Thames Valley
Strategic Clinical Network

BOSUTINIB

INDICATION

Licensed & Funded Indication (BLUETEQ required – NICE TA 401)
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

Available as 100mg, 400mg and 500mg tablets

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea and electrolytes, liver function tests, bone profile, lipid profile, fasting glucose or HbA1c, BNP, amylase, urate, CK, HIV, Hepatitis B (including HB surface Ag and HB core antibodies) and C testing.
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 (extra Philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q or 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 or have undergone a hysterectomy.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. Record blood pressure
7. ECG (most TKIs can affect the QT interval)
8. Consider echocardiogram in selected patients at risk of cardiac disease
9. ELTS or SOKAL risk score should be documented at diagnosis for all CML patients (LINK)
10. 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)
11. 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.

12. 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.
13. Treatment should be agreed in the relevant MDT.
14. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).

DRUG REGIMEN / CYCLE FREQUENCY

BOSUTINIB 500mg PO once daily **with food**
In practice, the recommended starting dose is 400mg daily for most patients to minimize risk of GI toxicity. In elderly/frail patients, or patients with comorbidities, an even lower starting dose can be used e.g. 200mg daily, with uptitration on a monthly basis (100mg per month) as indicated. Dose can subsequently be titrated depending on tolerance and disease response.

Avoid grapefruit and grapefruit juice.

According to SPC, population pharmacokinetic analyses revealed that Asians had a 18% lower clearance corresponding to an approximately 25% increase in bosutinib exposure (AUC), so dose may need to be adjusted accordingly.

Continue until disease progression or unacceptable toxicity.

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 greater than 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 an additional 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. Once toxicity has resolved, restart at a dose reduced by 100mg once daily. If clinically appropriate, consider re-escalating to the previous dose once daily
Liver transaminases > 5 x ULN	Interrupt Bosutinib. Resume at a dose reduced by 100mg daily when ≤ 2.5 x ULN. If recovery takes > 4 weeks, consider discontinuing Bosutinib.
Liver transaminases ≥ 3 x ULN and Bilirubin > 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

Renal impairment	Hepatic impairment
CrCl ≥ 50mL/min: No dose adjustment needed. CrCl 30 - 50mL/min : 400mg PO once daily *Dose escalation to 500mg PO once daily CrCl < 30mL/min : 300mg PO once daily *Dose escalation to 400mg PO once daily HD: Consider 75% of original dose Note: Renal dosing varies dependent on indication, please refer to SPC and other resources.	Child-Pugh Stage A-C: 50% dose

INVESTIGATIONS & ON-TREATMENT MONITORING

Monitoring for Bosutinib		Frequency of Monitoring (Month 1)	Frequency of Monitoring (Month 2 and 3)	Frequency of Monitoring Once Stable
HIV, Hepatitis B and C serology	Baseline	N/A	N/A	N/A
Document Q-RISK score	Baseline	N/A	N/A	Annually
FBC	Baseline	1-2 weekly	Monthly	3 monthly
Biochemistry (U&Es, LFTs, bone profile)	Baseline	1-2 weekly	Monthly	3 monthly
BCR-ABL monitoring	Baseline	N/A	N/A	3 monthly *
Lipid profile	Baseline	N/A	N/A	Annually
BNP	Baseline	N/A	N/A	As clinically indicated
HbA1c	Baseline	N/A	N/A	As clinically indicated
TFTs	Baseline	N/A	N/A	As clinically indicated
Amylase	Baseline	N/A	N/A	As clinically indicated
Creatine kinase	Baseline	N/A	N/A	As clinically indicated
Blood pressure	Baseline	N/A	Monthly	3 monthly
ECG	Baseline	At least 1 ECG following initiation	As clinically indicated	As clinically indicated
Echocardiogram & Chest X-ray #	As clinically indicated	N/A	As clinically indicated	As clinically indicated
ABL1 kinase domain mutation	At diagnosis	N/A	N/A	At warning or failure of response

* BCR-ABL monitoring every 3 months until the achievement of a stable MMR (<MR 3 – sustained for 1 year), and thereafter at 3-6 months as clinically indicated, as per BSH/ELN guidelines.

CXR should be performed in all patients who are SOB for assessment of pleural effusion 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

Allopurinol 300mg PO once daily for 14 days can be considered if WBC >10
Loperamide PRN – give with first cycle
Consider GCSF support in patients with recurrent neutropenia.
Consider erythropoietin-stimulating agents (ESA) in anaemic patients.

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, St John's Wort, efavirenz, modafinil etc) as they may significantly reduce exposure to bosutinib, potentially increasing the risk of therapeutic failure. Caution with mild CYP3A4 inducers.
- Strong/moderate CYP3A4 inhibitors (ketoconazole, itraconazole, posazonazole, voriconazole, erythromycin, clarithromycin, verapamil, diltiazem etc) should be avoided if possible, as they could increase bosutinib exposure. If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered.
- 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 such as amiodarone, sotalol, chloroquine, halofantrine, clarithromycin, domperidone, haloperidol, methadone, and moxifloxacin etc.
- 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:
Diarrhoea is common during initial weeks of therapy but often settles with conservative management. Respiratory tract infection, nasopharyngitis, thrombocytopenia, neutropenia, anaemia, leucopenia, decreased appetite, dizziness, headache, tinnitus, cough, diarrhoea, vomiting, nausea, abdominal pain, increased AST, increased ALT, Hyperlipasaemia, rash, arthralgia, pyrexia, oedema, fatigue, pleural effusion, acute pancreatitis, pulmonary hypertension, QT prolongation.

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. Discuss with haematologist during surgery planning.

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

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TREATMENT RELATED MORTALITY

Very low (<1%).

REFERENCES

1. NICE (2016) TA 401. Bosutinib for previously treated chronic myeloid leukaemia. Published: 24/08/2016. Accessed via https://www.nice.org.uk/guidance/ta401.
2. Pfizer. Bosutinib Summary of Product Characteristics. Updated 05/2023. Accessed on 15/08/2023 via http://www.medicines.org.uk..
3. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation[Link]
4. Smith G et al (2020). A British Society of Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. B J Haem 191: 171-193#
5. Hocchaus A et al (2020). European LeukemiaNet 2020 recommendations for treating chronic myeloid leukaemia. Leukemia 34: 966-984
6. Hochhaus et al (2017) Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines. Ann Oncol 28(S4):iv41-51
7. Giraud, E.L. et al. (2023) 'Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: An update', The Lancet Oncology, 24(6). doi:10.1016/s1470-2045(23)00216-4

REVIEW

Name	Revision	Date	Version	Review date
Julia Wong. Nadjoua Maouche. Dr Adam Mead	New protocol	Mar 2017	1.0	
Cheuk-kie Cheung	General formatting	Apr 2017	1.1	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	1.2	Oct 2021
Dr Oni Chowdhury and Prof Adam Mead, Consultant Haematologists. Yen Lim, Zishaan Ramzan Haematology Pharmacists. NSSG Myeloid Group.	Updated as per BSH/ELN guidelines and SPC. Addition of monitoring table, treatment-free period and reinitiation guidance. Annual protocol meeting 2022.	Aug 2023	2.0	Nov 2025