Recommendations for the Management of *BCR-ABL*-positive Chronic Myeloid Leukaemia

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Abstract

The management of patients with CML in chronic phase has changed dramatically with the advent of imatinib. For children with HLA-identical donors there is still debate as whether allogeneic transplant should or should not be offered as front-line therapy but for all new adult patients not in clinical studies it is now standard practice to start treatment with imatinib 400 mg daily. The initial response can be assessed by cytogenetic analysis of bone marrow at 3 month intervals until complete cytogenetic remission (CCyR) is achieved. Thereafter patients in CCyR may be monitored by measurement of BCR-ABL transcript levels performed every 3 months. Patients who fail to respond to imatinib or who having responded response lose their response should be treated with a second generation tyrosine kinase inhibitor, such as dasatinib, nilotinib or bosutinib, unless they have a T315I kinase domain mutation, which would render their leukemia resistant to all these agents. Allogeneic stem cell transplantation may be considered for patients with suitable donors as an alternative to a second generation TKI or if they fail such treatment. Interferon-alfa or hydroxycarbamide may still be valuable for patients still in chronic phase who have failed treatment with imatinib and a second generation TKI.

1.0   Introduction

The use of the original Abl tyrosine kinase (TK) inhibitor, imatinib mesylate (IM), to treat patients with Philadelphia (Ph)-chromosome positive chronic myeloid leukaemia (CML) in chronic phase appears to prolong life quite substantially in comparison with interferon or interferon plus cytarabine (O'Brien et al, 2003; Druker et al, 2006; Roy et al, 2006; Kantarjian et al, 2006a). Its advent has therefore changed fundamentally the accepted approach to the management of newly diagnosed patients. The arrival subsequently of the second generation TK inhibitors, notably dasatinib and nilotinib, has added complexity to the process of making therapeutic decisions, and newer agents active against the T315I mutant sub-clone, such as MK-0457, are now in development or have already entered clinical practice (Giles et al, 2007). In this rapidly moving field, to produce formal evidence-based guidelines would be impossible. Instead, we have opted to produce 'recommendations' based on past experience and recently published results of the use of TK inhibitors on both sides of the Atlantic, which we hope will be valid for at least a year after their publication.

2.0 Evaluation at diagnosis

2.1 Confirmation of diagnosis

It is always important to confirm that the suspected diagnosis of Ph-positive CML. Essential investigations include a full blood count ideally with a 1000 cell differential performed by microscopy, a bone marrow aspirate and trephine biopsy together with bone marrow cytogenetics and real-time quantitative reverse transcriptase (RQ-PCR) for *BCR-ABL* transcripts. Fluorescence in situ hybridization (FISH) studies on a peripheral blood will confirm the presence of a BCR-ABL gene but can also be designed to detect a possible deletion in the der(9) chromosome. Neutrophil alkaline phosphatase is no longer routinely measured. HLA typing for the patient and family members may prove useful if the patient is aged less than 65 years. It is not currently recommended that peripheral blood stem cells should routinely be collected and cryopreserved at diagnosis, but a number of research laboratories in the UK appreciate receiving cells (after appropriate approval from their Research Ethics Committee and relevant informed consent have been obtained).

2.2 Assessing the phase of disease

It is conventional to classify a patient's disease at the time of diagnosis as chronic phase, accelerated phase or blastic transformation, though in some cases categorisation can be extremely difficult. Accelerated and blastic phases may be grouped together as advanced phase. Criteria for defining the three phases of CML have been proposed by the International Bone Marrow (IBMTR), the MD Anderson Cancer Center in Houston and by the WHO Health Organisation (reviewed by Cortes et al, 2006); the criteria specified for the purposes of the studies using tyrosine kinase inhibitors differ to a minor degree from all three. In general the MD Anderson classification re-stated in the recent Leukemia-Net publication (Baccarani et al, 2006) is used most widely (Table 1). The WHO classifies as accelerated phase a patient with cytogenetic evidence of clonal evolution in the absence of any other criteria of acceleration; such a patient would be classified as chronic phase by Leukemia-Net criteria.

2.3 Estimating prognosis

The Sokal prognostic score (Sokal et al, 1984), which takes into account a patient's age, spleen size, percentage of blood blasts and platelet count was introduced in 1984 and was derived from survival figures for patients treated predominantly with busulphan. The Euro or Hasford score (Hasford et al, 1998) is a modification of the Sokal score that incorporates also basophil and eosinophil numbers; it is based on assessment of patients treated primarily with interferon.

Preliminary experience suggests that these scoring systems can still discriminate when patients are treated with imatinib, but molecular characterisation, eg gene profiling (Radich et al, 2006), may eventually prove more informative.

3.0 Initial management

3.1 Patients presenting in chronic phase

There is general agreement that the majority or all patients who present with CP disease should be treated initially with imatinib or in the context of a clinical study with an imatinib-containing regimen. The possible exceptions are a child who has an HLA-identical sibling (Pulsipher, 2004) or a patient fortunate enough to have a syngeneic twin. Economic considerations may also dictate choice of therapy outside the UK; thus for a patient in a developing country who might be unable to pay for imatinib on a long-term basis a single payment for transplantation could be the more realistic option.

The standard starting dose is 400 mg/day for an adult. It may be that starting treatment at a lower dose, eg 100 or 200 mg/day, encourages the development of drug resistance and should therefore be avoided. Reports from the MD Anderson Cancer Center show more rapid cytogenetic and molecular responses with a starting dose of 800 mg/day but this higher dose is not always well tolerated and does not demonstrably prolong survival. The two dose levels, 400 mg/day and 800 mg/day, are now being compared in prospective studies in Europe and North America. Until results of these trials are available, 400 mg day may be the best approach for a patient not entered into a clinical trial.

Grade 3/4 adverse effects are relatively rare with standard dose imatinib but lesser degrees of toxicity are not uncommon. They include rashes, bone pain, fluid retention, anorexia, depression, weight gain and other symptoms. Myelosuppression may necessitate temporary interruption of therapy but may respond to haemopoietic growth factors including eryrthropoietin and G-CSF. Use of short term corticosteroids may be indicated for treatment or prevention of rashes or abnormal levels of hepatic enzymes (Marin et al, 2002; Deininger et al, 2003).

3.2 Patients presenting in advanced phase

Patients presenting with advanced phase disease who will not previously have been exposed to imatinib may be treated initially with IM at 600 or 800 mg/daily. For those with blastic transformation who initially respond the duration of response may be short and continuing

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treatment immediately after initial response should involve use of conventional chemotherapy with or without an allogeneic stem cell transplant.

3.3 Patients progressing to advanced phase

For patients whose disease progressed to advanced phase while they were taking IM, there is no logic to continuing the same drug. They may respond to one or other of the second generation of TK inhibitors. Allogeneic stem cell transplantation should be considered if feasible if a suitable donor can be identified.

4.0 Monitoring patients on imatinib

4.1 Cytogenetics and FISH

Patients in chronic phase who achieved complete haematological remission with interferon-alfa were in the past monitored with regular bone marrow aspirates to assess the level of Ph-negativity or less commonly with FISH studies to detect the presence of the BCR-ABL fusion gene in peripheral blood cells. Now that 80% or more of patients with CML in CP treated ab initio with imatinib achieve a complete cytogenetic remission, it is logical to perform routine bone marrow examinations, perhaps every 3 months, only until complete cytogenetic remission (CCyR) is achieved and then to rely principally on the much more sensitive RQ-PCR for BCR ABL transcripts. Some experts recommend continuing to perform bone marrow aspirates for cytogenetic studies at one year intervals even in responding patients to detect possible clonal abnormalities in Ph-negative cells (Baccarani et al, 2006) but their clinical significance is not clear and it may not be essential if transcripts number remain low.

4.2 Realtime quantitative PCR for BCR-ABL transcripts

The mainstay for monitoring patients who seem to be responding to treatment should be RQ-PCR for *BCR-ABL* transcripts. The technology is demanding (Hughes et al, 2006) and results from laboratories where the test is done relatively infrequently are quite often unreliable. An attempt is now being made to standardise use of control genes. Eventually internationally validated reference reagents will be available but until that time it is hazardous to compare directly numerical values between different laboratories. For a patient whose response seems to be slow, bone marrow cytogenetic analysis may be repeated at three month intervals.

It was agreed at the Bethesda meeting convened by the NIH in October 2005 that the optimal way of expressing results of measuring *BCR-ABL* transcripts was to use the ratio of *BCR-ABL* transcript copy numbers to the number of transcript copies of a suitable control gene converted to a percentage (Hughes et al, 2006). The alternative would be to express copy numbers as a log reduction from a laboratory specific standardised baseline value of 100% (Hughes et al, 2003), though this method also would not take adequate account of the patients own baseline level. By this method a value of 1% (or lower) would be regarded as a 2 log reduction and usually consistent with complete cytogenetic remission (CCyR) and a value of 0.1% (or lower) would be a 3 log reduction and has been termed a 'major molecular response'. The term complete molecular remission has been used but this takes no account of the fact that the sensitivity of the assay may vary substantially in different laboratories; the term 'undetectable transcripts' may be preferable.

4.3 Frequency of testing

For the patient who seems to be responding, measuring *BCR-ABL* transcripts in a reliable laboratory is arguably the single most important method for monitoring response. It might be informative to repeat the bone marrow aspirate for cytogenetics at 3 months after starting treatment with IM, but the level of Ph-positivity can in fact be extrapolated with reasonable accuracy from knowledge of the transcript levels and by six months most patients should have achieved a CCyR. At that point further estimates of the quantity of residual disease must be based on results of RQ-PCR, which typically has a sensitivity of 1 in 10^5 or even 1 in 10^6. FISH provides little useful information after a patient has achieved CCyR. **A reasonable recommendation is that for the responding patient *BCR-ABL* transcript levels should be measured at three month intervals indefinitely.** There is a case for performing routine marrow cytogenetic studies at 12 month intervals in patients believed to be in continuing CCyR; this will identify clonal cytogenetic abnormalities in the Ph-negative population, the clinical significance of which is undetermined.

If the level of *BCR-ABL* transcripts appears to be rising, the test should be repeated as soon as convenient without waiting the full three months. If the repeat test shows that the level has risen by 0.5 or 1.0 log the next step should be to search for kinase domain mutations in the same cDNA that was used for RQ-PCR and to examine the bone marrow from for Ph-positive cells and clonal evolution. The additional information gained from these tests will contribute to the therapeutic decision.

5.0 Imatinib response and failure

5.1. Definitions (Table 2)

On the assumption that a patient with CML starts treatment with imatinib as a single agent, the factors that must be considered for assessing response are (a) Duration of treatment, (b) Technology employed, ie blood counts, cytogenetics/FISH and RQ-PCR, and (c) Actual dosage consumed by the patient. Each technology has various 'landmarks' which can be defined with varying degrees of accuracy, ie

Haematology: Complete haematological remission implies resolution of splenomegaly (if previously present), restoration of normal blood counts and loss of marrow hypercellularity

Marrow cytogenetics: The absence or proportion of persisting Ph-positive marrow metaphases defines a CCyR (or CCgR), a partial cytogenetic response (PCyR or PCgR)) and a minor haematological response. Taken together CCyR and PCyR are referred to as a major cytogenetic response (MCyR).

RQ-PCR: A 3-log reduction is referred to as a major molecular response. The absence of detectable transcripts is sometimes referred to as a complete molecular remission (CMolR) but the term 'undetectable transcripts' is preferred since it implies that the level of detection or non-detection depends on the sensitivity of the assay (see above).

Kinase domain mutations: The clinical significance of *BCR-ABL* kinase domain (KD) mutations is not yet clear. Some are clearly associated with resistance to imatinib and one mutation, coding for a threonine to isoleucine substitution at position 315 (T315I), produces a sub-clone resistant both to imatinib and to dasatinib and nilotinib. Patients with such mutations may be eligible for treatment with one of the third generation of TK inhibitors. Conversely other mutations that remain at low levels for long periods may be insignificant.

5.2 Definition of response

Responses may be defined at the haematological, cytogenetic and/or molecular levels and these are of course dependent on time from starting treatment and drug dosage. The terminology recommended by Leukemia-net for describing haematogical, cytogenetic and molecular responses is summarised in Table 2. Patients failing to satisfy one or other of these criteria at a given time point are classified as non-responders (see 'Definitions of Failure' below)

5.3 Definition of failure

The European Leukemia-Net has recently proposed that patients at diagnosis or after starting treatment with imatinib should be classified into one of three categories (Baccarani et al, 2006).

The criteria for the categories, which may in fact overlap to some extent, are specified in Table 3 and the clinical implications of these categories are:

(a) Failure - Indicates that imatinib should be discontinued and some other treatment initiated.

(b) Sub-optimal response – Indicates that treatment with imatinib should be reassessed and treatment may be changed immediately or in the foreseeable future

(c) Warnings – A patient has features at diagnosis or developing during treatment that suggest that his/her leukemia may become resistant to IM and/or progress to advanced phase and therefore needs closer monitoring than average.

5.4 Options for further management

It is difficult to make a firm recommendation for how to continue treatment for the patient judged to have failed first-line imatinib. This will depend in part on whether the patient is still in chronic phase or is in advanced phase. For the patients still in chronic phase there are a number of possible options (listed in Table 4) but in practice only the first three are relevant in the first instance. For a patient who is taking imatinib 400 mg daily it is reasonable to increase the dose to 600 or even 800 mg daily and this will reverse the features of resistance in some cases; usually however the response is transient and another avenue will need to be explored. The encouraging results with use of dasatinib for patients resistant to or intolerant of imatinib (Hochhaus et al, 2007) mean that this agent should probably be standard second-line treatment for imatinib failure, though allogeneic stem cell transplant can be considered for the younger patient with an HLA-identical sibling donor. It is likely that nilotinib will be licensed soon in the UK and this agent may prove just as effective as dasatinib (Kantarjian et al, 2006b). Bosutinib may also prove valuable for such patients (Puttini et al, 2005) though it is not yet widely available. If however the patient fails to respond well to dasatinib (or nilotinib) or if he/she proves to have a T315I mutant subclone, then a transplant should be considered even in the absence of a matched sibling (Jabbour et al, 2006). The aurora kinase inhibitor MK-0457 may be active in patients with the T315I subclone but its clinical value is not yet established (Giles et al, 2007). A reasonable third line alternative for a patient still in chronic phase who is resistant to both imatinib and dasatinib would be interferon-alfa or hydroxycarbamide.

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Table 1

Criteria for defining phases of CML

Chronic phase	Accelerated phase (any of the features below)	Blast phase (BP)
None of the criteria for AP or BP have been met	- Blast cells 15-29% in PB or BM - Blast cells plus promyelocytes in PB or BM >30%, with blast cells <30% - Basophils in blood >20% - Persistent thrombocytopenia (<100 X 10^9/L) unrelated to therapy	- Blast cells ≥30% in PB or BM - Extramedullary blast involvement

Notes:

1. The criteria are based on those proposed by the Leukemia-Net (Baccarani et al, 2006)
2. PB, Peripheral blood; BM, Bone Marrow
3. The terms Blastic phase (BP) and Blast crisis (BC) are synonymous
4. This system differs from the WHO proposal in that the finding of new cytogenetic changes in a CP patient does not by itself lead a patient to be classified as AP

Table 2 –

Definitions of response to treatment

Haematologic response (HR)	Cytogenetic Response (CyR)	Molecular response (MolR)
Complete (CHR) Platelets <450 x 10^9/L WBC <10 x 19^9/L Differential: No immature granulocytes and <5% basophils	*Ph-pos* *metaphases* *Complete (CCyR)* 0% *Partial (PCyR)* 1-35% *Minor* 36-65% *Minimal* 66-95%	*Complete* Transcripts not detectable *Major* 0.1%

Notes:

1. The complete and partial cytogenetic response rates may be combined and referred to as the major cytogenetic response (MCyR) rate.

2. A major molecular response is equivalent to a 3-log reduction from a standardised baseline value of 100%.

3. The term 'Transcripts not detected' or 'Transcripts not detectable' is preferred to 'Complete molecular remission'.

4. There is no current agreement as to whether RQ-PCR technology is as sensitive as nested PCR and thus whether the finding of undetectable transcripts by RQ-PCR needs to be confirmed with nested PCR.

Table 4

The various options that can be considered for the patient deemed to have failed intial treatment with imatinib

- Simply increasing the dose of imatinib
- Switching to a second line agent, eg dasatinib, nilotinib, bosutinib, or MK-0457
- Allogeneic stem cell transplantation, with conventional or possibly reduced intensity conditioning
- Classical cytotoxic drugs, eg cytarabine, hydroxycarbamide (hydroxyurea), busulphan, homoharringtonine, decitabine, arsenicals, or interferon-alfa
- Experimental agents, eg downstream signal transduction inhibitors such as farnesyl transferase inhibitors, mTOR inhibitors, PI3K inhibitors
- Autografting with cells collected at diagnosis or after achieving CCyR
- Immunotherapeutic strategies

Table 3   Definitions of failure or sub-optimal response to imatinib

TIME	FAILURE	SUBOPTIMAL RESPONSE	WARNINGS
Diagnosis	NA	NA	- High risk by Sokal or Euro score - Del(9q+) - Additional chromosome abnormalities in Ph-positive cells
3 months	- No hematologic response (HR) (stable disease or disease progression	- Less than Complete HR (CHR)	
6 months	- Less than Complete HR (CHR) - No cytogenetic response (CyR) (Ph+ more than 95%)	- Less than Partial CyR (PCyR) (Ph+ more than 35%)	
12 months	- Less than PCyR (Ph+ more than 35%)	- Less than Complete CyR (CCyR)	- Less than major MolR (MMolR)
18 months	- Less than CCyR	- Less than MMolR	
Any time	- Loss of CHR - Loss of CCyR - Mutation (ie T315I)	- ACA in Ph+ cells - Loss of MMolR - Mutation	- Any rise in transcript level - Other chromosome abnormalities in Ph-negative cells

1. Table slightly modified from Baccarani et al. (2006)
2. The relevance of mutations differs according to the percentage and type of the mutant sub-clone (see text)
3.   For abbreviations see Table 2.