IMATINIB (CML)

INDICATION

Licensed / NICE indication

- Standard-dose Imatinib is recommended as first-line treatment of adults with chronic phase Ph+ chronic myeloid leukaemia (CML) [NICE TA70, TA426]

- Imatinib is recommended for the treatment of patients with Ph+ CML who initially present in the accelerated phase or with blast crisis. Additionally, Imatinib is recommended for patients who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received Imatinib previously. [NICE TA70]

- For patients in chronic-phase CML currently receiving interferon alpha (IFN-α) as first-line treatment, the decision to change to Imatinib should be based upon disease response to current treatment and by the patient's tolerance to IFN-α. This decision should be made after informed discussion between the patient and clinician, taking into account individual benefit-risk assessment of Imatinib, and patient's preference [NICE TA70]

Licensed / unfunded indication

NICE does not recommend high-dose Imatinib for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose Imatinib. Patients currently receiving high-dose Imatinib for the treatment of CML should have the option to continue treatment until they and their clinicians consider it appropriate to stop. [NICE TA 425]

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 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 blood pressure
6. Record height and weight.
7. ECG (most TKIs can affect the QT interval)
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 imatinib)
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. There is a degree of uncertainty, but most evidence supports that it is safe to continue imatinib for male considering parenting. As imatinib can cause reduced fertility, consider sperm storage/ cryopreservation in appropriate patients.
14. Treatment should be agreed in the relevant MDT.
15. For patients prescribed oral chemotherapy, pre-chemotherapy counselling should be considered in line with NPSA recommendation and chemotherapy measures.

**DRUG REGIMEN / CYCLE FREQUENCY**

**IMATINIB**  
400mg PO once daily in chronic phase CML  
600mg PO once daily in accelerated phase or blast crisis  
100mg PO once daily in FIP1L1/ PDGFRA associated chronic eosinophilic leukemia

Once diagnosis is confirmed imatinib can be initiated first line (hydroxy carbamide should be reserved for patients where leucostasis is a concern whilst awaiting the diagnosis).

Continue treatment until disease progression. The effect of stopping treatment after the achievement of CCyR has not been investigated.

For patients unable to swallow tablets, disperse the tablets in a glass of still water or apple juice as follows: approximately 50ml for a 100mg tablet, and 200ml for a 400mg tablet. Stir the suspension and take immediately after tablet(s) completely disintegrate.

**TREATMENT-FREE PERIOD**

Refer to Interim Expert Opinion document available on NSSG website [LINK]
DOSE MODIFICATIONS

Dose adjustment for Haematological Toxicity

<table>
<thead>
<tr>
<th>Indication</th>
<th>Counts</th>
<th>Modification</th>
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<tbody>
<tr>
<td>Chronic phase CML (400mg)</td>
<td>ANC &lt; 1.0 x 10^9/L and/or Plt &lt; 50 x 10^9/L</td>
<td>1. Stop Imatinib until ANC ≥ 1.5 x 10^9/L and Plt ≥ 75 x 10^9/L</td>
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<td>2. Resume treatment at previous dose</td>
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<td>3. Recurrence of ANC &lt; 1.0 x 10^9/L and/or Plt &lt; 50 x 10^9/L, repeat step 1 and resume Imatinib at 300mg.</td>
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<td>4. Consider GCSF if recurrent neutropenia</td>
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<td>Accelerated phase CML and blast crisis (600mg)</td>
<td>ANC &lt; 0.5 x 10^9/L and/or Plt &lt; 10 x 10^9/L occurring after at least 1 month of treatment</td>
<td>1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy).</td>
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<td>2. If cytopenia unrelated to leukaemia, reduce dose of Imatinib to 400mg.</td>
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<td>3. If cytopenia persists for 2 weeks, reduce to 300mg.</td>
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<td>4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop Imatinib until ANC ≥ 1 x 10^9/L and Plt ≥ 20 x 10^9/L, then resume treatment at 300mg.</td>
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</table>

Dose adjustment for Non-haematological Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Modification</th>
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<tbody>
<tr>
<td>Any severe non-haematological toxicity</td>
<td>Withhold treatment until resolved. Resume treatment depending on the initial severity of the event.</td>
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Renal / Hepatic Impairment

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
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<tbody>
<tr>
<td>Use with caution.</td>
<td>Start at 400mg OD minimum dose with any impairment. Reduce dose if not tolerated.</td>
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<tr>
<td>Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400mg OD. Reduce dose if not tolerated or increase dose for lack of efficacy.</td>
<td>Dose adjustment for adverse reactions if bilirubin &gt; 3 x ULN (not Gilberts related) or liver transaminases &gt; 5 x ULN, withhold until bilirubin &lt; 1.5 x ULN and liver transaminase &lt; 2.5 x ULN. Resume at reduced dose: 400mg to 300mg; 600mg to 400mg</td>
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</table>
INVESTIGATIONS

- See pre-assessment above
- BCR-ABL monitoring, as per ELN guidelines.
- 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
- Monthly for next 2 months: ECG as clinically indicated, FBC, U&E, LFT and Bone, glucose, amylase, CK
- 3-4 monthly: amylase, 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

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.
Consider allopurinol 300mg OD for 7 days at diagnosis.
Consider GCSF support in patients with recurrent neutropenia.
Consider Epo in anaemic patients.

EMETIC RISK

Low

DRUG INTERACTIONS

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

- Concomitant use of CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John’s Wort) as they may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Consider checking imatinib levels if suspected interaction.

- Caution should be taken when co-administering imatinib with CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase imatinib exposure.

- Caution should be taken when co-administering imatinib with a CYP3A4 substrate with narrow therapeutic index (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) as they could increase exposure to the CYP3A4 substrate.

- Paracetamol can be safely administered with imatinib in patients with normal liver function.
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Very commonly reported:
Neutropenia, thrombocytopenia, anaemia, headache, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, periorbital oedema, dermatitis/eczema/rash, muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain, fluid retention and oedema, fatigue, weight increase.

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

Extremely rare (<1%).

REFERENCES

## REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Julia Wong</td>
<td>Protocol has been re-drafted</td>
<td>Mar 2017</td>
<td>4.0</td>
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<tr>
<td>Cheuk-kie Cheung</td>
<td>General formatting</td>
<td>May 2017</td>
<td>4.1</td>
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<tr>
<td>Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group</td>
<td>Annual protocol meeting</td>
<td>Oct 2019</td>
<td>4.2</td>
<td>Oct 2021</td>
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