitinib and its primary metabolite are mainly metabolised by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate impairment compared to subjects with normal hepatic function. Data are not available in those with sever hepatic impairment		
	Mild	Bilirubin >1.0-1.5 x ULN **OR** AST > ULN	No adjustment required
	Moderate	Bilirubin 1.5-3 x ULN	
	Severe	Bilirubin >3.0 x ULN	Clinical decision

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

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

Investigations and treatment plan:

	Pre	Cycle 1	Mid cycle	Cycle 2	Mid cycle	Cycle 3	Mid cycle	Cycle 4 +	Ongoing
Informed Consent	X								
Clinical Assessment	X		X		X		X	X	Every 4 weeks during cycle 1 to 3 Every 12 weeks thereafter
SACT Assessment (to include PS and toxicities)	X	X		X		X		X	Every cycle
FBC	X	X	X	X	X	X	X	X	At the start of cycle and mid cycle for cycle 1 to 3 Every cycle thereafter
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	X	At the start of cycle and mid cycle for cycle 1 to 3 Every cycle thereafter
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	X	At the start of cycle and mid cycle for cycle 1 to 3 Every cycle thereafter
CT scan	X								At the end of treatment and if clinically indicated
ECG									If clinically indicated
Blood pressure measurement	X	X	X	X	X	X	X	X	At the start of cycle and mid cycle for cycle 1 to 3 Every cycle thereafter
Respiratory Rate									If clinically indicated
Weight recorded	X								Dosing non-weight dependent. Repeat only if significant change in weight
Height recorded	X								
Blood glucose	X								Repeat if clinically indicated
hCG Pregnancy Test **(woman of childbearing potential only)**		X		X		X		X	Every cycle

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.

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

Haematological toxicity (if required):

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

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. Grades 3 and 4 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:** Metoclopramide 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. *Systolic 140-150 mmHg or Diastolic <90 mmHg:* -Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary. *Systolic 150-160mmHg or Diastolic 90-100mmgh:* -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. *Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):* -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

References:

Electronic medicines compendium. *Sunitinib 25 mg hard capsules.* Available from: https://www.medicines.org.uk/emc/product/14645/smpc [accessed on: 25/04/2023] Last updated 11/05/2022

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
BNF available via: https://bnf.nice.org.uk/

NICE TA179 Sunitinib for the treatment of gastrointestinal stromal tumours. Published: 23 September 2009 https://www.nice.org.uk/guidance/ta179/chapter/2-The-technology [accessed: 25/04/23]

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
1.0	25/04/23	**Anna Taylor (Pharmacist)**	**New protocol**
1.1	27/06/23	**Rob Challoner (Pharmacist)**	**Protocol reviewed with Dr Ali. Removed info on renal cell carcinoma (previously for combined indications). Now just for GIST to allow information on continuous dosing option in GICT. Added info on blood pressure monitoring to patient counselling. Removed supportive meds as not required prophylactically (not on existing GIST Meditech build)**
1.2	12/07/23	**Rob Challoner (Pharmacist)**	**Feedback: NICE guideline referenced were obsolete – updated. References updated. Mid cycle bloods added as per Sunitinib renal protocol.**