Systemic Anti Cancer Treatment Protocol

Regorafenib in GIST

PROTOCOL REF: MPHAREGSA
(Version No: 1.0)

Approved for use in:

3rd line treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on prior treatment with, or are intolerant to, imatinib and sunitinib.

Dosage:

Drug	Dosage	Route	Frequency
Regorafenib	160mg	oral	Once daily for 21 days followed by 7 days off, until disease progression or unacceptable toxicity

Supportive treatments:

None required routinely

Administration:

Regorafenib is for oral administration, should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal that contains less than 30% fat.

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. In case of vomiting after regorafenib administration, the patient should not take additional tablets.

Drug Interactions

Imatinib is metabolized by cytochrome CYP3A4 and UGT1A9 and therefore drugs that induce or inhibit these enzymes should be avoided where possible.

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

INHIBITORS (increase regorafenib levels): Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil, mefenamic acid

Co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, prazosin, glyburide, nitrofurantoin, dipyridamole, statins, and cimetidine). Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.

Main Toxicities:

Infection, thrombocytopenia, anaemia, decreased appetite and food intake, haemorrhage, hypertension dysphonia, diarrhoea, stomatitis, vomiting, nausea, hyperbilirubinaemia, increase in transaminases, palmar-plantar erythrodysesthesia syndrome, rash, asthenia/fatigue, pain, fever, mucosal inflammation, weight loss

Investigations and Treatment Plan:

	Pre	C1	C2	C3	C4	Ongoing
Medical Assessment	X	X	X	X	X	Every cycle
Nursing Assessment		X	X	X	X	Every cycle
FBC	X		X	X	X	Every cycle
U&E & LFT	X		X	X	X	Every Cycle **and** LFTs should be monitored at least every 2 weeks during first 2 months of treatment
Thyroid function tests	X					If clinically indicated
CT scan	X				X	Every 12 weeks
Informed Consent	X					
ECG / BP	X					If clinically indicated
PS recorded	X	X	X	X	X	
Toxicities documented	X	X	X	X	X	
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets > 50 x 10^9/L

Below these limits, defer for one week and recheck. If recovered then resume at current dose.

Non-haematological toxicity

Infection	In cases of worsening infection events, interruption of Regorafenib treatment should be considered.
Skin toxicity	**Grade 1 -** Maintain dose level and immediately institute supportive measures for symptomatic relief. **Grade 2 (1st occurrence)** - Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician. **Grade 3 (1st occurrence) -** Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
Haemorrhage	Regorafenib has been associated with an increased incidence of fatal haemorrhagic events. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation should be considered
Gastrointestinal perforation and fistula	Discontinuation of Regorafenib is recommended in patients developing gastrointestinal perforation or fistula
Cardiac ischaemia and infarction	Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Regorafenib is recommended until resolution and should be permanently discontinued if there is no resolution.

Hepatic impairment

Regorafenib is predominantly metabolised by the liver.

≤5 times upper limit of normal (ULN) (maximum Grade 2)	Continue Regorafenib treatment. Monitor liver function weekly until transaminases return to <3 times ULN (Grade 1) or baseline.
>5 times ULN ≤20 times ULN (Grade 3)	Interupt then monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity but reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks. Discontinue Regorafenib permanently upon re-occurrence.
>20 times ULN (Grade 4)	Discontinue Regorafenib permanently
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Discontinue Regorafenib permanently and monitor weekly (see SPC for exceptions)

References:

Stivarga SPC: http://www.medicines.org.uk/emc/medicine/28270# (accessed 15th Nov 2017)

NICE Final appraisal determination: Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours https://www.nice.org.uk/guidance/gid-ta10089/documents/html-content (accessed 6th Dec 2017)