

## Recommendations for the management of adult chronic myeloid leukaemia in South Africa

V J Louw, L Dreosti, P Ruff, V Jogessar, D Moodley, N Novitzky, M Patel, A Schmidt, P Willem

**Introduction.** Chronic myeloid leukaemia (CML) is a chronic myeloproliferative disorder characterised by a chromosomal translocation between the long arms of chromosomes 9 and 12 resulting in the formation of the *BCR-ABL* fusion gene. The management of CML has undergone major changes over the past decade. Novel treatment approaches have had a dramatic impact on patient outcomes and survival. Nevertheless, these outcomes can only be achieved in the context of expert management, careful monitoring of disease response, appropriate management of adverse events and timeous adjustments to therapy when responses are not achieved within stated time frames.

**Aim.** With the advent of novel treatments providing molecular responses, both the monitoring and management of CML have become more complicated. The aim of these recommendations was to provide a pragmatic yet comprehensive roadmap to negotiate these complexities.

**Methods.** Recommendations were developed based on local expert opinion from both the academic and private medical care

arenas after careful review of the relevant literature and taking into account the most widely used international guidelines. About five meetings were held at which these recommendations were discussed and debated in detail.

**Results.** A comprehensive set of recommendations was compiled with an emphasis on diagnosis, investigation, treatment and monitoring of disease. Careful attention was given to circumstances unique to South Africa, funding constraints, availability and access to laboratory resources, as well as the effects of concurrent HIV infection.

**Conclusion.** Most patients with CML can live a reasonably normal life if their disease is appropriately managed. These recommendations should be of value to all specialists involved in the treatment of haematological disorders.

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These recommendations are for the use of Fellows, specialist physicians, clinical haematologists and medical oncologists with an interest in the treatment of haematological disorders.

### 1. Scope

This guideline was developed to address the diagnosis and management of chronic myeloid leukaemia (CML) in the South African setting, with particular reference to the prescribing of *BCR-ABL* tyrosine kinase inhibitors (TKIs), and the management of their side-effects. Special focus is also given to the monitoring of response to treatments, given the constraints and shortage of skills in this area in South Africa. The guideline is endorsed by the South African Society of Haematology.

### 2. Methods

The development of these recommendations was based on local expert opinion, best clinical practice and available treatment options, together with review of the latest international recommendations and recent clinical data. The 2009 International

European LeukemiaNet (ELN) and 2010 National Collaborative Cancer Network (NCCN) guidelines for the diagnosis, monitoring and management of CML, and the major clinical trials for the three TKIs that are registered in South Africa, imatinib, dasatinib and nilotinib, were considered.

### 3. Limitations of the recommendations

These recommendations do not represent all the possible methods of management applicable to all patients; do not exclude any other reasonable methods; and will not ensure successful treatment in every situation. The unique circumstances of each patient, disease stage, co-morbid conditions and treatments available should be taken into account by the responsible physician when deciding on any specific therapy.

### 4. Introduction and overview

Chronic myeloid leukaemia is a disease of the haematopoietic stem cell characterised by a chromosomal translocation between the long arms of chromosomes 9 and 22 which leads to formation of the so-called Philadelphia chromosome. This t(9;22) translocation results in the formation of the *BCR-ABL* fusion gene, which codes for a novel protein tyrosine kinase (TK) that is constitutively activated and therefore leads to increased proliferation of myeloid cells, decreased apoptosis and adhesion, and genetic instability of the leukaemic cells. This genetic instability forms the basis for resistance to treatment and progression of disease.

The incidence of CML is cited at 2/100 000/year with a slight male preponderance; however, local South African incidence or prevalence data are lacking. Since the widespread use of TKIs, the number of patients surviving worldwide has increased greatly, resulting in a progressively increasing prevalence of this disease.

### 5. Diagnosis of CML

Many patients are asymptomatic and are diagnosed incidentally on the basis of a raised white blood cell (WBC) count. Clinical

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features include symptoms such as fatigue, malaise, weight loss, abdominal fullness and early satiety (due to splenomegaly), and rarely bleeding due to platelet dysfunction. Clinical findings may include hepatosplenomegaly, gouty arthritis, pallor, bone tenderness or features of hyperviscosity in patients with a high WBC count (e.g. headaches, visual and neurological disturbances, dyspnoea and angina). Patients should be carefully evaluated for extramedullary disease beyond the liver and spleen, which may have prognostic and staging implications (Table I). Clinical findings, especially spleen size, should be carefully documented for follow-up purposes and for calculation of the Sokal score, which is of prognostic value (online calculator available at [www.roc.se/sokal.asp](http://www.roc.se/sokal.asp)).

## 6. Disease phases

CML occurs in three different phases (chronic phase (CP), accelerated phase (AP), and a blastic phase (BP)). Most patients present in the CP. Classification is either by the European LeukaemiaNet (ELN) or the World Health Organization (WHO) criteria.

## 7. Laboratory investigations

Table II sets out the required laboratory tests for a newly diagnosed patient with CML. These are key to the correct staging of the patient, form the basis for further follow-up, and have direct bearing on prognosis.

## 8. Treatment with tyrosine kinase inhibitors

Before the introduction of the TKIs, the treatment of CML included hydroxyurea, interferon alpha (IFN- $\alpha$ ), low-dose cytarabine and allogeneic haematopoietic stem cell transplantation. With the advent of imatinib, which specifically targeted the TK activity of the oncogenic proteins encoded by *BCR-ABL*, the management of CML changed dramatically. The following sections provide an overview of the available data supporting the use of TKIs in CML.

### 8.1 Imatinib

Imatinib is a selective inhibitor of the BCR-ABL TK. Imatinib induces a complete haematological response (CHR) in 80 - 90% of patients with newly diagnosed CP CML (CP-CML), a complete cytogenetic response (CCyR) in 70 - 80%, and a major molecular response (MMR), i.e. 3-log reduction of *BCR-ABL*: *BCR* or other control gene

levels compared with a standardised pre-treatment level by real-time quantitative polymerase chain reaction (RQ-PCR), or RQ-PCR <0.05 - 0.1%, in 40% of patients.<sup>2</sup>

The landmark IRIS (International Randomized Study of Interferon and STI571) trial results led to the recommendation of imatinib as first-line therapy for patients with CML.<sup>3</sup> The IRIS trial was a phase III,

**Table II. Initial work-up**

### Baseline laboratory investigations

FBC + differential

Urea and electrolytes, liver enzymes, serum LDH, serum urate

Pregnancy test

### BM aspirate and trephine biopsy for:

Morphology, including differential count to determine phase of disease

Assessment of fibrosis

Cytogenetic assessment on BM to determine:

- % Philadelphia-positive cells (preferably 20 metaphases)
- Presence of variant Philadelphia chromosome translocation
- Presence of additional abnormalities, e.g. double Ph, isochromosome 17q, trisomy 8

FISH analysis optional:

- Only done where conventional cytogenetics not available or fails
- Or, to document a *BCR-ABL* positivity for variant translocation and masked Ph

*Note:* If BM material unavailable (e.g. due to marrow fibrosis), analysable metaphases may also be obtained from blood leukocytes

### Real-time RQ-PCR on PB to establish:

- A baseline level
- The transcript type (1 - 2% have atypical *BCR-ABL* fusion products that are undetectable by standard RQ-PCR)

FBC = full blood count; LDH = lactate dehydrogenase; BM = bone marrow; FISH = fluorescence *in situ* hybridisation RQ-PCR = real-time quantitative polymerase chain reaction; PB = peripheral blood.

**Table I. Phases of chronic myeloid leukaemia**

European LeukaemiaNet (ELN) criteria <sup>1</sup>	WHO criteria
<b>Chronic phase (CP)</b>	
None of the criteria for AP or BP met	
<b>Acceleration phase (AP)</b>	
Blast cells in PB or BM 15 - 29%	Blasts 10 - 19% of WBCs in PB and/or nucleated BM cells
Blast cells + promyelocytes in PB or BM >30%; with blast cells <30%	Peripheral blood basophils $\geq$ 20%
Basophils in PB $\geq$ 20%	Persistent thrombocytopenia (<100 $\times$ 10 <sup>9</sup> /l) unrelated to therapy or persistent thrombocytosis (>1 000 $\times$ 10 <sup>9</sup> /l) unresponsive to therapy
Persistent thrombocytopenia (platelets <100 $\times$ 10 <sup>9</sup> /l) unrelated to therapy	Increase in spleen size and increase in WBC unresponsive to therapy
	Cytogenetic evidence of clonal evolution
<b>Blastic phase (BP)</b>	
Blast cells in PB or BM $\geq$ 30%	Blasts $\geq$ 20% of peripheral blood white cells or nucleated bone marrow cells
Extramedullary involvement (excluding liver and spleen)	Extramedullary blast proliferation
	Large foci or clusters of blasts in the bone marrow biopsy specimen

*Note:* Clinical trials often use the ELN criteria while most diagnostic laboratories report the WHO criteria. PB = peripheral blood; BM = bone marrow.

multicentre, randomised, open-label, crossover trial in which 1 106 patients with newly diagnosed CML were randomised to receive initial therapy with either 400 mg imatinib or IFN- $\alpha$  plus low-dose cytarabine.<sup>3</sup> Responses were significantly in favour of imatinib, with a CHR rate at 18 months of 97% versus 69%, a major cytogenetic response (MCyR) rate of 87% versus 34.7%, and a CCyR rate of 72.6% versus 14.5% in the imatinib and low-dose cytarabine plus interferon arms, respectively.<sup>3</sup> These results were obtained despite 90% crossing over from the interferon plus low-dose cytarabine arm to the imatinib arm.<sup>3</sup> After 8 years of follow-up of the IRIS trial, the estimated event-free survival (EFS) and overall survival (OS) rates were 81% and 85%, respectively.<sup>4</sup>

About 10% of patients never achieve a CHR on imatinib by 3 months and about 25% do not achieve a CCyR by 18 months, thus fulfilling the ELN 2009 criteria of treatment failure.<sup>5,6</sup> Treatment failure usually results from the development of mutations in the TK domain of the *BCR-ABL* gene which affects the binding of imatinib to the adenosine triphosphate (ATP) binding site of the *BCR-ABL* protein. About 20% of patients who initially achieve a CHR or a cytogenetic response lose their responses over time with subsequent disease progression.<sup>3</sup> Intolerance to treatment and poor compliance are also reasons for treatment failure and discontinuation.<sup>7,8</sup> To overcome the problem of resistance, novel TKIs have been studied, two of which are commercially available in South Africa, namely nilotinib and dasatinib. South African regulatory authorities have approved both these TKIs for treatment of patients with resistance or intolerance to imatinib.

## 8.2 Dasatinib

Dasatinib is an oral Src and Abl kinase inhibitor with a potent *BCR-ABL* inhibitory effect.<sup>9,10</sup> Approval by the Food and Drug Administration (FDA) for the treatment of all phases of imatinib-resistant CML and Philadelphia (Ph)-positive

acute lymphoblastic leukaemia (ALL) was granted in 2006. This was based on the efficacy and safety findings of the open-label phase 2 START studies (Sarcoma (SRC)/ABL Tyrosine Kinase Inhibitions Activity Research Trials of Dasatinib) aimed at patients resistant or

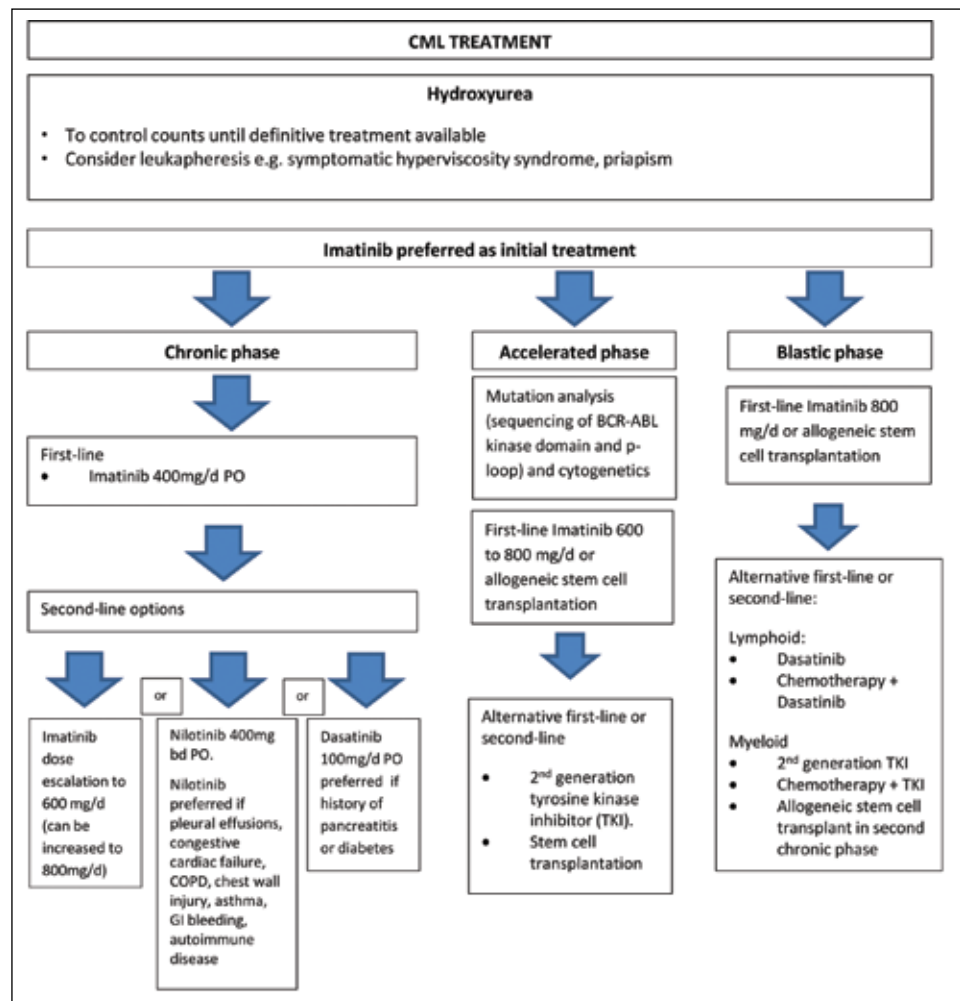


Fig. 1. Treatment of chronic myeloid leukaemia.

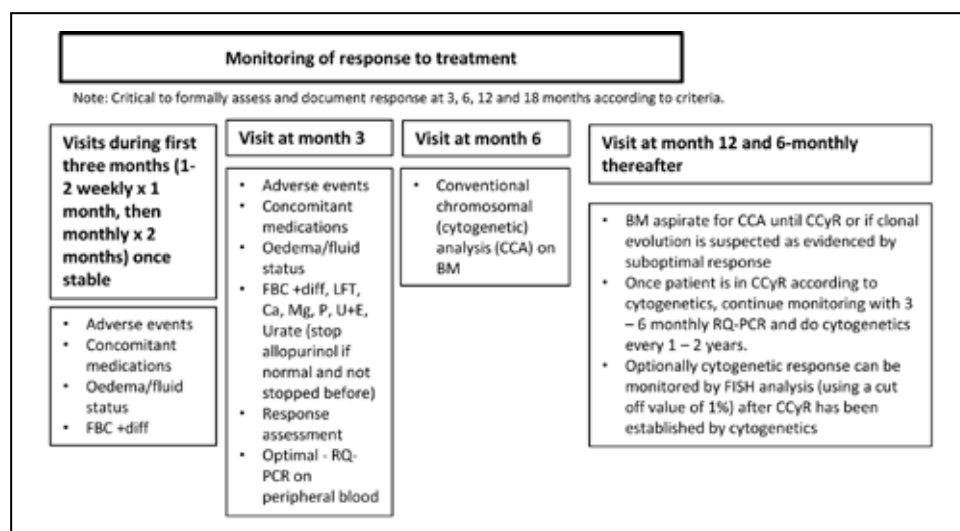


Fig. 2. Monitoring response to treatment in chronic myeloid leukaemia. Note: The recommended monitoring time-frames are for responding patients only. Patients not fulfilling the various response criteria should be evaluated more frequently and offered alternative management.

**Table III. Definitions of response**

<b>Haematological</b> (check every 2 weeks until CHR, then 3-monthly)	Complete (CHR)	WBC <10×10 <sup>9</sup> /l Basophils <5% No myelocytes, promyelocytes, myeloblasts in the differential count Platelet count <450×10 <sup>9</sup> /l Spleen non-palpable
<b>Cytogenetic</b> (check every 6 months until CCyR, then every 1 - 2 years)	Complete (CCyR)	No Ph+ metaphases
	Partial (PCyR)	1 - 35% Ph+ metaphases
	Minor (mCyR)	36 - 65% Ph+ metaphases
	Minimal (minCyR)	66 - 95% Ph+ metaphases
	None (noCyR)	>95% Ph+ metaphases
<b>Molecular</b> (every 3 months once CCyR until MMR, then every 3 - 6 months)	Major (MMR)	Ratio of BCR-ABL to ABL (or BCR or GUS) ≤0.1% on the international scale
	Complete (CMR)	Undetectable BCR-ABL mRNA transcripts by real-time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity >10 <sup>4</sup> )

Note: CHR, CCyR and MMR should be confirmed on 2 subsequent occasions. CCyR is evaluated by morphologic cytogenetics of at least 20 bone marrow metaphases. FISH of peripheral blood cells should be used only if marrow cells cannot be obtained. Molecular response by PCR is assessed on peripheral blood cells.

**Table IV. South African modified ELN recommendations for goals of first-line therapy (imatinib) for CML**

	Optimal response	Failure	Warnings
Baseline	N/A	N/A	Clonal chromosomal abnormalities (CCA)/Ph+
3 months	CHR	Less than CHR	N/A
6 months	At least PCyR (Ph+ ≤35%)	No CyR (Ph+ >95%)	N/A
12 months	CCyR	Less than PCyR (Ph+ >35%)	Less than MMR
18 months	MMR	Less than CCyR	Less than MMR
Any time	Stable or improving MMR	Loss of CHR Loss of CCyR Mutations* CCA/Ph+	CCA/Ph- confirmed loss of MMR

\*BCR-ABL mutations known to be poorly sensitive to imatinib.

intolerant to imatinib.<sup>11-15</sup> In the START-R study, high-dose imatinib (400 mg twice daily) was compared with dasatinib (70 mg twice daily) in 150 imatinib-resistant (to 400 - 600 mg daily) patients in CP CML.<sup>15</sup> Significantly higher response rates were seen with dasatinib when compared with high-dose imatinib at 24 months, with a CCyR rate of 44% versus 18% in the two groups, respectively.<sup>15</sup> These responses were durable, with MCyR maintained in 90% of dasatinib responders compared with 74% of imatinib responders.<sup>15</sup> Evidence from dose optimisation studies led to a change in the recommendations, with 100 mg as a once-daily dose recommended for CML in CP and 140 mg once daily for CML in advanced-phase CML (AP and BP) and Ph-positive ALL.<sup>16,17</sup> The phase III dasatinib versus imatinib study in treatment-naïve CML patients (DASISION) compared the efficacy and safety of dasatinib (100 mg once daily) with imatinib (400 mg once daily) in patients with newly diagnosed CP CML and confirmed a CCyR at 12 months of 77% and 66% ( $p=0.007$ ) with dasatinib and

imatinib, respectively.<sup>18</sup> The impact of these recent findings within the current registered indications, recommendations and current socio-demographic and socio-economic setting in South Africa is still under review. In South Africa, dasatinib remains registered for the treatment of CML, following intolerance or resistance to imatinib or other first-line therapies for CML and Ph-positive ALL.

### 8.3 Nilotinib

Nilotinib is also a second-generation TKI that inhibits the BCR-ABL TK more potently and selectively than imatinib.<sup>6,19,20</sup> Nilotinib was approved by the FDA and the Medicines Control Council (MCC) for treating imatinib-intolerant and resistant patients with CML in CP and AP (but not for BP or Ph-positive ALL). In a phase II open-label study evaluating 280 CP-CML patients who had imatinib resistance or intolerance, MCyR and CCyR rates of 48% and 31%, respectively, were achieved.<sup>21</sup> Responses were found to be durable

**Table V. Managing common imatinib side-effects**

Side-effect	Mechanism	Management
<b>Non-haematological</b>		
Superficial oedema (peri-orbital)	Inhibition of PDGFR in dermal dendrocytes Occurs in >50% of pts Related to dose, older age and females	Dose interruption seldom required Limit salt intake Topical phenylephrine 0.25% Diuretics in severe cases, especially with severe peripheral oedema
Nausea and vomiting	Local irritation gastric mucosa Dose-related	Take imatinib with largest meal of day (2 hours before bedtime in pts with history of oesophagitis or hiatus hernia) Anti-emetics if symptoms persist If on higher dose (600 or 800 mg) – split dose in two
Muscle cramps		Calcium and magnesium supplements High fluid intake
Diarrhoea	Inhibition of c-KIT in interstitial Cajal cells Dose-related	Anti-diarrhoeals, e.g. loperamide Take imatinib with large meal and water
Rash	Inhibition of c-KIT in the skin	Topical steroids effective in majority of cases In severe cases, oral corticosteroids, dose interruptions or occasionally discontinuation may be required
Hepatic toxicity		With grade 2 - 3 toxicities, dose interruption until toxicity is grade 1, followed by resumption of therapy at a reduced dose Alternative therapies should be considered for grade 4 toxicity
Hypophosphataemia	Multiple effects on bone turnover by inhibition of PDGFR	Phosphate replacement if severe
<b>Haematological toxicity</b>		
Neutropenia	Inhibition of c-KIT, which is essential for the development of normal blood cells Suppression of the malignant clone until normal haematopoiesis replaces the marrow	Dose interruption is not recommended for grade 1 - 2 toxicity Grade 3 - 4 toxicity is defined as ANC $<1 \times 10^9/l$ : dose interruption until ANC $1 - 1.5 \times 10^9/l$ , then resume at 400 mg/d if recovery within 2 weeks In the event of recurrent grade 3 - 4 toxicity or delayed recovery, dose reduction to 300 mg Consider growth factors for patients with recurrent or persistent grade 3 - 4 toxicity
Thrombocytopenia	Inhibition of c-KIT, which is essential for the development of normal blood cells Suppression of the malignant clone until normal haematopoiesis replaces the marrow	Dose interruption is not recommended for grade 1 - 2 toxicity Grade 3 - 4 toxicity is defined as a platelet count $<50 \times 10^9/l$ : dose interruption until platelet count is $50 \times 10^9/l$ , then resume at 400 mg/d if recovery within 2 weeks In the event of recurrent grade 3 - 4 toxicity or delayed recovery, dose reduction to 300 mg
Anaemia	Inhibition of c-KIT, which is essential for the development of normal blood cells Suppression of the malignant clone until normal haematopoiesis replaces the marrow	Dose interruption is not indicated for toxicity of any grade Dose reductions may help in patients with chronic anaemia

Note: Toxicity grades according to CTCAE (Common Terminology Criteria for Adverse Events) criteria.  
PDGFR = platelet-derived growth factor receptor.



with long-term follow-up without the development of additional safety issues.<sup>22</sup> Nilotinib was studied in first-line therapy in a phase III study, the Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients (ENESTnd) study, which compared the efficacy and safety of nilotinib (at a dose of either 300 mg or 400 mg twice daily) with that of imatinib (400 mg per day) in patients with newly diagnosed CP-CML.<sup>23</sup> The rates of CCyR by 12 months were significantly higher for nilotinib, namely 80% and 78% in the nilotinib 300 mg twice daily and 400 mg twice daily arms versus 65% in the imatinib 400 mg arm ( $p < 0.001$ ). A significant improvement in the time to progression to AP or blast crisis was seen in the nilotinib arms.<sup>23</sup> In South Africa nilotinib is registered as second-line therapy for CML, following intolerance or resistance to imatinib.

## 9. Management of CML

This should be done by a trained clinical haematologist or oncologist with experience in the management of patients with CML. Fig. 1 outlines the initial treatment of all three phases of CML.

### 9.1 Monitoring response in patients on imatinib

Monitoring of response to TKI therapy is very important (Fig. 2). Reaching specific goals within a given time has direct bearing on patient outcome. The aim is to get the patient to CCyR within 18 months. Table III provides definitions of response and Table IV the criteria against which response is monitored. We believe that one of the most important ways of ensuring that a patient reaches CCyR is by monitoring and acting early when action is required. Failure to do so may jeopardise a patient's chance of having a long-term response. On the basis of the degree of haematological response (HR), cytogenetic response (CyR), and molecular response (MR), and the time when these responses are achieved, the overall response to imatinib can be defined as optimal, suboptimal and failure.

### 9.2 Managing common side-effects of imatinib

Imatinib is generally well tolerated and has a favourable safety profile with an overall low incidence of severe adverse events in newly diagnosed CP-CML patients. The general management of common side-effects are outlined in Table V.

## 10. Pregnancy and breastfeeding

For the management of patients who are pregnant, want to fall pregnant or are breastfeeding, see Table VI.

**Table VI. Pregnancy and breastfeeding**

Pregnancy	Refer to specialised centres
	Discuss with patient in detail
	Multidisciplinary approach is required
	Interferon- $\alpha$ has been used, although there are risks
	Although the risk of fetal abnormalities is low with imatinib, avoidance of imatinib during conception and gestation is recommended
Breastfeeding	Effective contraception is recommended for men and women using TKIs
	Imatinib is secreted in the breastmilk
	Owing to the potential for serious adverse events in the infant, breastfeeding is not recommended

## 11. Human immunodeficiency virus (HIV) infection and CML

The occurrence of CML in association with HIV infection is likely to be coincidental rather than causal. Globally this association is rarely described.<sup>24</sup> However, in South Africa, in the era of the HIV pandemic, it is being observed more frequently (M Patel, *et al.* – unpublished data).

CML in association with HIV presents with atypical and aggressive disease.<sup>24</sup> Both CML and HIV may cause myelosuppression and immunosuppression. Despite this, both chemotherapy/TKIs and combination antiretrovirals (cARVs) have been used safely and effectively. cARVs should be commenced in all patients with HIV-CML, irrespective of the CD4 count (as the CD4 count is usually elevated, mirroring the high white cell count and therefore not a reliable indicator of the stage of HIV in CML).

Drug interactions between cARVs and TKIs such as imatinib may require adjustment of treatment. Imatinib is mainly metabolised by the cytochrome P450 (CYP3A4) iso-enzyme, and concurrent administration of antiretroviral and antimicrobial drugs that induce or inhibit CYP3A4 may lead to drug-drug interactions.

In individuals who harbour both diseases, concurrent treatment with the TKIs (imatinib) and cARVs can result in appropriate control of the CML and HIV infection and long-term survival.

## 12. Role of allogeneic haematopoietic stem cell transplantation in CML

Since the introduction of imatinib in CP-CML, allogeneic stem cell transplantation is no longer considered as first-line treatment. Table VII lists indications for allogeneic stem cell transplantation.

## 13. Summary and conclusions

CML is a chronic myeloproliferative disorder characterised by a chromosomal translocation between the long arms of chromosomes 9 and 12 resulting in the formation of the *BCR-ABL* fusion gene. This gene codes for a novel 210 kD TK leading to myeloid cell over-proliferation, as well as genetic instability that forms the basis of resistance to treatment and progression to accelerated and blastic phases. The management of CML was revolutionised with the advent of imatinib, a small-molecule BCR-ABL TKI, approved in South Africa in 2002, which results in a MCyR in nearly 90% of patients and a CCyR in over 70%.<sup>3</sup> After 7 years of follow-up of the landmark IRIS trial, CCyR has been maintained in 75% of patients with estimated EFS, OS and CML OS (the survival rate looking only at patients who died of CML) rates of 81%, 86% and 93%, respectively.

Unfortunately, up to 25% of patients fail to achieve a MMR by 18 months, and a further 20% lose their responses, primarily owing to resistance to imatinib. Nilotinib, an imatinib analogue, and dasatinib,

**Table VII. Indications for stem cell transplantation in advanced disease**

1. At diagnosis in AP or BP as first- or second-line therapy, preferably after imatinib
2. 2nd or subsequent CP
3. T315I mutation
4. Imatinib failure in patient with good transplant risk score (EBMT risk score 0 - 2) and who is not a good candidate for a 2nd-generation TKI
5. All patients failing a 2nd-generation TKI

EBMT = European Group for Blood and Marrow Transplantation.

an Src and Abl TKI, overcome imatinib resistance in most patients, except those with T315I mutations. Dasatinib has also been approved for patients in blast crisis. Nilotinib and dasatinib also show better molecular responses than imatinib in newly diagnosed patients, but this indication has not been approved in South Africa. Allogeneic stem cell transplantation plays a role in patients in subsequent CP after a blast crisis and with T315I mutations, although novel agents such as ponatinib may overcome resistance in these otherwise TKI-resistant patients.

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Disclosure of financial interest		Prof. L M Dreosti	Prof. N Novitsky	Dr A Schmidt	Prof. V Louw	Prof. M Patel	Prof. P Ruff	Dr P Willem
Novartis	Research grants/donations	Yes	Yes	No	Yes	Yes	Yes	Yes
	Honoraria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Consulting fees	Yes	Yes	No	Yes	No	Yes	No
	Congress attendance/assistance	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bristol Myers Squibb	Research grants/donations	Yes	Yes	No	Yes	Yes	Yes	No
	Honoraria	Yes	Yes	No	Yes	Yes	No	Yes
	Consulting fees	Yes	Yes	No	Yes	No	No	No
	Congress attendance/assistance	No	Yes	Yes	Yes	Yes	No	No
Pfizer	Research grants/donations	Yes	Yes	No	Yes	Yes	Yes	No
	Honoraria	Yes	No	No	No	No	Yes	No
	Consulting fees	Yes	No	No	No	No	No	No
	Congress attendance/assistance	Yes	No	No	No	Yes	Yes	No

## References

- Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2006;108:1809-1820.
- Kantarjian HM, Talpaz M, O'Brien S, et al. Survival benefit with imatinib mesylate versus interferon-alpha-based regimens in newly diagnosed chronic-phase chronic myelogenous leukemia. *Blood* 2006;108:1835-1840.
- 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* 2003;348:994-1004.
- Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. American Society of Hematology Annual Meeting 2009. <http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1126?maxtooshw=&hits=10&RESULTFORMAT=&fulltext=deininger&searchid=1&FIRSTINDEX=0&volume=114&issue=22&resource=HWCIT> (accessed 13 September 2011).
- Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355:2408-2417.
- Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 2009;27:6041-6051.
- Apperley JF. Part I: mechanisms of resistance to imatinib in chronic myeloid leukaemia. *Lancet Oncol* 2007;8:1018-1029.
- Apperley JF. Part II: management of resistance to imatinib in chronic myeloid leukaemia. *Lancet Oncol* 2007;8:1116-1128.
- Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 2004;305:399-401.
- O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res* 2005;65:4500-4505.
- Cortes J, Rousselot P, Kim DW, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007;109:3207-3213.
- Guilhot F, Apperley J, Kim DW, et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007;109:4143-4150.
- Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007;109:2303-2309.
- Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007;110:2309-2315.
- Kantarjian H, Pasquini R, Levy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). *Cancer* 2009;115:4136-4147.
- Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. *J Clin Oncol* 2008;26:3204-3212.
- Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. *Blood* 2009;113:6322-6329.
- Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2010;362:2260-2270.
- Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006;354:2542-2551.
- Jabbour E, Cortes J, Kantarjian H. Novel tyrosine kinase inhibitors in chronic myelogenous leukemia. *Curr Opin Oncol* 2006;18:578-583.
- Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007;110:3540-3546.
- Jabbour E, Cortes J, Kantarjian H. Long-term outcomes in the second-line treatment of chronic myeloid leukemia: a review of tyrosine kinase inhibitors. *Cancer* 2011;117:897-906.
- Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010;362:2251-2259.
- Tsimberidou A-M, Medina J, Cortes J, et al. Chronic myeloid leukemia in a patient with acquired immune deficiency syndrome: complete cytogenetic response with imatinib mesylate: report of a case and review of the literature. *Leuk Res* 2004;28:657-660.

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