SORAFENIB in thyroid cancer

Indication: Treatment of papillary or follicular thyroid carcinoma (unlicensed indication)

NCDF criteria to be met:
- Inoperable or metastatic disease
- Refractory to radioiodine

**NOTE:** sorafenib must be prescribed by specialist medical staff specifically trained and accredited in the use of systemic anti-cancer therapy and on the Trust’s register of systemic anticancer therapy prescribers

Cancer drug fund application and approval is required prior to starting treatment.

Regimen details: Sorafenib 400mg TWICE daily PO Continuous therapy

Administration: Sorafenib tablets 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. Tablets should be swallowed with a glass of water. Avoid grapefruit or grapefruit juice.

Frequency: Prescribed every 28 days - continue treatment until disease progression or unacceptable toxicity occurs

Extravasation: N/A

Anti-emetics: Low emetogenicity – follow local anti-emetic policy.

Supportive medication: Diarrhoea can be managed with loperamide. Various approaches may be considered for management of PPE/skin rash (rash usually appears during first 6 weeks of therapy) – see dose modifications below and discuss with consultant.

Regular investigations:
- FBC Monthly
- U&Es Monthly
- LFTs Monthly
- LDH Monthly
- Thyroglobulin Monthly
- Thyroid function tests Monthly
- Clinical toxicity assessment Monthly
- Blood pressure Weekly for first 6 weeks then monthly thereafter if stable
- MUGA/ECG Prior to each cycle (ONLY in patients with cardiac risk factors)

Comments: Due to potential drug interactions, update medication list at each clinic visit.

Toxicities: Ventricular arrhythmias (prolonged QT), nausea, fatigue, anorexia, stomatitis, diarrhoea, constipation, hoarse voice, hypertension, thyroid dysfunction – should be managed with modification of replacement thyroid hormone therapy, hepatitis, electrolyte disturbances (phosphate, calcium, potassium, sodium), increased amylase and lipase levels, sensory neuropathy (mild – moderate), maculo-papular rash, hand-foot skin reaction (otherwise
known as palmar-plantar erythrodysaethesia PPE), alopecia, pain (muscle, joint), impaired wound healing. Other severe events include bleeding, gastrointestinal perforation, interstitial lung-like events and cardiac ischemia or infarction.

Dose modifications:

Haematological toxicity **DISCUSS ANY DOSE REDUCTIONS FOR HAEMATOLOGICAL TOXICITY WITH THE CONSULTANT** Myelosuppression may occur, but often resolves spontaneously without discontinuing treatment. However, if Grade 3 or 4 neutropenia or thrombocytopenia, treat as below:

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Sorafenib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 - 0.9 x 10^9/L or 25 - 49 x 10^9/L</td>
<td>Delay next cycle until above these limits, then continue at the same dose. If more than one delay for this reason, consider reducing the dose to 400mg ONCE daily at the next cycle.</td>
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<tr>
<td>&lt; 0.5 x 10^9/L or &lt; 25 x 10^9/L</td>
<td>Delay next cycle until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L, then reduce the dose to 400mg ONCE daily and resume treatment.</td>
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</tbody>
</table>

If complicated neutropenia, withhold dose until toxicity is grade ≤ 2 (neutrophils > 1.0 x 10^9/L) or has returned to baseline, then reduce dose to 400mg ONCE daily.

Renal impairment No dose modifications required

Hepatic impairment

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Bilirubin</th>
<th>Albumin</th>
<th>Sorafenib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild and ≤ 1.5 x ULN</td>
<td>400mg TWICE daily</td>
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<tr>
<td>Moderate (Child-Pugh class B) and/or 1.51- 3.0 x ULN</td>
<td>200mg TWICE daily</td>
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<tr>
<td>Severe (Child-Pugh class C) and/or &gt; 3.0 x ULN</td>
<td>Do not treat</td>
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</tbody>
</table>

≤ 25g/L 200mg ONCE daily

Non-haematological toxicities: **ALL DOSE MODIFICATIONS MUST BE CHECKED WITH THE CONSULTANT**

<table>
<thead>
<tr>
<th>Grade</th>
<th>PPE</th>
<th>Maculo-papular rash</th>
<th>Diarrhoea</th>
<th>Fatigue</th>
<th>Occurrence</th>
<th>Sorafenib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal skin changes or dermatitis (e.g. erythema, edema or hyperkeratosis) without pain</td>
<td>Macules/papules covering &lt;10% BSA with or without symptoms e.g. pruritis, burning, tightness)</td>
<td>Increase of &lt;4 stools per day over baseline</td>
<td>Fatigue relieved by rest</td>
<td>Any</td>
<td>Continue sorafenib and consider topical/supportive therapy for symptomatic relief.</td>
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</tbody>
</table>

Reason for Update: addition to NCDF
Approved by Oncology Consultant: Mary Lei
Version: 1
Date: 18/06/2013
Supersedes: All other versions
Checked by (Principal Pharmacist): Jacky Turner
Prepared by: Lisa Yuen 06/06/13
Date: 20/06/2013
<table>
<thead>
<tr>
<th></th>
<th>Skin changes (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain; limiting instrumental ADL</th>
<th>Macules/papules covering 10-30% BSA with or without symptoms e.g. pruritis, burning, tightness);limiting instrumental ADL</th>
<th>Increase of 4-6 stools per day over baseline</th>
<th>Fatigue not relieved by rest; limiting instrumental ADL</th>
<th>1st</th>
<th>Consider sorafenib 400mg ONCE daily for 28 days. If it does not improve, delay therapy for 1 week until ≤ grade 1 and re-start at 400mg ONCE daily. If ≤ grade 1 for 28 days, consider re-escalating to full dose.</th>
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<tbody>
<tr>
<td>2</td>
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<tr>
<td>2nd or 3rd</td>
<td>As for 1st occurrence, but do NOT re-escalate if delay of therapy required.</td>
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<tr>
<td>4th</td>
<td>Consider discontinuing sorafenib.</td>
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<td>Severe skin changes (e.g. peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL</td>
<td>Macules/papules covering &gt;30% BSA with or without associated symptoms; limiting instrumental ADL</td>
<td>Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; limiting self care ADL</td>
<td>Fatigue not relieved by rest; limiting self care ADL</td>
<td>1st</td>
<td>Delay sorafenib for 1 week until ≤ grade 1 and re-start at 400mg ONCE daily. If ≤ grade 1 for 28 days, consider re-escalating to full dose.</td>
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<tr>
<td>2nd</td>
<td>As for 1st occurrence, but do NOT re-escalate.</td>
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<tr>
<td>3rd</td>
<td>Consider discontinuing sorafenib.</td>
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<tr>
<td>4</td>
<td>Disabling</td>
<td>Life threatening consequences; urgent investigation indicated</td>
<td>Discontinue therapy</td>
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**Hypertension**

Mild to moderate hypertension can occur which may be manageable with antihypertensive therapy. Severe or persistent hypertension or hypertensive crisis despite adequate treatment may lead to dose interruption and/or discontinuation.

**Wound healing**

No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of
therapy following surgery - the decision to resume sorafenib should be based on clinical judgement of adequate wound healing.

Discontinue sorafenib for myocardial infarction/ischaemia and bleeding requiring intervention

Drug interactions:
Sorafenib is primarily metabolised by CYP3A4 and undergoes glucuronidation by UGT enzymes. Sorafenib is affected by drugs that induce UGT enzymes but does not itself induce this pathway.
Rifampicin and inducers of CYP3A4 activity and/or glucuronidation (phenytoin, carbamazepine, phenobarbital, dexamethasone and hypericum perforatum/St John’s wort, grapefruit/grapefruit juice) may decrease sorafenib concentrations
Neomycin decreases sorafenib exposure
Warfarin: INR needs to be monitored regularly
Sorafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp) in vitro, and may increase plasma concentrations of P-gp substrates such as digoxin
Concomitant drugs that affect the QT interval (eg amiodarone, sotalol, chloroquine, clarithromycin) may cause ventricular arrhythmias – monitor electrolytes and ECG periodically throughout treatment.

References:
Renal drug handbook 3rd ed. 2009