Imatinib for Philadelphia chromosome positive CML, first line

Indication:
First line treatment of Philadelphia chromosome positive (Ph+) CML chronic phase
Ph+ CML accelerated phase
Ph+ CML blast crisis
Patients pre-treated with Interferon alpha who have failed to respond, had side effects or wish to change treatment after full discussion

Regimen details:
For chronic phase:
Imatinib 400 mg od orally continuous
Consider dose escalation to 600mg od after 3 - 6 months dependent on PCR result, discuss with a Consultant Haematologist.
After a further 3 months if not in complete cytogenetic remission, discuss with a Consultant Haematologist, consider early use of second generation TKIs or escalating dose to 400mg TWICE daily.

For accelerated phase or blast crisis:
Imatinib 600mg od orally continuous
Consider using a second generation TKI if disease progression, or after 3 months if not in a satisfactory haematological remission providing there is no severe adverse drug reaction or severe non leukaemia- related neutropenia or thrombocytopenia. Support with blood products where appropriate.

Changing from hydroxycarbamide (hydroxyurea) or interferon to imatinib:
In patients receiving hydroxycarbamide who have normal counts, the hydroxycarbamide should be tapered in the first week of imatinib therapy.
In patients receiving hydroxycarbamide who have raised counts, the hydroxycarbamide should be continued for 2-3 weeks after starting imatinib, while closely monitoring the white blood cell count.
In patients with thrombocythaemia receiving anagrelide who have elevated platelet counts, the anagrelide should be tapered over 4-5 weeks.
For patients receiving interferon, the interferon is stopped at the time of commencing imatinib. If patients have neutropenia or thrombocytopenia as a result of interferon treatment then the interferon should be stopped and the counts allowed to normalise before commencing imatinib.

Available as 100mg and 400mg strength tablets

Administration:
Orally
Imatinib should be taken with meals and a glass of water.
For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50ml for 100mg tablet, 200ml for 400mg tablet). The suspension should be taken immediately.

Premedication:
None required
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**Frequency:** Continuous  
(28 day cycles)

**Extravasation:** Not applicable

**Anti-emetics:** Minimal emetogenic potential (< 10%)

**Supportive medication:** Allopurinol 100mg – 300mg daily (dependent on renal function) if WCC > 100 x 10⁹/L

**Regular investigations:**
- **FBC**
  - Every week for 4 weeks after initiation of therapy or following a dose increase. If no toxicity, monitor fortnightly for 8 weeks, then monthly for next 3 months and then every 3 months thereafter, if stable.

- **LFTs**
  - Weekly monitoring for 4 weeks after initiation of therapy or following a dose increase. If no toxicity, monitor fortnightly for 8 weeks, then monthly for next 3 months and then every 3 months thereafter, if stable.

- **U&Es**
  - Monthly

- **Bone profile**
  - Monthly

- **Peripheral blood analysis +/- bone marrow**
  - At 3 months after initiation of therapy, 6/9 months, if clinically indicated and at 1 year.

- **ECHO / Cardiology Assessment**
  - Before initiating treatment in patients with cardiac disease or risk factors for cardiac failure.

**Dose Modifications**

**Haematological Toxicity**

Toxicity usually manifests as neutropenia (13%) and thrombocytopenia (9%) and is more common in advanced stage disease. In trials, imatinib induced prolonged aplasia in 1% of patients in blast crisis. Myelosuppression begins to occur in the first 2 to 4 weeks of therapy in blast crisis and later in accelerated or chronic phase. Myelosuppression induced by imatinib is mainly due to its effects on Ph+ve cells rather than on normal progenitor cells. Imatinib’s toxic effects on normal haematopoiesis usually only occur with doses greater than 800mg per day.

| Chronic phase CML, (starting dose 400 mg) | ANC < 1.0 x 10⁹/l and/or platelets < 50 x 10⁹/l | 1. Stop imatinib until ANC ≥ 1.5 x 10⁹/l and platelets ≥ 75 x 10⁹/l.  
2. Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction).  
3. In the event of recurrence of ANC < 1.0 x 10⁹/l and/or platelets < 50 x 10⁹/l, repeat step 1 and resume imatinib at reduced dose of 300 mg. |
| Accelerated phase CML and | ANC < 0.5 x 10⁹/l | 1. Check whether cytopenia is related to leukaemia |

**Reason for Update:** Network Protocol Development  
**Approved by Consultant:** Deepti Radia

**Version:** 2  
**Approved by Chair Haem TWG:** Maj Kazmi

**Supersedes:** All other versions  
**Date:** 25/02/2011

**Prepared by:** Laura Cameron  
**Checked by (Network Pharmacist):** Jacky Turner
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**blast crisis and Ph+ ALL (starting dose 600 mg) and/or platelets < 10 x 10^9/l**

(marrow aspirate or biopsy).

2. If cytopenia is unrelated to leukaemia, reduce dose of imatinib to 400 mg.

3. If cytopenia persists for 2 weeks, reduce further to 300 mg.

4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop imatinib until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg.

**Hepatic insufficiency:**
Imatinib is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated.

**Renal insufficiency:**
Since the renal clearance of imatinib is negligible, a decrease in free imatinib clearance is not expected in patients with renal insufficiency. Patients with mild or moderate renal dysfunction (creatinine clearance = 20–59 ml/min) should be given the minimum recommended dose of 400 mg daily as starting dose. Although very limited information is available, patients with severe renal dysfunction (creatinine clearance = < 20 ml/min) or on dialysis could also start at the same dose of 400 mg. However, in these patients caution is recommended. The dose can be reduced if not tolerated, or increased for lack of efficacy.

**Toxicities:**

- **Diarrhoea** is a common side effect and is dose related, if severe manage with loperamide.
- **Muscle cramps** may occur in the hands, feet calves and thighs. Despite normal serum calcium and magnesium levels patients may benefit from calcium and magnesium supplementation. Quinine sulphate can offer symptomatic relief.
- **Oedema** can occur in up to 50% of patients and is dose related, periorbital oedema is most common. Patients may develop pulmonary oedema, pleural and pericardial effusions, ascites and cerebral oedema. Risk factors for developing oedema include female gender, age >65 and previous cardiac and renal disease. Observe closely for development of oedema and start diuretics (e.g. furosemide) early. Imatinib should be discontinued temporarily if fluid retention is severe. Mild periorbital oedema may respond to antihistamines however **if severe imatinib should be discontinued**.
- **Skin rashes** can occur in up to 30% of patients. Rashes are usually maculopapular on forearms, trunk and face and are often self-limiting. Patients with basophilia may have urticarial eruptions early in treatment, they should be pre-medicated with and antihistamine prior to imatinib dose until the basophil count is normal. Mild rashes can be treated symptomatically with menthol and aqueous cream, if severe treat with oral steroids. **Steven Johnson syndrome can occur, imatinib should be discontinued immediately**.

**Arthralgia and bone pain** often settle spontaneously after a few weeks. Control with simple analgesia. Consider a NSAID if renal function and platelet count are normal and the patient does not have a history of GI bleeding or ulceration.

**Headache and fatigue**
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Drug interactions:

Drugs that inhibit or induce cytochrome P450 isoenzyme CYP3A4 activity could affect imatinib concentrations.

The following drugs increase plasma levels of imatinib: clarithromycin, erythromycin, itraconazole. The following drugs decrease plasma levels of imatinib: carbamazepine, dexamethasone, phenytoin, rifampicin.

Drugs whose plasma levels may be increased by imatinib: ciclosporin, statins, warfarin. Imatinib may inhibit the metabolism of warfarin, consider using a low molecular weight or unfractionated heparin in patients requiring anticoagulation.