Suggestions for the management of patients with Chronic Myeloid Leukaemia- August 2007

Investigations at diagnosis

Before initiation of treatment:

- Full history including any occupational exposure to potential carcinogens and family tree.
- Physical examination including a measure of the size of the liver and spleen below the costal margins, height & weight.
- Full blood count and manual differential.
- Bone marrow aspirate and trephine biopsy. Samples for cytogenetic analysis and cell banking.
- Immunophenotyping of peripheral blood and BM if accelerated phase or blast crisis.
- Peripheral blood PCR analysis for BCR-ABL transcripts
- Peripheral blood for tissue banking and serum for proteomics(research)
- Consider fertility issues if patient is of childbearing age
- Calculate the Sokal score

If the patient is a potential transplant candidate and a chronic phase leukapheresis is being considered:

- Virology including Hepatitis B & C, HIV, HTLV, CMV status

If allogeneic HSCT is being considered:

- HLA typing of patient and siblings.
- consider VUD search

Register the patient with local/regional CML patient registry

WHO criteria for the definition of phases of CML[1].

Chronic Phase

- Absence of other criteria suggestive of accelerated or blastic phase

Accelerated Phase

- Blasts 10-19% in bone marrow or peripheral blood.
- Peripheral blood basophils $\geq$ 20%
- Persistent thrombocytopenia ($<100 \times 10^9$/l) unrelated to therapy, or persistent thrombocytosis ($>1000 \times 10^9$/l) unresponsive to therapy.
- Increasing spleen size and increasing WBC count unresponsive to therapy
- Cytogenetic evidence of clonal evolution

Blastic Phase

- Blasts in peripheral blood or bone marrow $\geq$ 20%.
- Extramedullary blast proliferation
- Large foci or clusters of blasts in the bone marrow biopsy.

Megakaryocytic proliferation occurring in sizeable sheets and clusters associated with marked reticulin or collagen fibrosis and/or severe granulocytic dysplasia should be considered as suggestive of AP-CML.

Allografting for chronic myeloid leukaemia:

AIM: to achieve a complete molecular response and potential cure

Eligible patients in accelerated phase or blast phase CML should be considered for allografting, following treatment with imatinib/dasatinib/nilotinib/novel agents/intensive chemotherapy. Current

evidence suggest that the responses to TKIs in these groups are not durable[2-5]. There is no evidence at present that pre-treatment with imatinib increases transplant-related mortality[6,7].

Some young patients in Chronic Phase CML with a suitable sibling donor may be considered for upfront allografting. This decision should be taken on an individual patient basis.

Some young patients in Chronic Phase CML with a suitable VUD donor may be considered for upfront VUD allografting. This decision should be taken on an individual patient basis.

First line therapy with imatinib mesylate: see flow charts

AIM: to achieve at least a durable complete cytogenetic response

The aim of tyrosine kinase inhibitor(TKI) therapy for CP-CML should be to achieve at least a complete cytogenetic response (CCyR). There is currently no statistical difference between a good complete cytogenetic response (CCyR) (generally >2 log reduction in bcr-abl) and a major molecular response (MMR)(>3 log reduction in bcr-abl) in terms of progression free survival[8].

Therapy with imatinib should be initiated at a dose of 300 to 400 mg/day. Doses below 300mg daily may not achieve sufficient intra-cellular concentrations to be effective and not be routinely prescribed[9].

Patients receiving imatinib should have:

1. Full blood cell count, renal and liver function weekly for the first 4 weeks, then every 2-3 weeks until a Complete Haematological Response (CHR) and every 4-12 weeks thereafter.
2. Real time quantitative PCR for BCR-ABL every 3 months on peripheral blood
3. Bone marrow aspirate and trephine biopsy with cytogenetics every 6 months until the patient reaches CCyR. Patients in confirmed CCyR (2 consecutive CCyR 6 months apart), should have bone marrow examinations at once every 12-18 months.
4. In potential transplant candidates, a Philadelphia negative leukapheresis and cryopreservation of stem cells may be considered again at this stage. However, patients who have achieved a good CCyR or MMR are not likely to require these cells[8].
5. If the patient becomes neutropenic (neutrophils < 1.0 x 10^9/l) or thrombocytopenic (platelets < 50 x 10^9/l), imatinib should be interrupted for 2 weeks. Imatinib can then be reinstituted at 300-400mg daily depending on the speed and extent of neutrophil and platelet recovery. Doses of less than 300mg daily should not routinely be prescribed.
6. Support with G-CSF (105µg, 263µg or 300µg one to three times per week) may be considered for all patients who do not tolerate imatinib because of neutropenia and/or thrombocytopenia.
7. Non-haematological toxicity may be managed symptomatically, and with gradual dose re-escalation in the majority of patients.
8. Please see SmPC for other prescribing information and potential drug interactions

Definitions of response[10]

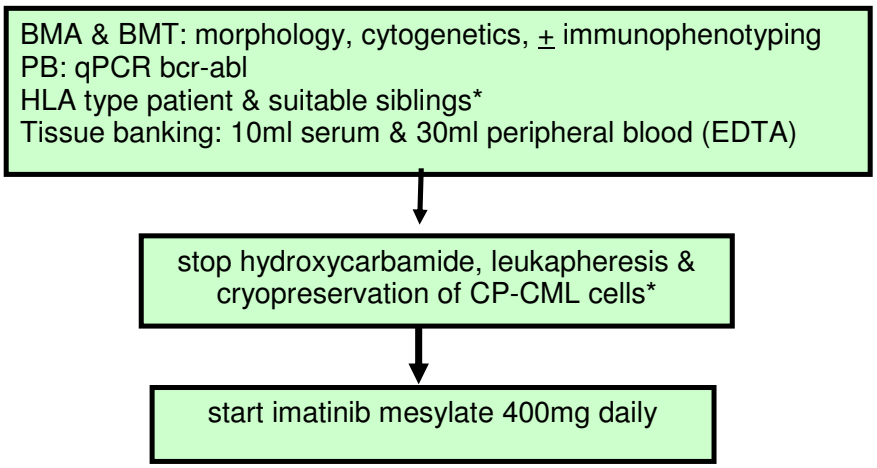
Haematologic response	Cytogenetic response	Molecular response
Complete: Platelet count <450x10^9/l; WBC < 10x10^9/l; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen	Complete: Ph 0% Partial: Ph 1-35% Minor: Ph 36-65% Minimal: Ph 66-95% None: Ph > 95%	"complete" indicates transcript nonquantifiable and nondetectable Major : $\leq$ 0.10 (int scale)

Time	Failure	Suboptimal	Warnings
Diagnosis	NA	NA	high risk; del9q+; ACAs in Ph + cells
3 months	no HR	less than CHR	
6 months	less than CHR; Ph>95%	Ph >35%	
12 months	Ph>35%	less than CCyR	less than MMR
18 months	less than CCyR	less than MMR	
Anytime	loss of CHR; loss of CgR	ACA; loss of MMR	rise in transcript levels; OCA in Ph neg cells

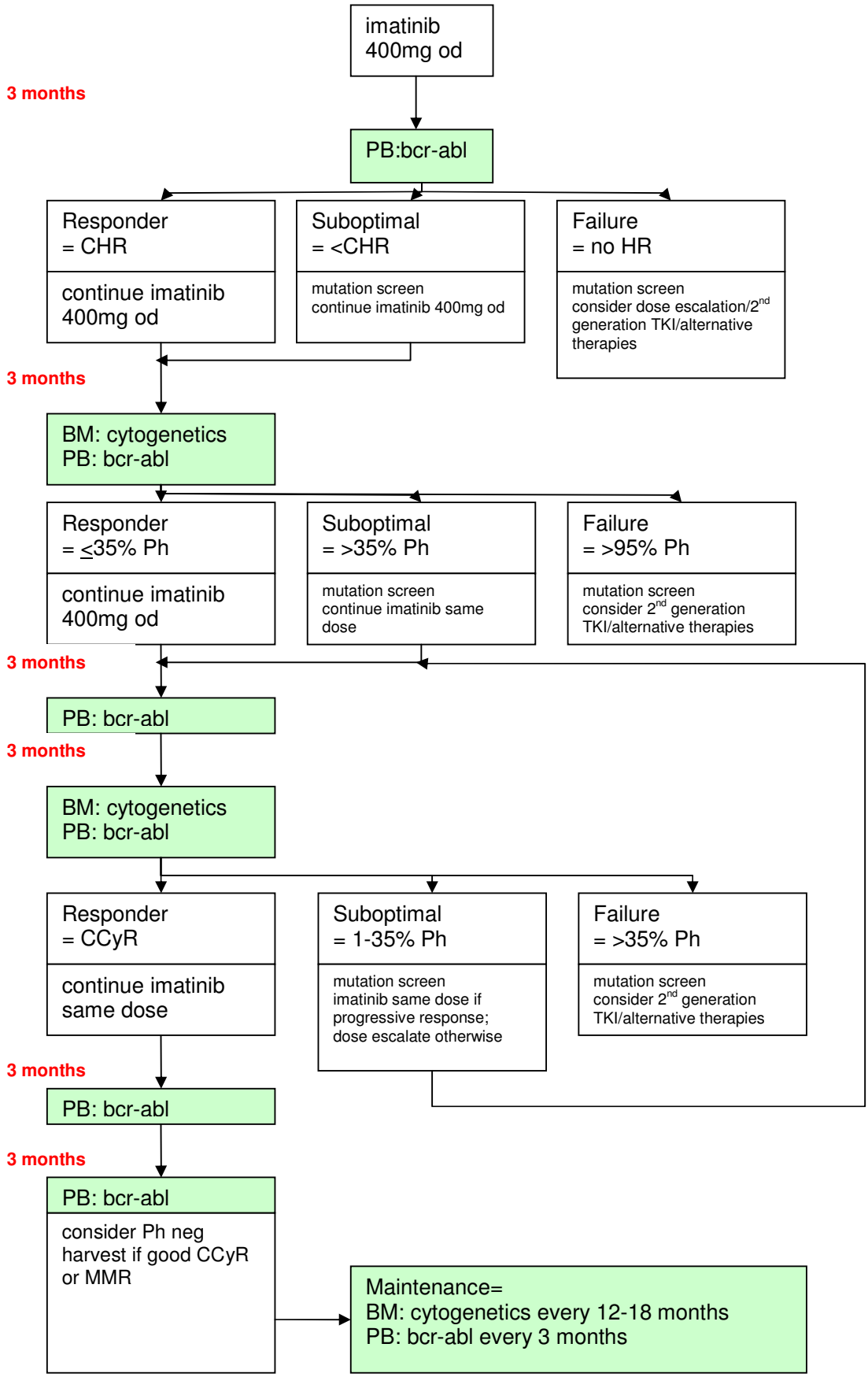
HR, haematological response; CHR, complete haematological response; CCyR, complete cytogenetic response; CgR, cytogenetic response; MMR, major molecular response; ACA, additional cytogenetic abnormalities; OCA, other cytogenetic abnormalities

- Failure implies that the patient should be considered for an alternative treatment plan
- Suboptimal response implies that the patient may still have a substantial benefit from continuing imatinib treatment but that the long-term outcome is not likely to be optimal, so the patient may be considered for other treatment plans
- Warnings imply that the patient should be monitored very carefully and may become eligible for other treatments.
- Until the International scale is fully adopted, a MMR is defined as a greater than 3 log reduction from the laboratory baseline (bcr-abl :abl %) and not the individual patient baseline [11].
- Philadelphia (Ph) positivity refers to the detection of Ph positive cells by conventional cytogenetics or FISH.

Ph' + CML, 1st Chronic Phase



*potential transplant candidates only


imatinib
400mg od
3 months
PB:bcr-abl
Responder
= CHR
continue imatinib
400mg od
Suboptimal
= <CHR
mutation screen
continue imatinib 400mg od
Failure
= no HR
mutation screen
consider dose escalation/2nd generation TKI/alternative therapies
3 months
BM: cytogenetics
PB: bcr-abl
Responder
= ≤35% Ph
continue imatinib
400mg od
Suboptimal
= >35% Ph
mutation screen
continue imatinib same dose
Failure
= >95% Ph
mutation screen
consider 2nd generation TKI/alternative therapies
3 months
PB: bcr-abl
3 months
BM: cytogenetics
PB: bcr-abl
Responder
= CCyR
continue imatinib
same dose
Suboptimal
= 1-35% Ph
mutation screen
imatinib same dose if progressive response;
dose escalate otherwise
Failure
= >35% Ph
mutation screen
consider 2nd generation TKI/alternative therapies
3 months
PB: bcr-abl
3 months
PB: bcr-abl
consider Ph neg
harvest if good CCyR
or MMR
Maintenance=
BM: cytogenetics every 12-18 months
PB: bcr-abl every 3 months

Dose escalation for suboptimal responders.

- 69% of patients would be expected to have achieved a CCyR within 12 months of treatment with imatinib 400mg daily, with an additional 10% at 24 months (dose escalation permitted)[8].
- Trough plasma levels correlate with response[12]
- Dose escalation has been demonstrated to be useful in patients with cytogenetic resistance or relapse; with 56% achieving <35%Ph positivity[13]. However these responses may not be sustained and benefited principally those with some degree of Ph negativity[14,15].
- Therefore dose escalation in suboptimal responders from 12 months may be considered, with the exception of demonstrated abl tyrosine kinase mutations which render insensitivity to imatinib. Multiple mechanisms for clinical resistance may be in play[16-18].
- Dose escalation in failures when there is no cytogenetic response(>95% Ph) to a meaningful trial of imatinib is not recommended. These patients should be considered for alternative therapies.
- Dose escalation would usually be from 400mg od; to 600mg od, then to 400mg bd.
- Patients should be assessed 3 monthly following dose escalation, allowing 3-6 months before re-escalation/switching therapies.
- Patients with the T315I mutation should not be considered for dose escalation or second generation TKIs. Alternative treatment plans are required.
- Prior to instituting changes to the treatment plan, an assessment of patient compliance with therapy must be undertaken.

Suggestions for the use of 2nd generation tyrosine kinase inhibitors (TKIs)(dasatinib, nilotinib) in patients with chronic phase chronic myeloid leukaemia.

Eligibility

1. Imatinib intolerant
    a. grade III to IV non-haematological toxicity persisting despite optimal supportive measures
    b. some grade II non-haematological toxicities persisting despite optimal supportive measures
2. Imatinib resistant
    a. Imatinib failure at any time on at least 600mg imatinib
    b. suboptimal responders : chronic phase CML who have not achieved a complete cytogenetic response on at least 600mg of imatinib mesylate, following at least 18 months of optimal imatinib therapy
    c. absence of haematological response after at least 3 months of imatinib therapy at escalated dose of at least 600mg daily
    d. progression to accelerated phase or blast crisis CML at any time; or failure of AP or BC to achieve complete haematological response to at least 600mg of imatinib daily. These responses are not durable [3,19,20]. If a 2nd generation TKI is considered, it should not be the sole intervention in the treatment plan.

Exclusions

1. demonstrated presence of T315I abl tyrosine kinase domain mutation
2. uncontrolled of significant cardiovascular disease
    a. uncontrolled angina
    b. MI within 6 months
    c. congestive cardiac failure within 6 months
    d. diagnosed or suspected long QT syndrome
    e. history of significant ventricular arrhythmias
    f. prolonged QTc >450 ms
    g. 2nd or 3rd degree heart block
    h. heart rate <50 bpm on ECG
3. other exclusions/cautions as in the respective SPCs.

Dose of 2nd generation TKIs.

The current recommended dose for dasatinib for patients with chronic phase CML is 100mg daily[21]. The current recommended dose of nilotinib is 400mg bd.

Assessment and duration of therapy with 2nd generation TKI's

In patients **resistant** to imatinib, dasatinib achieved a complete cytogenetic response rate of approximately 40%, compared with 16% in patients escalated to 800mg imatinib after a median follow-up of 15 months. Progression free survival favoured dasatinib [22]. Imatinib **intolerant(30%) or resistant(70%)** patients treated with nilotinib achieved 34% complete cytogenetic response after a median duration of treatment of 247 days [23].

Assessment of CP-CML patients on dasatinib and nilotinib should be according to the schedule defined for imatinib. Failure defined at 6 months should trigger a switch to an alternative treatment plan.

For accelerated and blast crisis patients, Insufficient data available currently, but would not be unreasonable to suggest absence of Major Haematological Response after 120 days of therapy for AP and BC patients (2x median time to response) should trigger a critical review of therapy. Note however that the median duration of response for lymphoid blast crisis and Ph positive ALL to dasatinib is less than 4 months, and myeloid BC less than 6 months [24].

Cost implications

	per month (ex VAT)	**per year (ex VAT)**
Imatinib 400mg daily	£1,557.36	£ 18,688.32
Imatinib 600mg daily	£2,336.04	£ 28,032.48
Imatinib 800mg daily	£3,114.72	£ 37,376.64
dasatinib 140mg daily	£2,432.85	£ 29,194.20
nilotinib 800mg daily	currently unknown	

(source British National Formulary 53 March 2007)

Depending on local arrangements, funding agreements with the respective PCTs may be required for higher dose imatinib and second generation TKIs.

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