Systemic Anti-Cancer Treatment Protocol

Sorafenib

Hepatocellular Carcinoma

PROTOCOL REF: MPHASORAGA
(Version No: 1.0)

Approved for use in

First line treatment of Child-Pugh A locally advanced or metastatic hepatocellular carcinoma (ECOG PS 0-2)

Patients need to be registered with NHS England via the Blueteq website prior to starting treatment (accessed at https://www.blueteq-secure.co.uk/trust/default.htm)

Dosage

Drug	Dose	Route	Frequency
Sorafenib	400mg	PO	Twice Daily*

*some patients may initiate on 400mg Once Daily due to co-morbidities or poor PS

Patients will initially be given a 14 day supply of sorafenib for the first two cycles and be reviewed prior. If well tolerated, supply will increase to 28 days on cycle 3.

Supportive Treatments:

Domperidone 10mg TDS PRN

Loperamide 4mg at onset then 2mg after each loose stool (max.16mg in 24hrs)

Administration

- Sorafenib is available in 200mg tablets.
- Sorafenib should be administered without food or with a low or moderate fat meal.
- If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal.

- The tablets should be swallowed with a glass of water.

Main Toxicities

- Nausea and vomiting
- Diarrhoea or constipation.
- Mucositis
- Skin reactions including dry skin, rash, pruritus, Hand-Foot Syndrome and alopecia
- Anorexia and reduced appetite
- Hypertension
- Fever
- Fatigue, myalgia, reduction in muscle mass
- Voice changes (hoarseness)
- Myelosuppression (including neutropenia and thrombocytopenia)
- Hypophosphataemia
- Hypothyroidism

Investigations and Treatment Plan

	Pre	C1	C2	C3	C4	Ongoing
Medical Assessment	X	X		X		Once stable, alternate cycles
Nursing Assessment	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
Phosphate	X	X	X	X	X	Every cycle
AFP	X	X	X	X	X	Every cycle
CT scan	X					Every 12 weeks
Informed Consent	X					
Blood pressure*	X	X	X	X	X	Every cycle
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
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 *

Discuss with consultant if:-

ANC ≤ 0.99 x 10^9/L	Platelets ≤ 49 x 10^9/L *

*Patients may have longstanding thrombocytopenia which is likely attributed to hypersplenism secondary to portal hypertension rather than being treatment-related. Review of the platelet trend over a period of time is therefore recommended to fully assess

Non-haematological Toxicity

Toxicity (CTC Grade)	Treatment Delay	Dose Reduction
Grade 1	No delay	No reduction
Grade 2 and 3	Delay treatment until Grade 1	Reduce down to next level
Grade 4	-	Discontinue

Dose Reduction Level	Dose
1	400mg ONCE daily
2	400mg on ALTERNATE days
3	200mg on ALTERNATE days

Hepatic impairment

No dose adjustments are required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. There is currently no safety data of sorafenib in severe (Child-Pugh C) hepatic impairment therefore it is not recommended.

Renal impairment

No dose adjustments are required in mild, moderate or severe renal impairment. There is currently no safety data on patients requiring dialysis.

Drug Interactions

CYP3A4 inducers - Rifampicin reduced the AUC of sorafenib by 37%. Other inducers such as St. John's wort, phenytoin, carbamazepine, phenobarbital and dexamethasone may also increase the metabolism of sorafenib and could decrease sorafenib concentrations.

CYP2C9 substrates -Concomitant treatment with sorafenib and warfarin did not result in changes to INR therefore an interaction is unlikely. However, patients taking warfarin should have their INR checked regularly whilst on sorafenib.

P-gp-substrates - *S*orafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp) in vitro studies therefore increased plasma concentrations of P-gp substrates such as digoxin cannot be excluded when given with sorafenib.

Neomycin - Co-administration of neomycin, a non-systemic antimicrobial agent used to eradicate gastrointestinal flora, interferes with the enterohepatic recycling of sorafenib resulting in decreased sorafenib exposure by as much as 54%. Effects of other antibiotics have not been studied but will depend on their ability to interfere with micro-organisms with glucuronidase activity.

References:

Nexavar 200mg film-coated tablets.
Summary of Product Characteristics. Bayer plc, Reading, 21/07/2011.
Available from https://www.medicines.org.uk/emc (last updated 05/07/2018)