Sorafenib (Thyroid Cancer)

Indication

First line tyrosine kinase inhibitor (TKI) option for the treatment of progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hurthle cell) in patients whose disease no longer responds to radioactive iodine.

No previous treatment with other TKI (eg. Lenvatinib) unless TKI stopped within 3 months of starting it because of toxicity that cannot be managed by dose delay or modification and in the absence of disease progression.

(NICE TA535)

ICD-10 codes

Codes with a prefix C73

Regimen details

Day	Drug	Dose	Route
1-28	Sorafenib	400mg BD	Oral

Cycle frequency

Continuously until disease progression or unacceptable toxicity.

Number of cycles

As above

Administration

Sorafenib is available as 200mg tablets.

The dose should be taken 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 tablet should be swallowed with a glass of water. If a dose is missed that dose should be omitted and the next dose taken at the usual time.

Grapefruit and grapefruit juice should be avoided while on sorafenib.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential

Additional supportive medication

Patients should be supplied with loperamide on commencing treatment.

Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment and to avoid activities that put pressure on hands and feet to minimise the risk of developing palmar plantar erythema.

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Blood pressure*	14 days
ECG for QTc interval**	14 days

*Blood pressure should be well controlled prior to commencing treatment.
** Review concomitant medications that may also lead to QTc prolongation. Electrolyte abnormalities, such as hypokalaemia, hypocalcaemia or hypomagnesaemia must be corrected prior to commencing treatment.
** Consider echocardiogram if concerns about cardiac status.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Every 2 weeks for first month then monthly
U+E (including creatinine)	Every 2 weeks for first month then monthly
LFTs	Every 2 weeks for first month then monthly
Ca	Every 2 weeks for first month then monthly
Mg	Every 2 weeks for first month then monthly
Thyroid function	Every three months
Blood pressure*	Weekly for first month, then monthly
ECG for QTc interval	Every 2 weeks for first month then periodically as indicated

* Hypertension may develop within a week of commencing TKIs. Patients should be encouraged to monitor their blood pressure at home regularly, ideally daily.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance (CrCl)	≥ 40ml/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	<ULN
Albumin	>25g/L
QTc	<500ms

Dose modifications

Management of suspected adverse drug reactions may require temporary interruption or dose reduction. Dose interruption followed by dose reduction is recommended for ≥G3 or intolerable G2 toxicity. Once recovered to ≤G1 sorafenib can be restarted at a lower dose as per table below:

Dose level	Sorafenib dose
1st dose reduction	600mg in divided doses, ie 400mg AM, 200mg ON
2nd dose reduction	400mg in divided doses, ie 200 mg BD
3rd dose reduction	200 mg OD

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L or platelets < 100 x 10^9/L, discuss with consultant.

- **Renal impairment**

The SPC states that no dose adjustment is required for patients with mild, moderate or severe renal impairment and that no data is available for patients requiring dialysis. However, the table below, adapted from the pharmacokinetic study by Miller, is a useful guide for choosing a starting dose for patients with renal impairment. If the patient tolerates the starting dose, then a dose increase can be considered at consultant's discretion.

Renal function (CrCl ml/min)	Starting sorafenib dose
≥40ml/min	400mg BD
20-39ml/min	200mg BD
<20ml/min	Insufficient data, could consider 200mg OD
Patient on haemodialysis	200 mg OD

- **Hepatic impairment**

The SPC states that no dose adjustment is required for patients with mild or moderate hepatic impairment and that there are no data for patients with severe hepatic impairment. However, the table below, adapted from the pharmacokinetic study by Miller, is a useful guide for choosing a starting dose for patients with hepatic impairment. If the patient tolerates the starting dose, then a dose increase can be considered at consultant's discretion.

Bilirubin	ALT/AST	Starting sorafenib dose
<1.5 x ULN	>ULN	400mg BD
1.5-3 x ULN	Any	200mg BD
3-10 x ULN	Any	Avoid
Albumin < 25 g/L, any bilirubin and any AST		200mg OD

- **Other toxicities**

Hypertension
Hypertension occurs early in treatment and is usually mild to moderate. It should be treated and monitored closely until stabilised. It is not a reason to stop sorafenib, unless patient develops severe hypertension.

Skin toxicity
Grade 2 + palmar plantar erythema or rash may require a 1-2 week break in treatment until resolved to Grade ≤ 1. The patient should be advised to moisturise their hands and feet regularly, and to keep them cool. Once symptoms have resolved to ≤ Grade 1, sorafenib may be re-introduced at next dose reduction level.

Bleeding
An increased risk of bleeding may occur while on sorafenib. Permanently discontinue sorafenib if any bleeding event requires medical intervention.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Haemorrhage
Hypertensive crisis
Aneurysms and artery dissections
Cardiac ischaemia and infarctions
Cardiac failure

QTc interval prolongation
Drug induced hepatitis
GI perforation
Pancreatitis
Hypoglycaemia
Wound healing complications
Thyroid dysfunction

- **Frequently occurring side effects**

Diarhoea
Fatigue
Palmar Plantar Erythema
Rash
Alopecia
Infection
Hypertension
Weight loss
Anorexia
Nausea
Hypocalcaemia
Hypophosphataemia

- **Other side effects**

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of sorafenib.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of sorafenib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to sorafenib.

Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.

P-gp subtrates e.g digoxin: sorafenib inhibits P-gp which may lead to increased plasma concentrations of P-gp substrates

Neomycin: interferes with enterohepatic recycling of sorafenib, reducing dorafenib exposure.

Additional comments

References

- NICE Technology Appraisal Guidance 535 – Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Accessed 12 Aug 2021 via www.nice.org.uk
- Summary of Product Characteristics Sorafenib (Bayer)accessed 12 Aug 2021 via https://www.medicines.org
- Brose MS, Nutting C, Jarzab B et al Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomised, double blind phase 3 trial. *Lancet* 2014; 384:319-328
- Miller AA, Murry DJ, Owzar K et al Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 6030. *J Clin Oncol* 2009; 27:1800-1805

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