## Chronic Myeloid Leukemia Clinical Practice Guideline Development Group (Malaysia)

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## Foreword

Chronic myeloid leukemia (CML) has taught us how to diagnose, monitor, treat and make progress in cancer therapy. As many questions are answered by clinical studies, more questions are generated in our endeavor to conquer the disease. It is important for doctors to keep abreast with recent development so that CML patients are given optimal treatment. It is a challenge for the haematologists and for all the health care staff involved in the care of such patients.

We hope the Clinical Practice Guideline (CPG) can provide some useful information for those involve in the care of Malaysian CML patients.

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## Chronic Myeloid leukemia – Clinical Practice Guidelines

## Preamble:

**Chronic myeloid leukemia (**CML) is a remarkable disease. It is the first human cancer whereby a consistent chromosomal abnormality was described. If untreated CML is invariably fatal. The advent of bone marrow transplant (BMT) as a potential curative treatment modality and the availability of tyrosine kinase inhibitors (TKI) have transformed the landscape of treating CML. Today, there is a potential for long term disease control or even cure.

Despite the excellent clinical practice guidelines (CPG) available e.g. NCCN guidelines, there are needs to develop customized guidelines in Malaysia. There are daunting challenges to overcome in providing the state of art care to our people. These include financial issue, patient compliance and the ability to provide medical personnel trained in haematology/haemopoietic stem cell transplant and the infrastructure to provide both the diagnostic services and the required therapeutic care. Not forgetting the geographical divide of East and West Malaysia and also the fact that our patients are a younger lot compared to the Western patients. The treatment milestones are useful guidelines and we will propose CML patients to be assessed in recommended centers at the time of diagnosis and at defined time schedule. Haemopoietic stem cell transplant has a more limited (largely due to remarkable treatment results of TKI) but definite role and patients who may benefit from transplant should be referred to transplant centers early. The management of CML requires a collaborative approach between primary care doctors and hematologists. Treatment should be guided by a hematologist or heamato-oncologist with expertise in the field of CML.

## 1) Initial work up at diagnosis

Treatment decisions are based on the diagnosis at presentation and the initial work up. The latter should always be as comprehensive as possible: it should provide sufficient information to confirm the diagnosis of CML, to assess the stage of the disease, the risk profile of the disease (Sokal/Hasford risk scores) and the risk profile for transplantation. Furthermore, it should include the personal and family history, the preferences of the patient (and his/her partner, family or donor) and the financial situation. A complete physical examination and laboratory investigations consisting of a complete blood count including examination of the blood film, qualitative molecular analysis for BCR-ABL from the peripheral blood and standard clinical chemistry analysis. Bone marrow investigation is mandatory and includes cytology, histology and cytogenetics. If no bone marrow aspiration can be obtained (dry tap), cytogenetics should be performed with the cells from the peripheral blood. Bone marrow biopsy is recommended to assess presence of myelofibrosis and possibility of paratrabecular collection of blast. For patients eligible and likely to need allogeneic hematopoietic stem cell transplant (HSCT), initial work up also includes complete family typing for HLA (all siblings and whenever possible both parents) and, in the absence of an HLA identical family donor, assessment of the likelihood to find a matched unrelated donor (donor search registration). Furthermore, initial work up should also include a cardiac evaluation (ECG, echocardiography) as baseline evaluation before initiating TKI treatment.

Once the diagnosis is confirmed, an expert in the field of CML should discuss with the patient, his/her family or partner and the patient's primary care provider the treatment options. This discussion should include the treatment algorithm and the need for continuous risk assessment that form the basis for the therapeutic strategy. It should also include a formal discussion on fertility issues, the possibilities of semen cryopreservation and the absolute need for contraception during TKI treatment.

**RECOMMENDATION: The diagnosis of CML is suspected from blood count and peripheral blood film but should be confirmed with cytogenetic and molecular tests. Bone marrow aspirate is mandatory and bone marrow biopsy is also advised.**

## 2) Prognostication and phase of CML

Most cases (85%) of CML are diagnosed in the chronic phase which is asymptomatic in up to 25% of patients. Common findings at presentation are fatigue, weight loss, abdominal fullness, splenomegaly, leukocytosis, anemia and thrombocytosis[1].

Less than 20% of patients are diagnosed in advanced phase. In more than 85% of all CML patients, accelerated phase is preceded by a prolonged chronic phase characterized by mild symptoms in most patients[2]. In accelerated phase, cells develop genetic and karyotypic abnormalities leading to an increased number of poorly differentiated cells in peripheral blood and marrow, splenomegaly, and often to the onset of constitutional symptoms[3,4,5,6]. Accelerated phase generally leads to a rapidly fatal blast crisis within 6 months[5,6]. The definition of chronic phase, accelerated phase and blast crises is outlined in Table 1.

Two sets of prognostic factors can be considered. One is used prior to treatment (baseline factors) and another during treatment (response-related factors). The main baseline factors are the phase of the disease (Table 1) and the relative risk (Table 2). The phase of the disease strongly influences the response, the duration of the response, and overall survival. The relative risk, either by Sokal[8] or Hasford[9] scores, predicts the cytogenetic response to imatinib therapy[10]. Moreover, the Sokal score has been reported to also predict molecular response to imatinib and overall survival[10].

**Table 1. Cytomorphological criteria for phases in CML according to different classification systems as measured on peripheral blood smears or bone marrow samples.**

| | WHO | IBMTR (www.ibmtr.org) | German CML Study Group (www.kompetenznetz-leukaemie.de) |
|---|---|---|---|
| CP | blasts <10% (bone marrow or peripheral blood) | blasts <10% (bone marrow and/or peripheral blood) | blasts and metamyelocytes <15% peripheral blood |
| AP | blasts 10-19% (bone marrow or peripheral blood)<br><br>>20% basophils or eosinophils (in peripheral blood) | blasts >10%, or blasts plus promyelocytes >20% (bone marrow and)<br><br>>20% basophils or eosinophils (in peripheral blood) | blasts plus (promyelocytes >10% (bone marrow or peripheral blood) or peripheral blood) >20% basophils or eosinophils (in peripheral blood) |
| BP | blasts ≥ 20% (bone marrow or peripheral blood) | blasts plus promyelocytes ≥ 30% (in bone marrow or peripheral blood) | blasts plus promyelocytes ≥ 50% (in bone marrow) ≥ 30% (in peripheral blood) |

C: chronic phase; AP: accelerated phase; BP: blast phase

## Table 2. Calculation of disease relative risk

| | Calculation by Sokal et al[24] | Calculation by Hasford et al[25] |
|---|---|---|
| Age | 0.116 X (age – 43.4) | 0.666 when age ≥ 50 y |
| Spleen* | 0.345 X (spleen – 7.51) | 0.042 X spleen |
| Platelet count, X $10^9$/L | 0.188 X ((platelet count ÷ 700)$^2$ – 0.563) | 1.0956 when platelet count ≥ 1500 X $10^9$/L |
| Blood myeloblasts, % | 0.0887 X (myeloblasts – 2.10) | 0.0584 X myeloblasts |
| Blood basophils, % | NA | 0.20399 when basophils > 3% |
| Blood eosinophils, % | NA | 0.0413 X eosinophils |
| Relative risk† | | |
| Low | <0.8 | ≤780 |
| Intermediate | 0.8-1.2 | 781-1480 |
| High | >1.2 | >1481 |

Risk according to Sokel et al[8] was defined on patients treated with conventional chemotherapy. Risk according to Hasford et al[9] was defined based on patients treated with riFNα-based regiments. We emphasize that calculation of the risk requires use of clinical and hematologic data at diagnosis, prior to any treatment.

NA indicates not applicable.

*Centimeters below costal margin, maximum distance.

†Relative risk for the Sokal calculation is expressed as exponential of the total; that for the Hasford calculation is expressed as the total X 1000.

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10. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl JMed 2003; 349:1421-32.

## 3) Treatment options for patients presenting with *chronic phase* CML

The treatment options include;

A. TKI based treatment – imatinib mesylate or second generations TKI such as nilotinib or dasatinib

B. Non TKI based treatment
   i) Interferon-alfa ± cytarabine
   ii) Allogeneic hematopoietic stem cell transplantation (HSCT)
   iii) Cytotoxic therapy – hydroxyurea, busulphan

## A. Imatinib mesylate:

Imatinib, a relatively specific bcr-abl tyrosine kinase inhibitor, has dramatically revolutionised the management of CML in the past decade. The pivotal IRIS trial[1] showed that imatinib is more effective and better tolerated than the combination of interferon-alfa and cytarabine in patients newly diagnosed with CML in chronic phase. The 6 -year update of the IRIS trial confirmed that patients on imatinib continued to do extremely well with a low rate of disease progression[2]. Results with imatinib have been outstanding with over 80 % of patients achieving

a complete cytogenetic remission and excellent event-free survival rates. It is now accepted that imatinib is the best initial treatment for patients diagnosed with CML in chronic phase[3]. Though both nilotinib and dasatinib have been approved by FDA for frontline treatment of newly diagnosed CML, imatinib would still be the recommended drug as very few patients unassisted can afford the second generation TKIs which appear to achieve higher and faster rate of disease response[4] (cytogenetic and molecular) but no data on improved survival is yet available.

**RECOMMENDATION: All patients who present with CML in chronic phase should, if possible, receive imatinib as their initial treatment.**

**Starting dose of imatinib:** The FDA approved starting dose for chronic phase CML is 400mg daily. Recent studies suggest that higher starting doses are associated with more rapid and higher response rates. For the present, there is no definitive evidence that doses higher than 400 mg daily lead to reduced risk of disease progression and prolonged survival[5]. Prospective studies are still ongoing and until the results of these studies are available, the starting dose of imatinib should be 400mg daily. High-dose imatinib should be considered for patients with suboptimal response, and could also be considered for patients with cytogenetic relapse on standard dose imatinib.

**RECOMMENDATION: The starting dose of imatinib in newly diagnosed CP-CML patients should be 400mg daily.**

**Duration of imatinib:** Studies have shown that cessation of imatinib resulted in a return of the disease with loss of haematological and cytogenetic remission in most patients. Discontinuation of imatinib is not recommended outside the context of clinical trial for patients who are responding to treatment[6]. It may be better to intermittently interrupt imatinib treatment than to lower the dose since doses of less than 300 mg/d are considered to be insufficient and may promote a selection of mutated clones.

**RECOMMENDATION: Patients responding to imatinib should continue on imatinib indefinitely.**

**B. Non TKI based treatment**

**i) Interferon-alpha and cytarabine.**

Prior to the availability of imatinib, interferon-alpha (IFN) and cytarabine were considered the standard treatment for newly diagnosed patients with CP-CML, not eligible for stem cell transplantation. Complete cytogenetic remissions and prolonged survival are seen in a small proportion of patients. However tolerability is a problem with a substantial number of patients developing adverse reactions requiring dose reduction and termination of treatment. IFN remains a useful treatment option for patients who cannot afford TKI or in whom imatinib has failed. It can be considered for the treatment of CML in pregnancy[7]. Pegylated interferon has largely replaced conventional interferon and has the advantages of weekly injections and fewer side effects.

**ii) Allogeneic SCT – see section on role of HSCT**

**iii) Cytotoxics**

Hydroxyurea and busulphan were the two most commonly used cytotoxic agents in CML prior to the availability of imatinib. Both are effective in controlling the clinical manifestations, inducing complete hematological remission in a majority of patients. Neither agent however affects the natural history of the disease with rare cytogenetic responses; progression from chronic to advanced disease is not affected.

Hydroxyurea is the preferred agent as it is more effective and has a lower toxicity profile than busulphan.

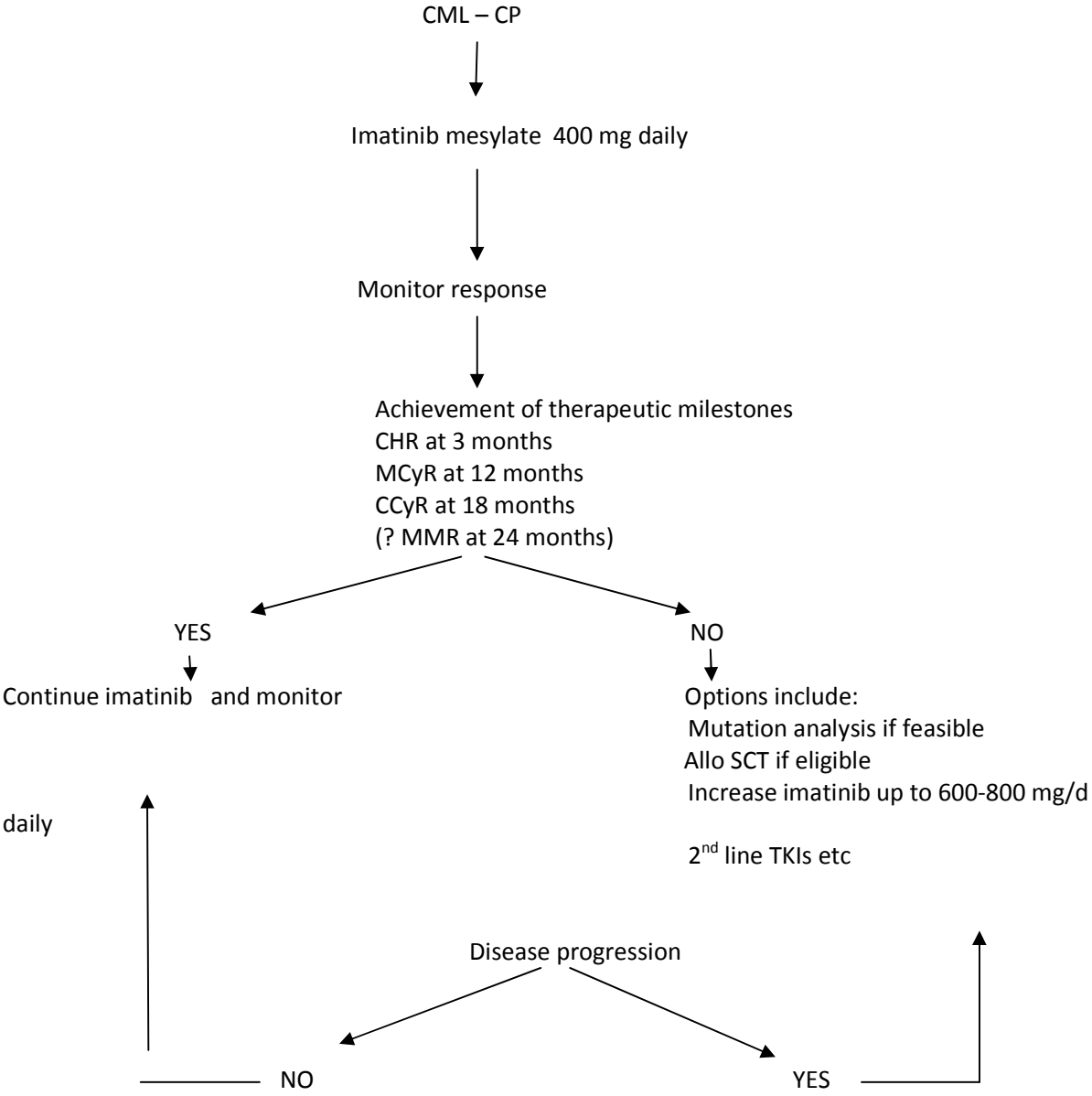
The use of hydroxyurea and busulphan should be confined to the following situations:

- as a temporary treatment to control haematological manifestations of CML prior to definitive treatment e.g. with imatinib.

- for rapid reduction of WCC in CML with hyperleucocytosis/leucostasis.

- in patients in whom TKI or IFN therapy is not an option (cost, intolerance, failure) and ineligible for HSCT

## Algorithm for upfront treatment of patients with CML-CP with imatinib

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2 Kantarjan HM, Talpaz M, O Brien S et al: Survival benefit with imatinib versus interferon alfa based regimens in newly diagnosed chronic myelogenous leukemia. Blood 108:1478-1484, 2006

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6 Baccarani M, Cortes J, Pane F, et al: Chronic myeloid leukemia:An update of concepts and management recommendations of European LeukemiaNet. J of Clinical Oncology 2009:35;6041-6051

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## 4) Monitoring Response and Resistance to Therapy in CML

Several monitoring methods are available to assess response and resistance to therapy in CML: 1) cytogenetics, 2) FISH, 3) qualitative PCR, and 4) mutational studies.

Bone marrow for morphology and **cytogenetics** should be done pretreatment then at 6 and 12 months (to assess imatinib response), then every 1-2 years if stable complete cytogenetic response. Cytogenetic karyotyping is the only routinely available assessment of all chromosomes.

**FISH** can help assess the cytogenetic response and can be done in peripheral blood. It can be easily used for long-term monitoring (e.g. every 6-12 months) although it would not allow for detection of chromosomal abnormalities in Ph-negative metaphases or development of new karyotypic abnormalities.

In cytogenetic CR, monitor with Quantitative Polymerase Chain Reaction **(QPCR)** every 6 months. Aim for a BCR-ABL/ABL ratio of <0.1% in the international scale (i.e., 3-log reduction

from standardized baseline). In a patient in cytogenetic CR, do not react drastically to rises in transcript levels unless consistent with loss of major molecular response (BCR-ABL/ABL ratio >0.1% in the international scale) and with a 1-log increase. Even if this occur, choose a lower-risk treatment option, (e.g. increase imatinib dose), before resorting to a higher-risk ones (e.g. allogeneic transplant).

In standard practice, **mutational analysis** is not recommended prior to treatment, or in patients showing good response to imatinib. Mutational studies are best done only in patients with cytogenetic or hematologic relapse on imatinib. In this group about 50% will show mutations. A T315I mutation should lead to consideration of allogeneic stem cell transplant. The mutation IC50 to a particular agent is a better guide to select therapy. For example, most P-loop mutations respond well to dasatinib, while mutations V299L and F317L respond well to nilotinib.

**Recommendation: Monitoring treatment response is essential for optimal management of CML patients and cytogenetic assessment is important for delineating response[1]. Molecular study such as QPCR is increasingly gaining acceptance and should be done if available.**

## Guidelines for Monitoring of Patients with CML

| Tests | At diagnosis | 3 months | 6 months | 12 months | 18 months |
|---|---|---|---|---|---|
| Morphology – bone marrow and trephine biopsy<br><br>Morphology – peripheral blood film | To diagnose<br><br>To determine disease phase<br><br>Monitor 2 weekly or monthly till CHR | | | | |
| Flow cytometry – bone marrow | To determine leukaemia lineage in accelerated and blast phase. | | | | |
| Cytogenetics – bone marrow | To confirm diagnosis<br><br>Evaluate other karyotype abnormalities | | Check at least every 6 months until complete response achieved thereafter at least 12monthly | | |
| FISH – bone marrow or peripheral blood | To confirm diagnosis<br><br>To identify cryptic bcr-abl translocation. | | | | |

| | | |
|---|---|---|
| RT-PCR - bone marrow or peripheral blood | To confirm diagnosis<br><br>To determine the transcript types | |
| Q-PCR -bone marrow or peripheral blood | | PB sample for monitoring of molecular response -check every 3-6 months till MMR. Thereafter repeat 12 monthly. (mutation analysis in cases of failures, suboptimal responses or transcripts level increase.) |
| ABL Kinase Domain Mutation Analysis | - Indicated in patients with cytogenetic or hematologic relapse on imatinib | |

## Definition of responses:

| Terminology | Definition |
|---|---|
| RT-PCR | Reverse-transcription PCR |
| Q-PCR | Quantitative PCR |
| Complete Haematologic Response (CHR) | Defined as the combination of all of the following:<br>– Platelet count <450 x $10^9$/L<br>– White blood cell count <10 x $10^9$/L<br>– Differential without immature granulocytes and <5% basophils<br>– Non palpable spleen |
| Cytogenetic Response (CyR) | Several cytogenetic response outlined :<br><br>'None' - >95% Ph+ metaphases<br>'Minimal' - 66 – 95% Ph+ metaphases<br>'Minor' - 36 – 65% Ph+ metaphases<br>'Partial' (PCyR) - 1- 35% Ph+ metaphases<br>'Complete' (CCyR) - 0% Ph+ metaphase<br><br>Major cytogenetic response (MCyR) = "Partial" & "Complete" cytogenetic response |
| Molecular Response (MR) | Molecular response is measured based on the number of bcr-abl transcripts, expressed as a ratio |

| | |
|---|---|
| | of *BCR-ABL* to a control gene e,g Bcr or Abl gene.<br><br>Major Molecular Response (MMR) is defined as 3-log reduction from baseline of the number of transcripts, expressed as a ratio of *BCR-ABL* to a control gene.<br>Using the International Scale (IS), the standardised baseline is represented by 100% and a MR is correlating with 0.1%. |
| Treatment failure2 | No haematological response at 3 months<br>No cytogenetic response at 6 months<br>Less than MCyR at 12 months<br>No CCyR at 18 months<br>Loss of CHR, loss of CCyR or positive mutation analysis at any time |

**Recommendation: Monitoring of cytogenetic and molecular response should at least be done at 6 months and 1 year to assess treatment response to imatinib. In the case where treatment milestones are met, yearly cytogenetic study or 6 monthly RQ-PCR is recommended indefinitely[2].**

References
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## Management of advanced phases

## Accelerated Phase (AP)

The recommended treatment for AP is use of TKI ( tyrosine kinase inhibitor) i.e. Imatinib 600mg daily or nilotinib 400mg bd or dasatinib 100mg daily followed by allogeneic bone marrow transplant whenever possible.

DEFINITIONS OF BLAST CRISIS

| World Health Organization (WHO) Criteria[1] | International Bone Marrow Transplant Registry[2] |
|---|---|
| • Blasts ≥ 20% of peripheral blood white cells or of nucleated bone marrow cells<br>• Extramedullary blast proliferation<br>• Large foci or clusters of blasts in the bone marrow biopsy | • ≥ 30% blasts in the blood, marrow, or both<br>• Extramedullary infiltrates of leukemic cells |

[1] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.
[2] DeVita VT, Hellman S et al: Cancer: Principles and Practice of Oncology, 6th Edition. Vol 2., pgs 2433-2447, 2001, Lippincott, Williams & Wilkins©

## Blast Crisis (BC)

Dasatinib alone or in combination with chemotherapy followed by allogenic BMT if feasible is the treatment of choice for both myeloid and lymphoid blast crisis. TKI such as nilotinib may be use in place of dasatinib. Imatinib can be considered in de novo CML in BC. The initial dose of IM should be 600mg daily and adjust to 800mg daily if tolerable[1].

For myeloid blast crisis, anti AML induction therapy would be appropriate while anti ALL type of induction is indicated in lymphoid crisis. Patients who are not fit for chemotherapy may receive TKI as the only treatment. Even for patients who attain CR with TKI with or without chemotherapy, the CR is short-lived and if feasible should be followed by allogeneic transplant to have realistic chance for long term survival[2].

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## 6) Emergency Treatment

Hyperleucocytosis can present with CNS symptoms, blurred vision or respiratory distress. Leucopharesis is rarely needed as use of hydroxyurea (40mg/kg/day) with hydration and allopurinol tend to bring the elevated white cell count down quickly. Imatinib can be used in hyperleucocytosis if diagnosis of CML is confirmed by cytogenetic/molecular test. Priapism is a rare complication which should be treated medically with conservative urological measures.

## 7) Management of imatinib related side effects:

The side effects of imatinib are generally self-limiting and may allow re escalating to ideal dose in later date. Overall, imatinib is well tolerated. Although adverse events are seen in up to 50% of patients, these are usually mild and manageable[1]. Only 2% to 5% of patients have adverse events that require permanent discontinuation of therapy[2].

Severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites) have been reported in approximately 1 to 2% of patients[1]. Therefore, it is recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken.

Patients especially elderly and with pre-existing cardiac disease should be monitored closely. Before treatment was started, patients will given instructions on the administration of imatinib and are advised to avoid acetaminophen, alcohol, grapefruit, and caffeine. All patients are instructed to practice barrier contraception for as long as they are on imatinib.

### Dose adjustments for adverse reactions in CML patients

**i) Non-haematological adverse reactions**

If a severe non-haematological adverse reaction develops, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, imatinib should be withheld until bilirubin levels have returned to a < 1.5 x IULN and transaminase levels to < 2.5 x IULN. Treatment with imatinib may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg or from 600 to 400 mg.

**ii) Haematological adverse reactions**

During the course of treatment with imatinib and other tyrosine kinase inhibitors, 30% to 50% of patients develop grade 3 or 4 anemia, thrombocytopenia or neutropenia. Cytopenias most frequently occur during the first 2 to 3 months of therapy and in many instances they do not recur. This early myelosuppression is managed with a temporary treatment interruption if there is grade 3 or greater neutropenia (absolute neutrophil count <1 x 109/L) or thrombocytopenia (platelets <50 x 109/L). Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

## Dose adjustments for neutropenia and thrombocytopenia

| | | |
|---|---|---|
| Chronic phase CML (starting dose 400 mg) | ANC < 1.0 x$10^9$/L and/or platelets < 50 x$10^9$/L | 1. Stop Imatinib until ANC ≥ 1.5 x$10^9$/L and platelets ≥ 75 x$10^9$/L.<br>2. Resume treatment with IM at dose of 400 mg.<br>3. In the event of recurrence of ANC < 1.0 x$10^9$/L and/or platelets < 50 x$10^9$/L, repeat step 1 and resume IM at reduced dose of 300 mg. |
| Accelerated phase CML and blast crisis (starting dose 600 mg) | [1]ANC < 0.5 x$10^9$/L and/or platelets < 10 x$10^9$/L | 1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy).<br>2. If cytopenia is unrelated to leukaemia, reduce dose of IM to 400 mg.<br>3. If cytopenia persists for 2 weeks, reduce further to 300 mg.<br>4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop IM until ANC ≥ 1 x$10^9$/L and platelets ≥ 20 x$10^9$/L, then resume treatment at 300 mg. |
| ANC = absolute neutrophil count<br>[1]occurring after at least 1 month of treatment | | |

## Measures for other side effects:

| | |
|---|---|
| 1) Nausea | - imatinib to be taken with meals<br>- infrequent need for antiemetic drugs |
| 2) Diarrhoea | - generally responds to antispasmodic<br>- need to rule out other causes such as lactose intolerance |
| 3) Neutropenia | - dose reduction or temporary cessation of imatinib with return to 400mg daily<br>- very rarely growth factor support is needed |
| 4) Hepatic dysfunction | - early and usually transient occurrence<br>- avoid concomitant and excessive alcohol intake |
| 5) Rash | - usually mild, maculopapular and transient |

| | |
|---|---|
| | - stop imatinib if very severe e.g. exfoliative dermatitis<br>- steroids can benefit some patients<br>- severe recurrent rashes preclude continued therapy with imatinib |
| 6) Fluid retention | - usually peripheral oedema and responses to intermittent use of diuretics |
| 7) Periorbital oedema | - poor response to diuretics<br>- reassurance that this is transient |
| 8) Fatigue | - generally mild but can be persistent<br>- reassurance that this is a drug-related effect |
| 9) Muscle cramps, myalgia and athralgia | - most prominent long-term side effect with unknown cause<br>- calcium and magnesium replacement may be useful but no evidence available<br>- some patient respond to isotonic beverages such as 100 Plus<br>- quinine may be effective in severe cases |
| 10) Macrocytic anaemia | - exclude B12 and folate deficiency<br>- more profound anaemia may be treated with erythropoietin |

**Recommendation: managing side effects of imatinib is challenging and generally most patients can be kept on imatinib with suitable adjustment in doses and frequency knowing that most of these side effects are somewhat self –limiting.**

References:

1. Kantarjian H, Sawyers C, Hochhaus A, et al: Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 346:645-652, 2002
2. O'Brien SG, Guilhot F, Larson RA, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348:994-1004, 2003

## Drug interactions

Imatinib is a substrate for the CYP3A4 metabolic pathway and can inhibit other cytochrome P-450 pathways.

CYP3A4 inhibitors that can increase imatinib levels include Diltiazem, Verapamil, Itraconazole, Ketoconazole, Clarithromycin, Erythromycin and Grapefruit juice.

CYP3A4 inhibitors that can decrease imatinib levels include Rifampicin, Phenobarbital, Phenytoin and St.John's wort.

Patients on warfarin should be carefully monitored.

## Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Since the renal clearance of imatinib is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

## Lactation

It is not known if imatinib is excreted in human breast milk. Women are not encouraged to breastfeed while on imatinib.

## 8. SECOND GENERATION TYROSINE KINASE INHIBITORS (TKIs) IN CML

Dasatinib or nilotinib are the first choice for patients with failed response or rapid loss of response under imatinib if an allogeneic HSCT is not an option. Both drugs differ from one another in regard to chemical structure, binding to BCR-ABL, including BCR-ABL conformation, spectrum of target inhibition, efficacy and safety profile. So far there have been no head to head comparative studies. In regard to side effects dasatinib has a higher risk of pleural or pericardial effusions. It should therefore be second choice only in patients with a history of pericardial or pleural effusions. Nilotinib has been associated with some sudden cardiac events, all in patients with a history of cardiac disease. Nilotinib has furthermore been associated with rare cases of pancreatitis and probably should not be given to patients with a history of pancreatitis[1,2].

### Dasatinib

Dasatinib is an orally available ABL kinase and SRC kinase inhibitor. Dasatinib is structurally unrelated to imatinib and is 300 times more potent inhibitor of Bcr-Abl kinase activity. It induces significant inhibition of the kinase activity of cells transfected with the wild-type Bcr-Abl as well as all mutants of Bcr-Abl, the exception being T315I.

Dasatinib induced haematologic as well as cytogenetic responses in a significant portion of patients with imatinib-resistant CML at all phases[3-6]. In imatinib-intolerant CP, the incidence of CCyR and MCyR were 63-75% and 71-76% respectively whereas in imatinib-resistant CP, they were 36-40% and 50% respectively. For patients in CP, the responses were sustained for 2 years[4,5].

Dasatinib at 100mg daily was as effective as 70mg b.d in CP patients with a lower incidence of myelosuppression, pleural effusion and dose interruptions[7].

Adverse effects include myelosuppression and fluid retention, pleural effusions, headache, GI upset, diarrhea and rash. The incidence of pleural effusions is 29% in CP, 50% in AP and 33% in BP.

Dasatinib is a CYP3A4 substrate. Drugs that inhibit CYP3A4 may increase dasatinib exposure whereas drugs that induce CYP3A4 may decrease dasatinib plasma concentrations. The absorption of dasatinib is pH dependent and antacids and H2blockers/proton pump inhibitors should be avoided. Grapefruit juice may increase plasma concentrations of dasatinib and should be avoided.

Dasatinib (70mg b.d.) is FDA-approved for CML in all phases resistant or intolerant to imatinib. Dasatinib at 100mg daily is also approved as the starting dose for imatinib-intolerant or resistant chronic phase patients.

## Nilotinib

Nilotinib is a highly selective BCR-ABL kinase inhibitor. It is 20-50 times more potent than imatinib. Nilotinib has also been shown to induce haematologic as well as cytogenetic responses in a significant portion of patients with imatinib-resistant CML at all phases[8-10].

In imatinib-intolerant CP the incidence of CCyR and MCyR were 35% and 47% respectively whereas in resistant CP, they were 30% and 48%. The responses were sustained in 96% and the 1-y OS was 95%[11].

In an upfront newly diagnosed CML CP study comparing nilotinib 300mg b.d. and nilotinib 400mg b.d. vs imatinib 400mg daily, the CCyR at 12 months were 80% and 78% vs 65% and MMR at 12 months were 44% and 33% vs 22% ($p<0.001$). The rate of progression to AP and BP was significantly improved in both the nilotinib arms[12].

Adverse effects include myelosuppression, fluid retention, edema, muscle cramps, headache, elevated lipase and prolongation of QTc interval.

Nilotinib is a competitive inhibitor of CYP3A4. CYP3A4 inducers will decrease nilotinib plasma concentrations whereas CYP3A4 inhibitors will decrease nilotinib levels. Grapefruit juice may increase plasma concentrations of nilotinib and should be avoided.

Nilotinib (400mg b.d.) is FDA-approved for the treatment of CP or AP-CML in patients resistant or intolerant to imatinib.

**Recommendation: Second generation TKIs are effective agents for Imatinib resistant or intolerant patients at different phases of CML. They are the treatment of choice in such circumstances especially if HSCT is not an option.**

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## 9. Haematopoietic stem cell Transplantation in CML

Allogeneic haemopoietic stem cell transplantation (HSCT) remains the only curative treatment option for CML. It however comes at the expense of increased toxicity and significant transplant related morbidity and mortality. In the era of Tyrosine Kinase Inhibitor (TKI) therapy, transplantation has taken a more "back seat" role, given the excellent response to TKIs and 5 year survival exceeding 90% for patients in the chronic phase[1]. On the other hand, TKI therapy is less effective in accelerated and blast crisis phase of the disease and responses seen may be short lived in the more advance phases of CML. The follow-up response to TKI therapy as well as the development of resistance to TKIs is also factors in the consideration of HSCT.

Major considerations in deciding if a patient is a suitable candidate for HSCT would be age, availability of a HLA matched donor and stage of disease.
HLA workup and counseling should be performed early in the course of illness for patients with CML who are potential candidates for HSCT.

1) First Chronic phase where there is:
- Primary resistance to TKI
- Cytogenetic resistance or suboptimal response to TKI e.g. lack of complete haematological response at 3 months, lack of major cytogenetic response at 6 months or lack of complete cytogenetic response at 18 months
- Progression on TKI therapy
- Intolerance to TKI

2) Accelerated phase CML
- early transplant if good risk e.g. low EBMT score, after initial TKI
- poor risk e.g. significant co-morbidities, high EBMT score, if there is progressive disease after initial response to imatinib

3) Blast phase CML : preferably after treatment with TKI +/- chemotherapy

With the advent of second generation TKIs as an alternative treatment to 1st generation TKI where there is intolerance or suboptimal response, the position and timing of HSCT is somewhat more uncertain. HSCT should be considered if 2nd generation TKIs are not available/accessible or if mutation analysis suggests a significant mutation such as T315I which confers resistance to second generation TKIs[2].

### Timing and Pre-treatment considerations

Busulphan should not be administered to any potential HCT candidate as this confers increased lung and liver toxicity after HCT. In the pre-TKI era, Hydroxyurea +/- Interferon was used prior to HSCT. It was thought that transplant in patients treated with this agent is best done within the first year of diagnosis although recent German data[3] suggests otherwise.

There is to date no clear evidence to suggest that pre-transplant TKI therapy will negatively influence the outcome of patients undergoing future transplantation.

### Types of transplant

1. Allogeneic HCT from a HLA matched sibling donor is the transplant of choice where there is a 6/6 matched sibling donor on low HLA resolution typing.

2. Bone marrow or blood stem cells may be used though patients should be counseled that the latter is associated with a higher risk of chronic graft-versus-host-disease (GVHD). Blood stem cells may be preferable in accelerated or blast phase patients as there is data to suggest a lower relapse rate compared to bone marrow as the stem cell source.

3. A "full" transplant using Standard Bu-Cy or Cy-TBI conditioning is recommended. Reduced intensity conditioning (RIC) allogeneic transplants may be considered in patients who are older or with significant co-morbidities.

4. In the absence of a matched sibling donor, a HLA matched unrelated donor is an alternative. In this instance, a 10/10 match using high resolution HLA typing is preferable.

## Post-transplant monitoring and therapy of relapse

Post-transplantation, patients should be monitored at intervals for cytogenetic status and PCR according to institutional practice. In patients who are in cytogenetic remission, qPCR monitoring 3 monthly for the first two years is an alternative.

Treatment options for relapse include:

i) TKI
ii) Donor lymphocyte infusion
iii) alpha Interferon

**Recommendation: HSCT is the treatment of choice in failed or insufficient response to imatinib or progressive disease or in patients having T315I mutation and in suitable patients in accelerated or blast crisis.**

References


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## 10. Pregnancy

IM is not recommended for pregnant women. Woman of child bearing age should practise contraception. Exposure to imatinib during pregnancy might result in an increased risk of serious fetal abnormalities or spontaneous abortion[1]. Women of childbearing potential should use adequate contraception while taking imatinib. Imatinib should be avoided in pregnancy unless the risk of interrupting therapy is deemed by the patient's physician to be unacceptable. In cases of accidental or planned pregnancy, risk/benefit evaluations must be carried out on an individual basis with careful counseling of both parents using the most recent data available.

Alternative therapies for CML include IFN-$\alpha$. Animal studies have shown this drug to be non-teratogenic in rats and rabbits, resulting in normal offspring, but it has also been shown to have abortifacient effects in rhesus monkeys at doses of 90 and 180 times the recommended intramuscular or subcutaneous dose of $2 \times 10^6$ IU/$m^2$. In view of this, the official recommendation is that IFN-$\alpha$ be avoided during pregnancy unless "the potential benefit justifies the potential risk to the fetus".

**Recommendation: Pregnancy is not recommended while patients are on imatinib. Interferon could be a" holding" drug for CML in pregnancy.**

Reference

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## 11. Patient's preference

The physician's wish is absolute patient compliance which is a real challenge in the modern era. To take any drug on a long term basis with the accompanying side effects can be difficult and it is not surprising that the lack of full compliance of drug is common. Economic issue can be a major factor for poor compliance. Change of therapy at the desire of the patient may become necessary. Patients should be informed about the risk of disease progression when imatinib is withheld or interrupted. Interferon alpha maintenance might be an option in pregnancy. In no case, TKIs should be given to pregnant women. All have the potential to interfere in embryogenesis and early pregnancy. Some young patients may prefer a transplant strategy with the potential for cure compared to a lifelong drug treatment.

**Recommendation: Engaging the patients with chronic illness like CML is crucial to ensure good compliance and success of therapy.**

### 12. Referral to a Hematology center

AS mentioned in the preamble, all new cases should be assessed by hematologists to draw up management plan. At any stage of management when there were severe or unexpected adverse side effects or occurrences of advanced disease or contrasting or unstable reesults, they should be reviewed by hematologists again on an urgent basis. An annual visit to a hematology center is recommended to ensure everything is on the right track.