NILOTINIB

INDICATION

Licensed / NICE

- Untreated chronic-phase Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) (TA426) who cannot have imatinib for clinical reason* (BLUETEQ required) or
- Chronic- or accelerated-phase Ph+ CML in adults who cannot have imatinib or their disease is imatinib-resistant (TA425)

*NHS England Circular 1732

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT FOR FIRST LINE TREATMENT

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 height and weight.
6. Record blood pressure
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 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. There is a degree of uncertainty but most evidence supports that it is safe to continue nilotinib for male considering partenting. As nilotinib may 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, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.

DRUG REGIMEN

Newly diagnosed CML in the chronic phase
Nilotinib 300mg PO TWICE daily. Consider increase dose to 400mg TWICE daily if suboptimal response (off-label).
For patients in sustained MMR and troublesome side effects, dose can be reduced to 400mg once daily.

Resistant CML or intolerance to prior therapy
Nilotinib 400 mg PO TWICE daily
Dose should be taken approximately 12 hours apart and must not be taken with food. No food should be consumed for 2 hours before and one hour after each dose.

TREATMENT-FREE PERIOD

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

Discontinuation of treatment may be considered in CML patients in chronic phase if
- who have been treated with nilotinib at 300 mg twice daily for a minimum of 3 years AND
- a deep molecular response is sustained for a minimum of one year

After discontinuation, it is recommended to check BCR-ABL levels and FBC
- monthly for the first year
- every 6 weeks for the second year
- every 12 weeks thereafter

For patients who lose MR4 (MR4=BCR-ABL/ABL ≤0.01%IS) but not MMR (MMR=BCR-ABL/ABL ≤0.1%IS) during the treatment-free phase, BCR-ABL levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4 for a minimum of 4 consecutive measurements can return to the original monitoring schedule.

Patients who lose MMR must re-initiate treatment within 4 weeks. Re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter.
DOSE MODIFICATIONS

Haematological toxicity

| Newly diagnosed chronic phase CML at 300 mg twice daily | ANC <1 x 10⁹/L and/or Platelet <50 x 10⁹/L | 1. Stop nilotinib, and monitor blood counts.  
2. Resume within 2 weeks at prior dose if ANC >1.0 x 10⁹/L and/or platelets > 50 x 10⁹/L.  
3. If blood counts remain low, a dose reduction to 400 mg once daily may be required. |
| Imatinib-resistant or intolerant CML in chronic phase at 400 mg twice daily | ANC <0.5 x 10⁹/L and/or Platelet <10 x 10⁹/L | 1. Stop nilotinib, and monitor blood counts.  
2. Resume within 2 weeks at prior dose if ANC > 1 x 10⁹/L and/or platelets > 20 x 10⁹/L.  
3. If blood counts remain low, a dose reduction to 400 mg once daily may be required. |

Non-Haematological toxicity

If clinically significant moderate or severe non-haematological toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to the starting dose of 300 mg twice daily in newly diagnosed patients with CML in the chronic phase or to 400 mg twice daily in patients with imatinib-resistant or intolerant CML in chronic phase and accelerated phase should be considered.

Elevated serum lipase: For Grade 3-4 serum lipase/amylase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase/amylase levels should be tested monthly or as clinically indicated.

Elevated bilirubin and hepatic transaminases: For Grade 3-4 bilirubin and hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated.

Nilotinib has been associated with an increased risk of cardiovascular complications. If a vascular event occurs during nilotinib treatment, consider a change of TKI. Nilotinib should be used with caution in patients with known vascular disease or with vascular risk factors with careful consideration of risk versus benefit.
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, amylase/lipase
  - Monthly for next 2 months: ECG as clinically indicated, FBC, U&E, LFT and Bone, glucose, amylase/lipase, CK
  - 3-4 monthly: Lipids, glucose, amylase/lipase, CK, FBC, U&E, LFT, Bone
  - TSH should be monitored during TKI therapy on a yearly basis (or when clinically indicated)
  - All patients should have blood pressure checked at all visits.
  - 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 in selected 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. phenytoin, carbamazepine, rifampicin, phenobarbital or St John’s Wort) as they may significantly reduce exposure to nilotinib, potentially increasing the risk of therapeutic failure.
- Caution should be taken when co-administering nilotinib with CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin), as they could increase nilotinib exposure.
- Caution should be taken when co-administering nilotinib with a CYP3A4 substrate with narrow therapeutic index (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) as they could increase exposure to the CYP3A4 substrate.
- Concomitant use of H₂ antagonists, proton pump inhibitors or aluminium hydroxide / magnesium hydroxide may reduce exposure to nilotinib therefore should be administered 2 hours prior to 2 hours after nilotinib.
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
(Consult with pharmacist and refer to SPC for full details)

Neutropenia, thrombocytopenia, anaemia, rash, pruritus, headache, nausea, upper abdominal pain, fatigue, myalgia, derranged LFTs (hyperbilirubinaemia very common), infections, electrolyte disturbances, increased lipase, cholesterol, and blood triglycerides

Nilotinib has been associated with an increased risk of cardiovascular complications. Careful attention to vascular risks is important during nilotinib therapy.

QT prolongation - use with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:
- with congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- Taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation

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%)
REFERENCE


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>Dr Adam Mead</td>
<td>Adverse effects reviewed, treatment intent and mortality added. Full review of Indications, Pre-assessment, Drug regimen, Dose modifications, Haematology toxicity, monitoring of disease respond, investigations and drug interaction sections</td>
<td>Nov 2016</td>
<td>2.0</td>
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<tr>
<td>Cheuk-kie Cheung (Pharmacist) and Dr Mead</td>
<td>Review if indication, pre-assessment and adverse regimen specific complications</td>
<td>Mar 2017</td>
<td>2.1</td>
<td></td>
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<tr>
<td>Cheuk-kie Cheung</td>
<td>Update of NHSE funding position for 1st line indication</td>
<td>Apr 2017</td>
<td>2.2</td>
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<tr>
<td>Cheuk-kie Jackie Cheung, Haematology Pharmacist, NSSG Myeloid Group</td>
<td>Treatment free period information added. Annual protocol meeting</td>
<td>Oct 2019</td>
<td>2.3</td>
<td>Oct 2021</td>
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