IMATINIB

First-line treatment of Ph+ CML in the chronic phase
An option for treatment of patients with Ph+ CML who present in accelerated phase or blast crisis

All patients should be screened for hepatitis B virus before starting treatment
This screen must include HBV surface antigen and anti-HBV core antibody

Drug/Dosage:	**Imatinib**	400mg po once daily in chronic phase CML 600mg po once daily in accelerated phase or blast crisis

Administration: Imatinib is available as 400mg and 100mg tablets, which are not scored or divisible. The daily dose should be taken once daily with a large glass of water, with or after food.

Patients unable to swallow the tablets may disperse each dose in water or apple juice (about 200ml for a 400mg tablet). Advise patient to stir with a spoon and drink the suspension immediately after disintegration.

Other Drugs: Allopurinol 300mg po od for the first four weeks

Frequency: continuous therapy until treatment no longer effective, or not tolerated

Main Toxicities: myelosuppression; fluid retention, commonly presenting as periorbital oedema; rash; muscle cramps; diarrhoea; cardiotoxicity (rare - see Comments)

Anti- emetics: none usually needed, but some patients may have mild nausea

Regular Investigations:	FBC	monthly initially, to monitor haematological response, increasing to 3 – 4 monthly in stable, responding patients
	Peripheral blood PCR	3 monthly initially, to assess molecular response, then 3-4 monthly in stable responders
	Bone marrow cytogenetics	annually until CCR and MMR achieved, and thereafter if concerns or loss of molecular response
	LFTs	monthly initially, then every 3 – 6 months
	U&Es	monthly initially, then every 3 – 6 months

Comments: The following are all clear indications for a switch to an alternative TKI:

- disease progression
- failure to achieve a satisfactory haematological response after 3 months treatment
- less than a complete haematological response after 6 months of treatment
- failure to achieve a partial cytogenetic response (Ph+ve > 35%) after 12 months of treatment
- less than a complete cytogenetic response after 18 months of treatment
- loss of a complete haematological and/or cytogenetic response

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Prepared by: S Taylor	Checked by: C Tucker

There is also an indication to consider a switch to an alternative TKI, in sub-optimal response:

- less than a complete haematological response after 3 months of treatment
- failure to achieve a partial cytogenetic response (Ph +ve > 35%) after 6 months of treatment
- less than a complete cytogenetic response after 12 months of treatment
- less than a major molecular response at 18 months

Elimination of imatinib is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. dexamethasone, phenytoin, St Johns wort) and imatinib should be avoided, as this may increase the risk of therapeutic failure.

Warfarin should only be used with caution and close monitoring, as imatinib may affect its metabolism. Alternative anticoagulants should be considered.

Severe, symptomatic LV systolic dysfunction has occasionally been reported in patients taking imatinib[1]. In most cases, patients had other co-morbidities or cardiac risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully. There is no advice regarding withdrawal of imatinib in the event of declining cardiac function.

Dose Modifications

Haematological Toxicity:

Treatment decisions for patients whose neutrophils are below 1.0 $x10^9$/l and/or platelets below 50 $x10^9$/l should be made by a Consultant only.

Although SPC for imatinib states that treatment should be withheld if neutrophils fall below 1.0 $x10^9$/l and/or platelets fall below 50 $x10^9$/l, current expert opinion is as follows:
In order to maximise response, every effort should be made to maintain a dose of no lower than 400mg daily, except in patients with really severe cytopenias.
G-CSF and red cell transfusions should be used as needed.

Hepatic Impairment:

If bilirubin > 3 x ULN or ALT/AST > 5 x ULN, proceed as follows:
Withhold imatinib until bilirubin < 1.5 x ULN or ALT/AST < 2.5 x ULN, then continue treatment at a reduced dose (400mg to 300mg or 600mg to 400mg).
Monitor peripheral blood counts and liver enzymes carefully.

Patient Information:

Macmillan leaflet for Imatinib

References:

Kantarjian, H et al; NEJM (2002); 346: 645 – 652
Hughes, TP et al; NEJM (2003); 349: 1423 - 1432
Deininger, MWN et al; JCO (2003); 21 (8): 1637 – 1647
[1]Kerkela, R et al; Nature Medicine (2006); 12: 881 - 882