Chemotherapy Protocol

Chronic Myeloid Leukaemia

Bosutinib

Regimen

- Bosutinib

Indication

- As an option for the treatment of patients with chronic phase, accelerated phase, and blast phase Philadelphia-chromosome-positive chronic myelogenous leukaemia previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, provided the company provide bosutinib at the discounted price agreed in the patient access scheme.

Toxicity

Drug	Adverse Effect
Bosutinib	Diarrhoea, headache, decreased appetite, cough, nausea, vomiting, abdominal pain, raised transaminases, rash, arthralgia, pyrexia, oedema, fatigue, hypertension, pericardial effusion and QT prolongation.

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for full details.

Monitoring

Drugs

- FBC, U&Es and LFTs at baseline, prior to starting bosutinib therapy.
- FBC, LFTs and U&Es weekly for the first month then monthly thereafter, or more frequently if clinically indicated.
- Hepatits B and C and HIV status should be checked prior to starting bosutinib therapy. Patients who are carriers of either hepatitis B or C and those with active disease should be discussed with a consultant hepatologist prior to starting bosutinib therapy.
- Magnesium and potassium levels at baseline, then periodically throughout therapy. If abnormal at baseline these should be corrected before starting bosutinib therapy.

  A baseline ECG prior to starting bosutinib is advised for all patients. Those patients with a prolonged QTc interval, and those at high risk for developing a prolonged QTc interval, should be treated with extreme caution and may require regular ECG surveillance during bosutinib therapy.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

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.

Haematological toxicity usually presents within eight weeks of starting therapy with bosutinib.

Consider blood transfusion if patient symptomatic of anaemia or where the haemoglobin is less than 8g/Dl (80g/L).

Neutrophils ($x10^9$/L)	**Dose Modifications**
Less than 1	1. Withold bosutinib and monitor blood counts. 2. If the neutrophils recover to more than or equal to 1 within two weeks, then resume bosutinib at the same dose. 3. If the neutrophils are less than 1 for longer than two weeks, then reduce dose by 100mg/day and resume the bosutinib. 4. If neutropenia recurs, reduce bosutinib dose by a further 100mg and resume treatment on count recovery. (Doses of less than 300mg a day have not been evaluated for clinical efficacy)
Platelets ($x10^9$/L)	**Dose Modifications**
Less than 50	1. Withold bosutinib and monitor blood counts. 2. If the platelets recover to more than or equal to 50 within two weeks, then resume the bosutinib at the same dose. 3. If platelets remain less than 50 for longer than two weeks, then reduce the dose by 100mg/day and resume bosutinib. 4. If thrombocytopenia recurs, reduce bosutinib dose by a further 100mg and resume treatment on count recovery. (Doses of less than 300mg a day have not been evaluated for clinical efficacy)

Hepatic Impairment

Drug	Bilirubin µmol/L		AST/ALT units		Alkaline Phosphatase	Dose Modifications
Bosutinib			More than 5xULN			Stop bosutinib until recovery to less than 2.5xULN. If within four weeks resume dose at 400mg once a day. If more than four weeks to recovery consider discontinuation of the bosutinib.
	More than 2xULN	and	More than or equal to 3xULN	and	Less than 2xULN	Discontinue the bosutinib.

Renal Impairment

Drug	Creatinine clearance (mL/min)	Dose Modifications
Bosutinib	30-50 (moderate impairment)	400mg once a day
	Less than 30 (severe impairment)	300mg once a day

Diarrhoea

If grade 3 or 4 diarrhoea occurs, withhold treatment until recovery to less than or equal to grade 1. Bosutinib should be restarted at a reduced dose of 400mg once a day. Loperamide may be used to prevent or treat the diarrhoea. Consider starting at a lower dose of bosutinib and escalating as tolerated.

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria)

Drug	Dose	Days	Administration
Bosutinib	500mg once a day	1-28 (inclusive)	Oral

Dose escalation to 600mg once a day may be considered in the following circumstances, providing severe or persistent moderate adverse reactions have not been experienced.

- Failure to achieve complete haematologic response within the first 8 weeks of therapy.
- Failure to achieve complete cytogenetic response within the first 12 weeks of therapy.

Doses above 600mg have not been studied and therefore should not be used.

Dose Information

- Bosutinib is available as 100mg and 500mg film-coated tablets.

Administration Information

- Bosutinib should be taken once a day with or just after food, or a meal.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to bosutinib.
- It must be made clear to all staff, including those in the community, that bosutinib should only be prescribed under the supervision of a consultant haematologist.
- Bosutinib interacts with many other agents. Always check for drug interactions.

Coding

- Procurement – X71.5
- Delivery – X73.1

References

1. Pfizer Limited (2106). Bosulif 100mg and 500mg Tablets Summary of Product Characteristics. Electronic Medicines Compendium. Online at http://www.medicines.org.uk/emc/medicine/27795, accessed 27 September 2016.
2. National Institute for Health and Care Excellence (2016). Bosutinib for previously treated chronic myeloid leukaemia [TA401]. London: National Institute for Health and Care Excellence.
3. Khoury, HJ., Cortes, JE., Kantarjian, HM., Gambacorti-Passerini, C., Baccarani, M. and Kim, D., et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood (2012); **119** (15); 3403-3412.

REGIMEN SUMMARY

Bosutinib

Cycle 1

Day 1-28

1. Bosutinib 500mg once a day for 28 days oral
   Administration Information
   Oral chemotherapy

   Take with or just after food, or a meal.

   Please supply the nearest original pack size according to local practice

2. Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).
Administration Instructions
Please supply 28 capsules or an original pack if appropriate

Cycle 2 onwards

Day 1-28

1. Bosutinib 500mg once a day for 28 days oral
   Administration Information
   Oral chemotherapy

   Take with or just after food, or a meal.

   Please supply the nearest original pack size according to local practice

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2017	None	Mrs Eleanor Taylor Pharmacist	Dr Andrew Duncombe Consultant Haematologist

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 that occur as a result of following these guidelines.