BOSUTINIB

INDICATION

Licensed / NICE TA401 (BLUETEQ required)
Chronic, accelerated and blast phase Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Licensed / Unfunded Indication
Newly diagnosed Ph+ CML

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea, creatinine, electrolytes, liver function tests, calcium, lipid profile, glucose, amylase, urate, CK.
2. Ensure diagnosis is confirmed prior to commencing treatment (usually PCR on peripheral blood and bone marrow aspirate morphology with FISH for Ph chromosome). Results of full karyotype are important to exclude major route abnormality (Ph+ amplification, trisomy 8, trisomy 19) but treatment can be commenced prior to the karyotype becoming available. For second line treatment for resistance, it is recommended to carry out bone marrow, cytogenetics and kinase domain mutation screen testing prior to switch of treatment.
3. Pregnancy Test - for all women of childbearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. ECG (most TKIs can affect the QT interval)
7. Record blood pressure
8. Consider echo in selected patients at risk of cardiac disease
9. Hepatitis B (including HB surface Ag and HB core antibodies) and C testing (reactivation of HBV has been reported with TKIs)
10. SOKAL risk score should be documented at diagnosis for all CML patients (LINK)
11. QRISK3 score (LINK - some TKIs have been associated with increased risk of cardiovascular disease and vascular risk factors should be considered and managed as appropriate)
12. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
13. Fertility - it is very important the patient understands the potential risk of infertility; all patients should be offered fertility advice (see fertility guidelines). Consider sperm storage/cryopreservation in appropriate patients.
14. Treatment should be agreed in the relevant MDT.
15. Ensure pre-treatment counselling in line with NPSA recommendation and chemotherapy measures.

**DRUG REGIMEN / CYCLE FREQUENCY**

**BOSUTINIB**  500mg PO once daily with food

In practice, the recommend starting dose is 400mg daily for most patients to minimize risk of GI toxicity. Dose can subsequently be titrated depending on tolerance and disease response.

Continue until disease progression or until no longer tolerated

**DOSE MODIFICATIONS**

**Dose Escalation**

The dose can be increased up to 600 mg PO once daily in patients who did not experience severe or persistent moderate adverse reactions, under any of the following circumstances:

- Failure to achieve Complete Haematologic Response (CHR) by week 8
- Failure to achieve BCR-ABL transcript level <10% by week 12

Doses > 600mg/day should not be given.

**Dose adjustments for Haematologic toxicity**

| ANC < 1 x 10^9/L and/or Plt < 50 x 10^9/L | Withhold Bosutinib until ANC ≥ 1 x 10^9/L and Plt ≥ 50 x 10^9/L. Resume treatment at the same dose if recovery occurs within 2 weeks. If blood counts remain low for > 2 weeks, reduce dose by 100mg and resume treatment. If cytopenia recurs, reduce dose by 100mg upon recovery and resume treatment. Doses less than 300mg/day have not been evaluated. |

**Dose adjustments for Non-Haematologic toxicity**

| Clinically significant moderate or severe non-haematological toxicity | Interrupt Bosutinib. Resume at 400mg PO once daily when toxicity has resolved. If clinically appropriate, consider re-escalating dose to 500mg PO once daily |
| Liver transaminases > 5 x ULN | Interrupt Bosutinib. Resume at 400mg PO once daily when ≤ 2.5 x ULN. If recovery takes > 4 weeks, consider discontinuing Bosutinib. |
| Liver transaminases ≥ 3 x ULN and Bilirubin > 2 x ULN and ALP < 2 x ULN | Discontinue Bosutinib. |
| Diarrhoea Grade 3 / 4 | Interrupt Bosutinib. Resume at 400mg PO once daily upon recovery to Grade ≤ 1 |
Renal / Hepatic Impairment

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously treated CML</strong></td>
<td><strong>Contra-indicated</strong></td>
</tr>
<tr>
<td>CrCl 30 - 50mL/min : 400mg PO once daily</td>
<td><strong>CrCl &lt; 30mL/min : 300mg PO once daily</strong></td>
</tr>
<tr>
<td><em>Dose escalation to 500mg PO once daily</em></td>
<td><em>Dose escalation to 400mg PO once daily</em></td>
</tr>
</tbody>
</table>

| **Newly diagnosed CML** | **Contra-indicated** |
| CrCl 30 - 50mL/min : 300mg PO once daily | **CrCl < 30mL/min : 200mg PO once daily** |
| *Dose escalation to 400mg PO once daily* | *Dose escalation to 300mg PO once daily* |

*Dose escalation may be considered in those who do not experience severe or persistent moderate adverse reactions, under any of the following circumstances:

- Failure to achieve Complete Haematologic Response (CHR) by week 8.
- Failure to achieve MMR by week 12.

INVESTIGATIONS

- See pre-assessment above
- BCR-ABL monitoring
- Monitoring for toxicity:
- Weekly in first month on treatment: ECG (at baseline and at least one ECG following TKI initiation for all patients. Additional weekly ECG if new symptoms or abnormal at baseline), FBC, U&E, LFT, Bone, amylase/lipase
- Monthly for next 2 months: ECG as clinically indicated, FBC, U&E, LFT and Bone, CK
- 3-4 monthly: CK, FBC, U&E, LFT, Bone
- TSH should be monitored during TKI therapy on a yearly basis (or when clinically indicated)
- CXR should be performed in all patients who are SOB for assessment of pleural effusion, particularly in patients with previous pleural effusion on dasatinib. Consideration should also be given to Echo in selected patients – for exclusion of pericardial effusion and assessment of left ventricular function as this can be affected by all TKIs

CONCURRENT MEDICATION

Not usually required.
Allopurinol 300mg PO once daily for 14 days can be considered if WBC >10
Loperamide PRN

EMETIC RISK

Low
DRUG INTERACTIONS
(Consult with pharmacist and refer to SPC for full details)

- Concomitant use of strong/moderate CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John’s Wort) as they may significantly reduce exposure to bosutinib, potentially increasing the risk of therapeutic failure.
- Caution should be taken when co-administering bosutinib with strong/moderate CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin, verapamil, diltiazem), as they could increase bosutinib exposure. Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided.
- Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic or other medicinal products that may lead to QT prolongation.
- Caution should be exercised when administering bosutinib concomitantly with proton pump inhibitors or H2 antagonists as they may reduce exposure to bosutinib. Short-acting antacids should be considered as an alternative and administration times separated (i.e. bosutinib in the morning and antacids in the evening) whenever possible.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
(Consult with pharmacist and refer to SPC for full details)

Very commonly reported:
Diarrhea is common during initial weeks of therapy but often settles with conservative management. Respiratory tract infection, thrombocytopenia, neutropenia, anaemia, leucopenia, decreased appetite, headache, cough, diarrhoea, vomiting, nausea, abdominal pain, increased AST, increased ALT, rash, arthralgia, pyrexia, oedema, fatigue.

Bosutinib may result in a clinically significant decline in renal function. Closely monitor patient with existing risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs). TKI should be discontinued 1 week before major surgery and restarted when risk of bleeding is considered to be minimal.

BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation

- Test patients for infection with hepatitis B virus (HBV) before starting treatment with BCR-ABL tyrosine kinase inhibitors
- Consult experts in liver disease and in the treatment of HBV before starting treatment with BCR-ABL tyrosine kinase inhibitors in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV during treatment
- Patients who are carriers of HBV who require treatment with BCR-ABL tyrosine kinase inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after stopping
- Suspected adverse drug reactions to BCR-ABL tyrosine kinase inhibitors should be reported via the Yellow Card scheme
TREATMENT RELATED MORTALITY

Very low (<1%).

REFERENCES


REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julia Wong. Nadjoua Maouche. Dr Adam Mead</td>
<td>New protocol</td>
<td>Mar 2017</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cheuk-kie Cheung</td>
<td>General formatting</td>
<td>Apr 2017</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group</td>
<td>Annual protocol meeting</td>
<td>Oct 2019</td>
<td>1.2</td>
<td>Oct 2021</td>
</tr>
</tbody>
</table>