REVIEW ARTICLE

Chronic Myelogenous Leukemia

Treatment and Monitoring

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SUMMARY

Background: The treatment options for bcr-abl positive chronic myelogenous leukemia (CML) include chemotherapy, immune therapy, allogeneic stem cell transplantation, and molecular therapy. The tyrosine kinase inhibitor imatinib was approved for the treatment of CML in 2002. Data from clinical trials allow a comparison of treatment options.

Methods: The literature on the treatment and monitoring of CML was selectively reviewed. A total of 94 original articles were analyzed, along with the recommendations of an international expert committee and the medical societies. This review is current as of November 2009.

Results: In a clinical phase 3 trial of imatinib treatment for patients in the chronic phase of CML, the rates of progression-free and overall survival at 6 years were 93% and 88%, respectively. Thus, imatinib is clearly superior to interferon-alpha, hydroxyurea, and busulfan with respect to survival. Allogeneic stem-cell transplantation is only a fall back option because of transplantation-associated mortality. One in four patients in the chronic phase of CML has an inadequate cytogenetic response to imatinib and therefore requires a change of treatment. Most imatinib-resistant patients in the chronic phase of CML go into remission again after switching to one of the new tyrosine kinase inhibitors, dasatinib and nilotinib.

Conclusion: Imatinib is now the standard initial first-line treatment for CML in the chronic phase. Regular hematologic and cytogenetic monitoring during treatment is indispensable so that patients with an inadequate response can be identified.

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Recommendations for the management of chronic myelogenous leukemia (CML) have been developed by an international team of experts (1, 2). These recommendations are the basis for treatment recommendations and guidelines (3, 4). Imatinib was approved for the treatment of bcr-abl-positive CML in 2002 and is currently regarded as the standard initial treatment for chronic-phase patients. The recommendations for the treatment and monitoring of CML are often not observed in practice. This means that for many patients the chance of long-lasting remission is irretrievably lost. Two other abl kinase inhibitors, dasatinib and nilotinib, have also been approved for the treatment of imatinib resistant or intolerant CML. This makes CML management more complex. The aim of this overview is to provide an aid to CML management on the basis of existing recommendations and in the light of current trial results. For this purpose, the authors carried out a selective search of the literature, including publications which examine the following aspects:

- Clinical trials on treatment and monitoring
- Prognostic implications of response during imatinib treatment
- Clinical trials of dasatinib or nilotinib in cases of resistance or intolerance to imatinib.

In view of the major significance of imatinib for the development and clinical research of new active substances in oncology, this overview also seems suitable for providing doctors not directly involved in treating CML with a general outline of treatment options.

Background information

CML is a neoplastic disease of the hematopoietic stem cells. Its incidence is 2 per 100 000/year. The peak age for the disease is 50 to 55 (e1). The Philadelphia chromosome (e2), the product of a translocation of chromosomes 9 and 22 (e3), is characteristic of CML. The resulting fusion protein acts as an active kinase. Kinase inhibitors such as imatinib block the activity of bcr-abl (e4, e5). CML is one of the few malignant diseases triggered by a single oncogene (bcr-abl) (e6, e7). This is the reason for the excellent efficacy of molecularly targeted CML therapy. Diagnosis requires evidence of bcr-abl translocation via cytogenetics, polymerase chain reactions (PCRs) or Western blot tests. CML is usually diagnosed in the initial, chronic phase (CP), which if left untreated advances to an accelerated phase (AP) after three to five years, and finally a blast crisis

(BC). Leukocytosis of more than 100 000/µL with continuous left shift leading to myeloblasts or promyelocytes and splenomegaly are characteristic of the chronic phase. The features of the accelerated phase are as follows:

- Increased numbers of blast cells in the blood or bone marrow
- Increased or decreased platelet count
- Increased numbers of basophils in the peripheral blood or
- Other chromosome anomalies (e8).

The blast crisis, with increased blast cell numbers (≥20%) in the blood or bone marrow, matches the clinical picture of acute leukemia. Monitoring of CML during therapy includes measuring bcr-abl levels in the blood and bone marrow, as well as blood counts. This is why three separate levels of response are distinguished (*Figure 1*, *Table 1*) (1, e9).

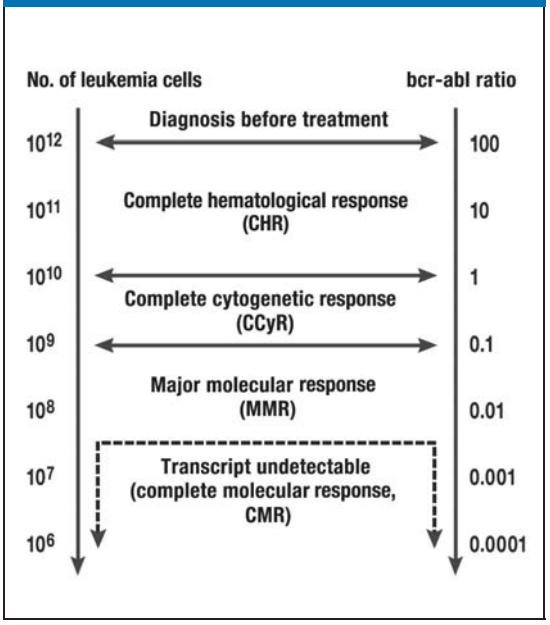
Chronic-phase treatment

During the chronic phase (CP), CML can be treated with imatinib (an abl kinase inhibitor), interferon alpha (IFN, sometimes in combination with low doses of cytarabine, a cytostatic), hydroxyurea (a cytostatic), or allogeneic stem cell transplantation. Hydroxyurea can achieve a hematological response but not a cytogenetic response (e10, e11), so nowadays hydroxyurea is used for initial or palliative cytoreduction. IFN therapy with or without cytarabine can achieve a hematological response in 70% to 80% of cases, and a complete cytogenetic response (CCyR) in 5% to 15% (e12–e15). In a meta-analysis, IFN showed better survival figures than hydroxyurea or busulfan (5-year survival 57% versus 42%) (e16). IFN with or without cytarabine was therefore used as conventional standard therapy for the chronic phase at the end of the 1990s.

Imatinib was developed as an ATP-competitive inhibitor of the tyrosine kinases PDGFR, cKit and abl (see *Glossary*) (e4, e5) and has been approved for the treatment of CML since 2002. In a phase II trial of imatinib 400 mg per day in CP patients with resistance or intolerance to IFN, 96% of patients achieved a complete hematological response (CHR) and 57% achieved CCyR (5). Progression-free survival at six years was 61%, overall survival 76%.

A phase III randomized trial of first-line therapy for CP of imatinib 400 mg per day demonstrated better hematological, cytogenetic, and molecular response figures than for IFN plus cytarabine (6, 7). After 19 months, the CCyR rate with imatinib was 76%, compared to 15% for IFN plus cytarabine (6). After six years, 63% of patients were still in CCyR and receiving the imatinib trial medication (8). In the IFN plus cytarabine treatment arm, 58% of patients had switched to the imatinib arm after 19 months, 43% because of side effects. These were mainly fatigue, depression, muscle or joint pains, neutropenia, and thrombocytopenia (6). This high crossover rate (65% after five years) makes it harder to compare the two arms of the trial, but comparison of the imatinib arm and the IFN plus cytarabine

FIGURE 1



Relationship between leukemia burden, response and number of bcr-abl transcripts in the peripheral blood of CML patients (adapted according to [1] and [15]). When the disease burden decreases, the first change is that the blood count returns to normal (hematological response). Cytogenetic response documents the decrease in Philadelphia-positive metaphases in the bone marrow. Molecular response demonstrates the decrease in bcr-abl transcripts in the peripheral blood or bone marrow. After a complete cytogenetic response (CCyR) has been achieved, bcr-abl monitoring is required, using quantitative real-time PCR (qRT-PCR). Molecular response is expressed as the ratio of bcr-abl to control genes (bcr-abl ratio) or as the "log reduction" in comparison to a standard (14). CMR, complete molecular response; bcr-abl transcripts not detectable, i.e. qRT-PCR and nested PCR negative).

TABLE 1

Definitions of response*[1]

Definition	Monitoring (CP CML, imatinib therapy)	
CHR (complete hematological response)	– WBC <10 G/L – Platelets <450 G/L – No granulocyte precursors in differential blood count – <5% basophils (all parameters are for peripheral blood) – Spleen not palpable	Every 2 weeks until CHR, then every 3 months
Cytogenetic response (bone marrow)	– Complete (CCyR): 0% Ph+ – Partial (PCyR): 1–35% Ph+ – Minor CyR: 36–65% Ph+ – Minimal CyR: 66–95% Ph+ – No CyR: >95% Ph+	Months 3 and 6, then every 6 months until CCyR achieved and confirmed, then every 12 months*[2]
Molecular response (qRT-PCR, peripheral blood)	– Complete (CMR) not detectable – Major (MMR) bcr-abl/control gene – ≤0.10	Every 3 months, every 6 months with CCyR + MMR

*[1]Current recommendations for monitoring chronic-phase CML during imatinib therapy; modified according to the recommendations of the European Leukemia Net (ELN) (1, 2, 14–16).

*[2] After confirmed CCyR, cytogenetic monitoring is recommended every 12 months, provided regular molecular monitoring cannot be guaranteed, and should always be carried out in the event of suboptimal response or treatment failure or unexplained anaemia, leukocytopenia and/or thrombocytopenia.

Ph, Philadelphia chromosome; G, giga

arm of another phase III trial shows better figures for imatinib after as little as three years: progression-free survival (PFS) of 90% versus 82%, and survival of 92% versus 84% (9). These trial results established imatinib 400 mg per day as the standard treatment for chronic-phase CML (1–4) and were also confirmed outside trials (10).

The only possible cure for CML today is allogeneic stem cell transplantation (e10, e17–e19). In the early CP, the 5-year survival after allogeneic transplantation is between 25% and 70% (1, e20–e22). This compares to a 6-year survival rate of 88% with imatinib (8). There are no randomized clinical trials which allow direct comparison of the two forms of therapy. Because of transplantation-associated morbidity and mortality, as well as efficacy and tolerability, the current consensus is that imatinib is the first-line therapy of choice for the chronic phase (1–4). One indication for allogeneic stem cell transplantation is resistance to imatinib treatment and newer tyrosine kinase inhibitors, or progression to the accelerated phase or blast crisis.

Side effects of imatinib

Overall, imatinib is a very well-tolerated drug. Serious side effects (Grade 3–4) mainly affect hematopoiesis and are partly caused by its anti-leukemia effect. The most common side effects are neutropenia (17% in CP, up to 64% in BC) (11, e23, e24), thrombocytopenia (9% in CP, up to 62% in BC) (11, e23, e24), elevated liver enzymes (5% in CP) (11) and fluid retention (5.8% in BC) (e23). Other relatively common side effects (>10% of patients) are mostly mild (Grade 1) or moderate (Grade 2). These include fluid retention (11% to 60%), nausea (50% to 65%), vomiting (17% to 49%), abdominal pain (10% to 37%), muscle cramps (25% to 49%), musculoskeletal pains (12% to 47%), fatigue (8% to 39%), skin rashes (22% to 40%), diarrhea (24% to 45%), and headaches (10% to 37%). Interestingly, these side effects tend to appear in the first two years of treatment, and side effects become significantly less frequent after this period (6, 11, e23, e24). Termination of imatinib treatment because of side effects is rare, with figures of between 3% and 5% in clinical trials (8, e23, e24). A rare but potentially dangerous side effect is congestive heart failure, which is observed in 0.2% to 0.6% of cases (e25–e29). Current recommendations should be observed for the management of imatinib side effects (4, 12, 13). Interactions with concomitant medication should be reviewed paying particular attention to active substances which induce or inhibit CYP4503A4/5 (4, 12, 13). Grapefruit and starfruit consumption can increase plasma concentrations of imatinib (4, 12, 13).

Monitoring during the chronic phase

Regular monitoring is needed to ascertain promptly whether patients are responding well to treatment. Recommendations for monitoring have been developed (*Tables 1 and 2*) (1–4, 14–16). With first-line imatinib therapy, achieving hematological and cytogenetic responses after 3, 6, and 12 months is prognostically

TABLE 2

Definitions of treatment targets and treatment failure*[1]

Time lapse	Resistance	Suboptimal response	Treatment target
3 months	No CHR	No cytogenetic response (Ph+ >95%)	CHR, minor CyR (Ph+ ≤65%)
6 months	No cytogenetic response (Ph+ >95%)	No PCyR (Ph+ >35%)	PCyR (Ph+ ≤35%)
12 months	No PCyR (Ph+ >35%)	PCyR (Ph+ 1% – 35%)	CCyR (Ph+ 0%)
18 months	No CCyR (Ph+ ≥1%)	No MMR (i.e. bcr-abl/control gene ratio >0.10)	MMR
Any time	– Loss of CHR – Loss of CCyR – Evidence of bcr-abl mutation*[2] – ACA in Ph+ cells	– Loss of MMR – Evidence of bcr-abl mutation*[2]	

*[1](Optimal response), suboptimal response and resistance (treatment failure) to imatinib treatment in chronic-phase CML; modified according to the recommendations of the European Leukemia Net (ELN) (1).
Definitions of hematological (CHR), cytogenetic (PCyR, CCyR) and molecular (MMR) response *(Table 1)*.
ACA: additional chromosomal abnormalities in bcr-abl-positive (Ph+) cells in cytogenetics.
bcr-abl mutation: resistance mutation in the bcr-abl gene.
Binding of the kinase inhibitor may be impaired by the resulting amino acid exchange in the protein. This may reduce efficacy.
*[2] The evidence of a mutation of the bcr-abl kinase domains with no residual sensitivity to imatinib determines therapy failure.
Evidence of a mutation of the bcr-abl kinase domain with residual sensitivity to imatinib determines suboptimal response.

relevant to progression-free and overall survival (9, 11, 17, 18). If treatment is continued without cytogenetic response, there is a danger of the disease progressing to the accelerated phase or blast crisis. Failure to achieve CCyR after 12 months was associated with lower survival figures at 5 years (98% versus 86%) in one trial (18). Complete molecular response (CMR) reflects a small disease burden (*Figure 1*), but cannot be considered a cure. If imatinib therapy is halted during CMR, half of patients suffer molecular relapse, and also cytogenetic and hematological relapse if treatment is not resumed (e30–e35).

Treatment of advanced CML

Treatment options include imatinib, cytostatic mono- or combination therapy, and allogeneic stem cell transplantation. In patients with CML in AP or BC, response rates with imatinib in phase II trials were lower than for the CP, but still significantly better than with conventional chemotherapy (e23, e24, e36–e38). With imatinib 400–600 mg, the survival rate for AP was 53% at 4 years and 43% after 7 years (e36, e37). For CML in BC, survival with imatinib 600 mg per day in a phase II trial was 11% after 3 years (e38). For advanced CML, the recommended dose of imatinib is 600 mg per day. Allogeneic stem cell transplantation should be attempted immediately for patients in BC (1, 3, 4, e38). For patients in AP, there is a correlation between CCyR achieved with imatinib 600 mg per day (approx. 20% of patients [e37]) and survival for more than 5 years (e36, e37). With close monitoring, these patients should receive allogeneic transplantation if cytogenetic or hematological response is lost.

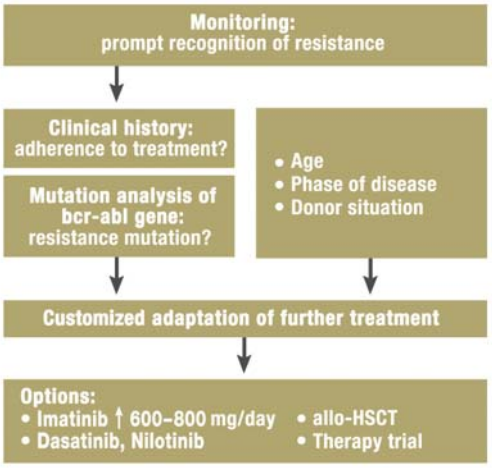
Imatinib resistance: frequency

Primary resistance to imatinib means that a hematological or cytogenetic response has not been achieved after a specific length of time (*Table 2*). In first-line therapy for the chronic phase, primary resistance to imatinib is associated with significantly worse survival rates (9, 11, 17, 18). Primary hematological resistance to imatinib occurs during the early CP in less than 5% of cases (6, e47). Primary cytogenetic resistance to imatinib is observed in 3% to 18% after 6 months (24, 18), 15% to 27% after 12 months (11, 18), and 23% to 49% after 18 months (9, 18). Secondary resistance is defined as the loss of previously achieved hematological or cytogenetic responses and progression to AP or BC. With imatinib first-line therapy for the chronic phase in a phase III trial, the yearly rate for secondary resistance and death from the second year (7.5%) to the sixth year (0.4%) fell steadily (8). In advanced CML, primary hematological resistance to imatinib is significantly more common, affecting 18% to 30% of patients in AP and 60% of patients in BC. At four years the resistance rates are 45% to 70% (AP) and 90% (BC) of cases (e36, e37, e39–e42).

Imatinib resistance: causes

One common cause of insufficient response is poor adherence to treatment (e43). Interruptions to treatment and dose reductions must be avoided. When there is

FIGURE 2



Customized treatment plan: proposed action in the event of clinical resistance to imatinib in CML patients (1–4, 18). Mutation analysis of the bcr-abl gene serves as evidence of mutations which may cause resistance to imatinib, dasatinib and/or nilotinib (14)

resistance, there are often mutations of the bcr-abl kinase domain (e44–e49). These affect the binding of imatinib. There may also be additional cytogenetic abnormalities (e46, e50, e51) or an amplification of the bcr-abl gene (e44, e52). Differences in pharmacokinetics may promote resistance (e53–e55). Different resistance mechanisms may coexist and interact with each other (e56–e58).

Action to take in the event of suboptimal response or resistance

If there is suboptimal response or resistance to imatinib in CP after 3, 6, or 12 months (*Table 2*), progression-free and overall survival rates are significantly lower (9, 11, 17, 18). This means the treatment must be changed. Increasing the dose to 600–800 mg can improve the quality of response (e59–e63). If increasing the dose has no effect, the patient should be switched to another approved abl kinase inhibitor (dasatinib, nilotinib) (2–4). Mutation analysis of the bcr-abl gene should be carried out if there is resistance or a reproducible increase in bcr-abl transcripts (1–4, 14, e64). Patients with a strongly imatinib-resistant mutation do not generally benefit from a higher dose of imatinib (e63). In such cases patients should be switched to nilotinib or dasatinib, provided these have an effect on the mutation (2–4, e65). In patients with T315I mutation, none of the approved kinase inhibitors is effective (e44, e66, e67). The options available in such cases are allogeneic stem cell transplantation or participation in a therapy trial (*Figure 2*) (1, 4, 9, 18). Substances which are active against bcr-abl/T315I are currently being tested in clinical trials. In the event of progression to AP or BC, dasatinib or nilotinib generally achieve only a short-term response, and allogeneic stem cell transplantation should therefore be attempted (4, 19, e68, e69).

Clinical results with approved 2nd-generation tyrosine kinase inhibitors

Dasatinib has been approved for the treatment of all phases of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), in cases which are resistant or intolerant to imatinib. Nilotinib has been approved for patients with CML in CP or AP who are intolerant or resistant to imatinib. Both substances, like imatinib, act as ATP competitors. Phase II trials successfully recorded clinical activity in imatinib-resistant CML for both substances (20–25, e70–e72).

Dasatinib: chronic phase

In a phase II trial involving CP with resistance or intolerance to imatinib, hematological and cytogenetic responses were successfully achieved using dasatinib at a dose of 2 x 70 mg (at 15 months: CHR 91%; CCyR 40% with resistance, 75% with intolerance) (20). At 15 months the overall survival rate was 96%, and progression-free survival (PFS) 90%. The rate of Grade 3–4 neutropenia was 49%, and Grade 3–4 thrombocytopenia 48%. The main non-hematological Grade 3–4 toxicities were dyspnea (5%) and pleural effusions (6%). In a randomized phase II trial, dasatinib 2 x 70 mg proved more effective than imatinib 2 x 400 mg in chronic-phase CML with resistance to imatinib 400 mg (PFS at two years: 86% versus 65%) (e72). A phase III trial showed comparable efficacy and better tolerance for a dose of 1 x 100 mg (24). This dose is therefore recommended for the treatment of chronic-phase CML with resistance or intolerance to imatinib.

Dasatinib: advanced CML

A phase II trial involving dasatinib 2 x 70 mg in patients with accelerated-phase CML and resistance or intolerance to imatinib yielded CHR and CCyR rates of 45% and 32% respectively at 14 months (21). Overall survival at one year was 82%, and PFS 66%. In a phase III trial, dasatinib 1 x 140 mg showed significantly fewer pleural effusions than 2 x 70 mg, with the same efficacy. This former dose is therefore recommended for patients with accelerated-phase CML and resistance or intolerance to imatinib (e73). In the event of BC and resistance or intolerance to imatinib, hematological and cytogenetic responses were demonstrated with dasatinib (22). However, PFS was less than 6 months, and overall survival less than one year. The recommended dose in such cases is 2 x 70 mg per day.

Nilotinib: chronic phase

In chronic-phase CML patients with resistance or intolerance to imatinib, a phase II trial involving nilotinib 2 x 400 mg achieved hematological and cytogenetic responses (at 6 months, CHR was 74%; CCyR 30% for resistance and 35% for intolerance) (23). The PFS rate at 12 months was 78%, and the overall survival rate was 95%. 29% of patients suffered Grade 3–4 neutropenia and thrombocytopenia. Grade 3–4 non-hematological toxicities included increased bilirubin (8%), blood glucose (13%), and lipase (15%) levels.

Nilotinib: advanced CML

In the AP with resistance or intolerance to imatinib, a phase II trial involving nilotinib 2 x 400 mg achieved CHR in 26% of patients after 6 months, and CCyR in 16% (25). After 12 months the PFS rate was 57% and the overall survival rate was 79%. In patients with BC and resistance or intolerance to imatinib, hematological and cytogenetic responses were observed in some patients in a phase II trial involving treatment with nilotinib 2 x 400 mg (Giles F, Larson R, Kantarjian H et al.: Nilotinib in patients [pts] with Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia in blast crisis [CML-BC] who are resistant or intolerant to Imatinib. 49th ASH Annual Meeting, 2007, Atlanta. Blood; 110: 310A). The overall survival rate in this trial at 12 months was 42%.

Treatment

There are still open questions regarding chronic myelogenous leukemia.

- The prognostic significance of 'suboptimal response' and 'resistance' or long term 'treatment failure' during imatinib therapy are currently being examined in trials. This will affect future recommendations and guidelines for the treatment and monitoring of chronic-phase chronic myelogenous leukemia.
- Can the results of imatinib in first-line therapy for chronic-phase CML be further improved? Planned and ongoing phase III trials compare imatinib 400 mg per day with imatinib plus interferon alpha, imatinib 800 mg per day and the alternative tyrosine kinase inhibitors dasatinib, nilotinib, and bosutinib.
- Could imatinib be curative in some patients? Ongoing trials are investigating whether stopping imatinib therapy in chronic-phase patients with a stable, complete molecular response leads to relapse in all patients. However, controlled discontinuation of imatinib should only take place within clinical trials.
- It is not yet known whether lasting remission can be achieved in imatinib-resistant CML with the approved second-line substances dasatinib and nilotinib.

Information (in German) on ongoing trials can be found on the official website, Akute und Chronische Leukämien ('Acute and Chronic Leukemias'): http://www.kompetenznetz-leukaemie.de/content/home.

Monitoring chronic-phase CML: criteria for defining relapse during treatment

For criteria for defining hematological, cytogenetic and molecular response, see also *Tables 1 and 2*.

- Hematological relapse: loss of CHR (differential blood count, size of spleen); corresponds to treatment failure or imatinib resistance
- Cytogenetic relapse: loss of CCyR (evidence of Ph+ metaphases in bone marrow); corresponds to treatment failure or imatinib resistance

GLOSSARY

abl:	Abelson kinase (chromosome 9), part of Philadelphia translocation t(9;22) and therapy target structure for the tyrosine kinase inhibitors imatinib, nilotinib and dasatinib
AP:	Accelerated phase of CML
BC:	Blast crisis of CML
bcr-abl:	Gene or protein product of Philadelphia translocation t(9; 22)
CCyR:	Complete cytogenetic response (see *Table 1* for definition)
CHR:	Complete hematological response (see *Table 1* for definition)
CML:	Chronic myelogenous leukemia
CMR:	Complete molecular response (see *Table 1* for definition)
CP:	Chronic phase of CML
IFN:	Interferon alpha
MCyR:	Major cytogenetic response (see *Table 1* for definition)
MMR:	Major molecular response (see *Table 1* for definition)
PCyR:	Partial cytogenetic response (see *Table 1* for definition)
PDGFR:	Platelet-derived growth factor receptor
PFS:	Progression-free survival (no progression in AP/BC)
Ph+ ALL:	Philadelphia chromosome-positive acute lymphatic leukemia
qRT-PCR:	Quantitative real-time polymerase chain reaction

KEY MESSAGES

- The standard treatment for chronic-phase CML is long-term imatinib therapy at a dose of 400 mg per day. Interruptions to treatment and dose reductions must be avoided. The aim of treatment is lasting complete cytogenetic response.
- Regular monitoring of disease activity is essential, to identify patients with insufficient response to imatinib (suboptimal response/resistance).
- Insufficient response to imatinib is associated with lower progression-free and overall survival rates. Unless changes are made to treatment, there is a risk of the disease advancing to the accelerated phase or blast crisis.
- If there is insufficient response to imatinib, the patient should be referred to a specialist center. The possible options are a higher dose of imatinib, nilotinib, dasatinib, allogeneic transplantation and participation in a therapy trial, depending on the resistance mechanism, age, disease phase, and donor situation.
- Dasatinib and nilotinib are abl kinase inhibitors which have been approved as second-line therapy. Clinical trials show good efficacy and tolerability of both substances in CML patients with resistance or intolerance to imatinib.

- Molecular relapse: loss of MMR (increase in bcr-abl/control gene ratio>0.10 in qRT-PCR in the peripheral blood); corresponds to suboptimal response to imatinib.

When there is increased disease activity during treatment, the next stage is generally loss of molecular response, followed by loss of cytogenetic and eventually also hematological response (*Figure 1*).

Conflict of interest statement
Both authors are members of the Novartis Advisory Board.

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REVIEW ARTICLE

Chronic Myelogenous Leukaemia

Treatment and Monitoring

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