Chemotherapy Protocol

Hepatocellular Cancer

Regorafenib

Regimen

- Hepatocellular – Regorafenib

Indication

- Regorafenib is recommended as an option for treating advanced unresectable hepatocellular carcinoma in adults who have had sorafenib and have an ECOG performance status of 0 or 1 and Child–Pugh grade A liver impairment.

Toxicity

Drug	Adverse Effect
Regorafenib	Infection, myelosuppression, hypothyroidism, haemorrhage, hypertension dysphonia, hepatotoxicity, GI disturbances, skin reactions including palmar-plantar erythrodysesthesia syndrome, electrolyte disturbances, proteinuria.

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

Monitoring

- ALT, AST and bilirubin at baseline then at least every two weeks during the first 2 months of treatment then every four weeks or as clinically indicated.
- U&Es including serum phosphate, calcium, sodium and potassium.
- Blood pressure at baseline and then every cycle
- Thyroid function at baseline, then every 12 weeks or as clinically indicated

Drugs

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities. 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 SACT 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. The following is a general guide only.

Dose interruptions and/or dose reductions of regorafenib may be required based on individual safety and tolerability. Dose modifications are to be applied in 40mg (one tablet) steps. The lowest recommended daily dose is 80mg. The maximum daily dose is 160mg.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing cycle 1 the following criteria must be met.

Criteria	**Eligible Level**
Neutrophils	Equal to or more than $1x10^9$/L
Platelets	Equal to or more than $50x10^9$/L

HCC 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 regorafenib toxicity.

Renal Impairment

No dose adjustment for regorafenib is necessary in patients with mild, moderate or severe renal impairment.

Hepatic Impairment

Regorafenib is eliminated mainly via the hepatic route.

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A).

There is limited data in patients with moderate hepatic impairment (Child Pugh B), no dose recommendation can be provided.

Regorafenib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).

AST/ALT (units/L)		Bilirubin (µmol/L)	Regorafenib dose adjustment
Grade 1-2 (less than or equal to 5xULN)	and	Less than or equal to 2xULN	Continue regorafenib treatment. Monitor weekly until AST/ALT returns to less than 3xULN or baseline.
Grade 3 (greater than 5 to 20xULN)	and	Less than or equal to 2xULN	1st Occurrence: Interrupt regorafenib treatment. Monitor weekly until AST/ALT returns to less than 3xULN or baseline. Restart, only If the potential benefit outweighs the risk of hepatotoxicity, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks. Re-occurrence: Permanently discontinue regorafenib.
Grade 4 (greater than 20xULN)	and	Less than or equal to 2xULN	Permanently discontinue regorafenib.
Greater than 3xULN	and	Greater than 2xULN	Permanently discontinue regorafenib.

Other

Toxicity NCI CTC Grade	Treatment Delay	Dose Reduction
1	No delay	No reduction
2 and 3	Delay treatment until NCI CTC grade 1 or below	Reduce a level
4		Discontinue

Dose Reduction Level	Dose
1	120mg once a day
2	80mg once a day
3	40mg once a day

Skin (palmar-plantar erythrodysesthesia syndrome)

NCI-CTC Grade	Occurrence	Dose modifications
1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
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 NCI CTC grade 0-1. A dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to NCI CTC 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.
	3rd occurrence	Interrupt therapy until toxicity resolves to NCI CTC 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.
	4th occurrence	Discontinue treatment with regorafenib permanently.
3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to NCI CTC 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.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to NCI CTC grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment with regorafenib permanently.

Regimen

28 day cycle continued as long as benefit is observed or until unacceptable toxicity occurs (twelve cycles will be set in ARIA)

Drug	Dose	Days	Route
Regorafenib	160mg once a day	1-21 (inclusive) followed by a 7 day break	Oral

Dose Information

- Regorafenib is available as 40mg tablets

Administration Information

- Regorafenib 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, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to regorafenib

- It must be made clear to all staff, including those in the community, that regorafenib should only be prescribed under the supervision of a consultant oncologist

- Regorafenib interacts with many other agents. Always check for drug interactions.

References

1. Bruix J, Qin S, Merle P et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2017; 389: 56-66
2. Regorafenib for previously treated advanced hepatocellular carcinoma NICE technology appraisal guidance [TA555] Published date: 09 January 2019

REGIMEN SUMMARY

Regorafenib

Day One

1. Regorafenib 160mg once a day for 21 days oral
   Administration Instructions
   Oral chemotherapy.
   Regorafenib is taken from day 1 to day 21 of a 28 day cycle (21 days of treatment followed by a 7 day break)
   Tablets should be taken at the same time each day, swallowed whole with water after a light meal that contains less than 30% fat. Avoid grapefruit juice.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Feb 2020	None	Rebecca Wills Pharmacist	

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 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 which occur as a result of following these guidelines.