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Chronic myeloid leukemia treatment guidelines: Brazilian Association of Hematology, Hemotherapy and Cell Therapy. Brazilian Medical Association Guidelines Project - 2012

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Chronic myeloid leukemia treatment guidelines: Brazilian Association of Hematology, Hemotherapy and Cell Therapy. Brazilian Medical Association Guidelines Project – 2012

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Introduction

The guidelines project is a joint initiative of the *Associação Médica Brasileira* and the *Conselho Federal de Medicina*. It aims to bring together information in medicine to standardize conduct in order to help decision-making during treatment. The data contained in this manuscript were prepared by and are recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular*. Even so, all possible conducts should be evaluated by the physician responsible for treatment depending on the patient's setting and clinical status.

Description of the method used to gather evidence:

These guidelines were drafted after constructing 19 questions relevant to the diagnosis and treatment of Chronic myeloid leukemia (CML). The questions were structured using the PICO (patient-intervention-comparison-outcome) methodology, thus enabling the creation of strategies to search for evidence (Appendix 1) in the main scientific electronic databases (Medline/PubMed, Embase, Lilacs/SciELO, Cochrane Library, PreMEDLINE via OVID). Moreover a manual search for evidence in dissertations and theses was carried out (*Biblioteca Digital de* Teses *e Dissertações do Instituto Brasileiro de Informação em Ciência e Tecnologia* – BDTD/IBICT). Evidence was selected by critical evaluation using discriminatory instruments (scores) according to the category of question: diagnosis (Quality in Diagnostic and Screening tests - QADAS) or therapy (JADAD for randomized clinical trials and Newcastle-Ottawa scale for non-randomized studies). After identifying potential studies to substantiate recommendations, the level of evidence and degree of recommendation were calculated using the classification of Oxford (available at www.cebm.net).

Summary of the degree of recommendation and level of evidence:

A: Major experimental and observational studies.
B: Minor experimental and observational studies.
C: Case reports (non-controlled studies).
D: Opinion without critical evaluation based on consensus, physiological studies or animal models.

Aims

To set parameters for clinical diagnosis, evaluate severity and standardize treatment, maintenance and monitoring options for CML patients. The target audience of these guidelines is the hematologist with the aim of contributing to decision making in the diagnosis and treatment of CML.

What are the diagnostic criteria for Chronic myeloid leukemia?

The diagnosis of CML is based on leukocytosis and often also thrombocytosis, and on the differential blood count (immature granulocytes, metamyelocytes, myeloblasts and basophilia). Diagnosis depends on the identification of the Philadelphia chromosome (22q) resulting from the t(9;22)(q34;q11) resulting in the head to tail fusion of Breakpoint Cluster Region (BCR) and the Abelson Murine Leukemia (AML) genes or identification of the result of this translocation in peripheral blood or bone marrow cells. In some cases, the Philadelphia chromosome cannot be detected and diagnosis is made by molecular methods. The typical clinical course has three stages: the chronic phase, the accelerated phase and the blast crisis phase. Most diagnoses are made in the chronic phase. The accelerated phase is defined as

the presence of 1% to 19% blasts in the blood or bone marrow, basophils > 20%, thrombocytosis or thrombocytopenia not related to therapy and clonal evolution in cytogenetic evaluation. The blast crisis phase is characterized by blasts > 20% of peripheral blood white cells or extramedullary blast proliferation[1-3](D).

Recommendation: Diagnosis of CML depends on the identification of the Philadelphia chromosome or the BCR-ABL rearrangement.

Is there any difference in the prognosis of CML patients with p210 e13a2(b2a2) and e14a2(b3a2) or (e1a2) p190 rearrangements?

The prevalence of the e1a2 BCR-ABL fusion transcript in CML patients is 1%. This rearrangement is associated with decreased therapeutic response to tyrosine kinase inhibitors (TKIs) as complete hematologic response is attained in only 30% of cases, complete cytogenetic response in 20% (3 to 18 months) and major molecular response in 10% of cases. Progression to other phases (accelerated or blast crisis) occurs in 60% of chronic phase patients[4](C).

The response of treatment-naïve CML patients to imatinib treatment is different for the b3a2(e14a2) and b2a2(e13a2) transcripts. In 12 months of treatment, patients with the b3a2(e14a2) transcript have a 29% increase in complete cytogenetic response, which is faster, and greater disease-free survival[5](B).

In CML patients on imatinib treatment for six months, the number of b2a2(e13a2) transcripts is lower when compared to the number of b3a2(e14a2) transcripts, suggesting greater sensitivity of the b2a2(e13a2) transcripts to imatinib and consequently prognosis is better[6](B).

Imatinib treatment in chronic-phase CML patients with the BCR-ABL b2a2(e13a2) transcript has better results compared to those with the b3a2(e14a2) transcript with a 31% increase in the major cytogenetic response and a smaller number of BCR-ABL transcripts[7](B).

Recommendation: the (e1a2)p190 transcript is associated to a reduced therapeutic response; there is controversy as to whether there is difference in response between the p210 e13a2(b2a2) and p210 e14a2(b3a2) transcripts.

At diagnosis, do the Philadelphia chromosome and 9q deletion have prognostic significance?

There is no difference in survival between CML patients with the chromosome 9q deletion on interferon alpha treatment and those without this deletion. However, there is a reduction in the survival of patients with the deletion spanning the BCR-ABL junction compared to those without this deletion. The survival rate is 44% higher in chronic phase patients submitted to bone marrow transplantation who do not have the deletion (Number needed to treat - NNT: 2)[8](B). There is evidence that the disease-free survival, overall survival and cytogenetic response is reduced in CML patients with the chromosome 9q34 deletion under treatment with interferon alpha[9,10](B).

A comparison of first-generation (imatinib) or second-generation (nilotinib or dasatinib) TKIs in the treatment of CML patients with chromosome 9 deletion shows that there is no significant difference in the overall survival, disease-free survival or in cytogenetic response between patients with and without the chromosome 9 deletion over a two-year follow-up[11,12](B). There is, however, evidence that there is a reduction in survival of patients with derivative chromosome 9 deletions[13](B).

The ABL deletion on derivative 9 (15.1%) in CML patients reduces disease-free survival, the BCR deletion reduces overall survival and combined ABL and BCR deletions reduce the overall and disease-free survival[14,15](B). There is evidence that only the ABL deletion reduces the survival time and the duration of the chronic phase[16](B).

Over a 5-year follow up of imatinib treatment, CML patients with variant Philadelphia chromosome translocations do not demonstrate significant differences in overall survival, disease-free survival, progression-free survival, complete hematological response, cytogenetic response or molecular response compared to patients without variant Philadelphia chromosome translocations[17,18](B). Other studies have shown that Philadelphia chromosome mosaicism increases mortality in 3.3 years by 21% (NNH: 5) and translocation variations reduce cytogenetic response[19,20](B).

Recommendation: Despite controversy on whether chromosome 9q, BCR deletions and variant Philadelphia chromosome translocations confer worse prognoses, there is evidence of reductions in overall and disease-free survival and in therapeutic response of CML patients treated with interferon alpha or first-generation and second-generation TKIs. ABL deletion reduces the overall and disease-free survival of patients. The presence of variant Philadelphia chromosome translocations and mosaicism also seem to confer worse prognosis in CML.

Do cytogenetic abnormalities in addition to the Philadelphia chromosome at diagnosis have prognostic significance?

In CML patients under treatment using first-generation (imatinib) and second-generation (dasatinib or nilotinib) TKIs, the presence of additional chromosomal abnormalities reduces disease-free and overall survival at 5 years[21](B).

The presence of additional chromosomal aberrations in CML patients under treatment with nilotinib increases mortality by 28% due to disease progression (NNH: 4). In addition, mortality is increased by 38% at 2 years in chronic phase patients with additional chromosomal aberrations (NNH: 3)[22](B).

Aberrations reduce the survival time of these patients[23,24](B). The presence of additional chromosomal aberrations increases

mortality by 36% (NNH: 3) and reduces the mean overall survival of CML patients submitted to stem cell transplantation[25](B).

CML-related disease-free and overall survival at 5 years is different in patients with cytogenetic changes compared to those without. The presence of major cytogenetic aberrations (major route abnormalities) (such as a second Philadelphia chromosome, trisomy 8, isochromosome 17q, or trisomy 19) reduces disease-free and overall survival at 5 years by 40%[26](B).

Recommendation: The presence of additional chromosomal aberrations at diagnosis (major route abnormalities) reduces the overall and disease-free survival and increases mortality by 36% to 40%.

Are the criteria of the World Health Organization comparable to other criteria to classify CML phases (chronic, accelerated and blast crisis phases)?

The use of the World Health Organization (WHO) classification of CML stratifies patients into chronic, accelerated and blast crisis phases at approximate rates of 77.8%, 15.5% and 6.7%, respectively[27](C). The appropriate classification allows the establishment of adequate estimates of response[28](D).

In the treatment of CML patients with imatinib, there is no difference in the overall classification of patients in the chronic, accelerated and blast crisis phases between the standard method and the WHO criteria. The distribution of patients according to the standard classification is about 60% in the chronic phase, 28% in the accelerated phase and 12% as blast crisis. Although there is no significant difference between the two classifications, 6% of patients classified in the chronic phase by the standard classification were reclassified in the accelerated phase (WHO). Similarly, 9% of patients classified in the accelerated phase were reclassified as blast crisis (WHO), and 7% in the chronic phase[29](B).

There are differences between the M. D. Anderson Cancer Center (MDACC), International Bone Marrow Transplant Registry (IBMTR) and WHO classifications and definitions of the accelerated phase of CML particularly in respect to the percentages of blasts and platelets (Table 1)[30](D):

Table 1 - A comparison between the M. D. Anderson Cancer Center, International Bone Marrow Transplant Registry and World Health Organization classifications and definitions of the accelerated phase of CML

Characteristic	MDACC	IBMTR	WHO
Blasts (%)	> 15	> 10	10 – 19
Platelets	< 100	No response	< 100 or > 1000

MDACC: M. D. Anderson Cancer Center; IBMTR: International Bone Marrow Transplant Registry; WHO: World Health Organization (main differences)

Recommendation: The WHO classification for the chronic, accelerated and blast crisis phases of CML are similar to the IBMTR and MDACC classifications.

Is it important to define risk in CML patients using the Sokal and Hasford scores?

The Sokal score can be determined using an online calculator (www.pharmacoepi.de). The score takes into account the size of the spleen (in centimeters) palpable below the left costal border, the platelet count, the percentage of blasts and the age, where a result < 0.8 corresponds to low risk, from 0.8 to 1.2 intermediate risk and > 1.2 high risk. The Sokal score has a predictive value in CML patients treated with imatinib, where molecular and cytogenetic responses are higher in low-risk patients. High-risk, intermediate-risk and low-risk patients who achieve cytogenetic response within 12 months have probabilities of survival of 90%, 94% and 97%, respectively.

The Hasford score considers the age, the percentage of eosinophils and basophils, platelet count, spleen size in centimeters and percentage of blasts; the patient has low risk when the result is ≤ 780, intermediate risk between 780 and 1480 and high risk ≥ 1480. The 5-year survival rate corresponding to each risk group is 76%, 55% and 25%, respectively[31](D)[32](B).

The Sokal score predicts treatment response of CML patients on interferon alpha therapy. The high-risk, intermediate-risk and low-risk groups include 48%, 29% and 23% of the cases with mean survival rates of 45, 76 and 105 months, respectively. The 10-year survival is 8%, 28% and 34%, respectively[33](B).

After the introduction of imatinib treatment, the Sokal score identified an increase in the 5-year survival rate of low-risk CML patients of 11%, intermediate-risk patients of 40% and of high-risk patients of 38%[34](B). Moreover, it is known that high-risk patients are more likely to evolve to the accelerated or blast crisis phases even on imatinib therapy[35](A). The Sokal score is also inversely related to cytogenetic response in high-risk patients[36](B), as, for high-risk patients, there is a 30.4% reduction in cytogenetic response[37](B).

The Hasford score identifies patients at low risk, with probability of survival at 9 years of 41%, intermediate risk, with probability of 0.16%, and high-risk, with a probability zero at 9 years. The Sokal and Hasford scores classify 23% and 9% of all patients as high-risk, respectively. Patients with low or intermediate risk who achieve complete hematological response, have probabilities of survival of 51% and 23%, respectively; those without complete hematologic response have probabilities of 26% and 12%, respectively. High-risk patients who achieve cytogenetic response have prognoses similar to those with low risk[38](B). Of the different groups as classified by Hasford, 57% of low-risk patients present complete cytogenetic response and 27% of intermediate-risk and high-risk patients achieve complete cytogenetic responses[39](B).

The Hasford and Sokal scores predict complete hematological responses mainly in low-risk patients[40](B).

Recommendation: The Sokal and Hasford scores are prognostic predictors of CML patients.

Is imatinib better than second-generation tyrosine kinase inhibitors as first-line treatment of chronic phase CML?

A comparison between dasatinib (100 mg) and imatinib (400 mg) as first-line treatment in chronic phase CML patients demonstrates that complete hematologic response is 11% higher, cytogenetic response is 11% higher and molecular response is 18% higher with dasatinib (NNT: 9)[41](B). The two-year follow-up of these patients upholds the higher beneficial effect of dasatinib compared to imatinib[42](B).

Initial treatment of chronic phase CML patients using nilotinib (300 mg or 400 mg twice daily) compared to imatinib (400 mg once daily) increases the molecular response at 12 months by 22% (NNT: 5), increases the cytogenetic response by 15% (NNT: 7) and reduces the likelihood of progression to the accelerated and blast crisis phases[43](A). In the two-year follow up, the effect of nilotinib increases the molecular response to 27% (NNT: 4), the cytogenetic response is 10% higher than imatinib (NNT: 10) with this difference being 5% lower than the evaluation at 12 months. The reduction in progression to the accelerated and blast crisis phases is maintained[44](A).

Recommendation: Dasatinib and nilotinib provide greater benefits than imatinib in the first-line treatment of chronic phase CML patients in respect to the molecular, cytogenetic and hematologic responses as well as to the progression of the disease.

Does the time between diagnosis and start of treatment with imatinib have prognostic importance?

In chronic phase CML patients, imatinib treatment may be started after diagnosis (early), or may be started after 24 months of treatment with interferon (late), leading to different results regarding toxicity and effectiveness. Early treatment reduces the risk of grade I and II adverse effects by 52% (NNT: 2) and grade III and IV adverse effects by 81% (NNT: 1), although it increases the risk of neutropenia and thrombocytopenia by 5% (NNH: 20). After one year of follow-up in patients who have not achieved complete cytogenetic response, early treatment produces a reduction in the risk of grade I adverse events by 3% (NNT: 33), grade II by 8% (NNT: 12) and grades III and IV by 7% (NNT: 14)[45](B).

In early treatment, there is a 16% increase in complete cytogenetic response (NNT: 7), a 2% reduction in the risk of relapse (NNT: 50) and a 15% increase in disease-free survival (NNT: 7)[45](B).

There is reduction in the risk of non-hematological adverse events with early treatment, including weight gain (11%), periorbital edema (12%), rash (9%), diarrhea (11%), and infections (19%), but there is increased risk of hemorrhage (5%) and bone pain (8%)[45](B).

Imatinib treatment at diagnosis of chronic phase CML (early treatment) increases the likelihood of major molecular response by 20% (NNT: 5) and increases the likelihood of response maintenance at 30 months by 36% (NNT: 3) compared to beginning treatment one year after diagnosis (late treatment). After one year of imatinib treatment, the likelihood of loss of or not achieving molecular response is 58% lower than patients treated early (NNT: 2)[46](B).

Treatment with 400 mg imatinib produced higher major and complete cytogenetic response rates compared to the interferon and cytarabine combination in chronic phase CML patients (87.1% vs. 34.7%) and higher progression-free survival to the accelerated and blast crisis phases (96.7% vs. 91.5%; p-value < 0.001)[32](A).

Recommendation: Imatinib treatment of chronic phase CML patients should be started as early as possible after diagnosis.

Does the cytogenetic evaluation have an impact on prognosis?

The identification of CML patients on imatinib treatment with cytogenetic clonal evolution provides some information on the prognosis that depends on the disease phase. The presence of this change in the chronic and accelerated phases is not associated to a different cytogenetic response, however it reduces the survival rate of patients. Cytogenetic response after three months of treatment is an independent prognostic factor. The absence of complete or partial response is associated with lower survival rates[47](B).

In CML patients on imatinib treatment, the presence of a cytogenetic response increases 4-year survival by 23% (NNT: 4) and disease-free survival by 38% (NNT: 3)[48](B).

The rate of cytogenetic response in patients in late chronic phase CML after interferon alpha intolerance or resistance was 55%. After 6 years of treatment with imatinib, 77% of the patients were still with stable complete cytogenetic response, with a survival rate of 91%. Among the 124 patients who never achieved a complete cytogenetic response, 54 (44%) progressed to the accelerated or blast crisis phases[49](B).

The expected loss of cytogenetic response in the first year of imatinib treatment is 0.6%, with the mortality rate at 2 years of patients who achieved response being lower. The estimated 8-year mortality rate of these patients is 4.8%[50](B).

For CML patients unresponsive to imatinib and thus treated with second-generation TKIs (dasatinib and nilotinib), a cytogenetic response confers 20% greater survival (NNT: 5), and when associated with hematological response, the increase in the survival rate is 42% (NNT: 2)[51](B).

The presence of minor or major cytogenetic response in chronic phase CML patients under treatment with second-generation TKIs, increases event-free survival, overall survival and disease-free survival by about 25% (NNT: 4)[52](B).

Recommendation: the cytogenetic evaluation of patients under TKI treatment can predict the prognosis by complete or partial response, associated or not to other factors.

Does molecular evaluation by quantitative real time polymerase chain reaction have an impact on prognosis?

The BCR-ABL/ABL ratio is almost always below 2% in chronic phase CML patients who attain cytogenetic response on imatinib treatment. Patients with the BCR-ABL/ABL ratio below 0.0001% are regarded as having complete molecular response. For patients who lose the cytogenetic response within 24 months (2.5%) the mean value of the ratio is 0.12%. Some relapsed patients evolve with disease progression (15.4%) with BCR-ABL/ABL ratios that vary from 0.3% to 0.0075%, which, within the usefulness of quantitative real time PCR (qPCR) in molecular evaluation defines the extremes of positive or negative residual disease, but with a great variability in the mean[53](B).

In CML patients investigated using qPCR, the estimated 5-year major molecular response rate is 67.1% and the cytogenetic response is 81.7%. In respect to event-free survival, including transformation to accelerated and blast crisis phases, death from any cause, loss of adherence to treatment or loss of cytogenetic response, patients who attain molecular response have a higher response compared to those who do not. Patients with major molecular response have better survival than patients with complete cytogenetic response, who do not achieve major molecular response[54](B).

The estimated molecular response obtained by PCR analysis in CML patients treated with imatinib, also allows a comparison with hematologic and cytogenetic responses over time. Thus, in an 18-month follow-up, the molecular, cytogenetic and hematologic responses were 79%, 83% and 93%, respectively[55](B).

Cytogenetic progression (loss of response, clonal evolution, 20% increase of the Philadelphia clone) occurs in 13% of CML patients under imatinib treatment in 2 years of follow-up. At the time of progression, none of these patients had major molecular response (reduction ≥ 3log in BCR-ABL). Thus, there is a suggestion that cytogenetic analysis should be restricted to cases that do not attain or lose molecular response as measured by qPCR[56](B).

To evaluate changes in the levels of BCR-ABL transcripts as prognostic markers by qPCR, monitoring during 4 years demonstrates major molecular response (≥ 3-log reduction) and predicts higher disease-free survival rates. A minimal increase of 0.5-log predicts shorter relapse-free survival. Loss of molecular response (< 2.5-log reduction) also defines reduction in disease-free survival. A complete molecular response (PCR undetectable) corresponds to an increased disease-free survival[57](B).

Recommendation: the prognosis (survival, relapse, progression) of CML patients under imatinib treatment can be predicted using qPCR.

Can cytogenetics be replaced by quantitative real-time polymerase chain reaction to monitor CML patients taking tyrosine kinase inhibitors who attain complete cytogenetic response?

There is a correlation between the levels of transcripts in the bone marrow and peripheral blood at 3 months of treatment and obtaining molecular response at 6 months[58](B).

The comparison between qPCR, cytogenetics and fluorescence in situ hybridization (FISH) to monitor response to treatment using TKIs in CML patients demonstrates the following correlations and/or concordances: qPCR in bone marrow and peripheral blood; cytogenetics in the bone marrow, FISH in peripheral blood and qPCR in peripheral blood[59](B).

Despite the correlation between qPCR and cytogenetic analysis, other prognostic factors may be associated with molecular or cytogenetic responses, affecting the outcomes during TKI treatment of chronic phase CML patients. This shows the need of multivariate analyses that estimate the impact of the interaction of prognostic factors present in the medical practice. However in multivariate analysis, just the 3-month cytogenetic response is predictive of the response at 6 months and disease-free survival at 2 years[58](B).

Relapse occurs at 24 months in 2.5% of patients who have obtained cytogenetic response and these patients may experience disease progression to the accelerated and blast crisis phases. The correlation between PCR analysis and cytogenetic response may contain a raneg of values that hamper interpretation and thus not favor the substitution of methods[53](B).

Three-monthly monitoring using qPCR may provide the prognostic data needed for decision making in CML patients thereby reducing the need of bone marrow aspirations. The reasons that PCR monitoring is sufficient include: the level of log reduction in the BCR-ABL/ABL ratio correlates with cytogenetic response; in the 12 -month follow-up, no patient has disease progression without there being an indication in the risk by qPCR (half-log increase or 5-fold increase in the previous value of the BCR-ABL/ABL ratio); and no patient has cytogenetic progression when they have molecular response[56](B).

Recommendation: qPCR in peripheral blood can be used as the examination of choice to monitor chronic-phase CML patients under imatinib treatment. Cytogenetics is a fundamental option for monitoring that may be used in association with PCR, or may be reserved for cases where either there is no molecular response or the molecular response was lost.

What is the treatment of choice for chronic-phase CML patients resistant to imatinib 400 mg?

A comparison of treatment with dasatinib 140 mg and an increase in the dose of imatinib (800 mg) in chronic phase CML patients resistant to imatinib 400 mg (lack of complete hematological response at 3 months or lack of cytogenetic response at 6 months, or lack of major cytogenetic response at 12 months of treatment) demonstrates the following results: complete hematologic response increases in 11% of patients (NNT: 9), complete cytogenetic response increases by 23% (NNT: 4) and major molecular response increases by 12% (NNT: 8). Moreover,

there are 27% and 15% reductions in the risk of swelling and water retention, respectively with dasatinib 140 mg. However, the risk of neutropenia and thrombocytopenia increases by 22% (NNH: 5) and 42% (NNH: 2), respectively[60](B). These results remain constant at 18 months of follow-up with an increase in disease-free survival[61](B).

The treatment of these patients (CML in chronic phase, resistant to imatinib) with dasatinib 100 mg/day compared to 140 mg/day leads to a similar clinical response in 6 months and 2 years of follow-up (complete hematologic response, cytogenetic response and disease-free survival), however the risk of pleural effusion is reduced by 9% (NNT: 11), of thrombocytopenia by 15% (NNT: 7) and of discontinuity of treatment[62,63](A).

The response rate of chronic phase CML patients under nilotinib treatment (400 mg b.i.d) is no different to patients resistant or intolerant to imatinib (600 mg/day). The lack of response to imatinib (hematologic or cytogenetic) predicts absence of response to nilotinib[64](B). Patients who attain a response with nilotinib remain with 96% to 98% of the response (hematologic or cytogenetic) at 6 months of follow-up[65](B). The mean time to obtain a complete hematologic response is 2.8 months and complete cytogenetic response is 3.2 months, with disease-free survival and overall survival at 24 months being estimated at 64% and 87%, respectively[66](B). Patients resistant to imatinib or dasatinib treatment attain 79% complete hematologic response and 24% complete cytogenetic response at 12 months[67](C).

In chronic phase CML patients resistant to imatinib and dasatinib, treatment with bosutinib (500 mg/day) produces complete hematological and complete cytogenetic responses in 62% and 31% of the cases, respectively. Patients resistant to imatinib and nilotinib treatment achieve complete hematological and complete cytogenetic responses in 75% and 35% of cases taking bosutinib (500 mg/day). In cases of resistance to imatinib or dasatinib, the likelihood of maintaining response, disease-free survival and overall survival from 12 months on are 27%, 32.4% and 72.9%, respectively. In patients resistant to imatinib and nilotinib treated with bosutinib, the odds of maintaining response, disease-free survival and overall survival from 12 months, are 22.2%, 44.4% and 77.7%, respectively[68](B).

Recommendation: Chronic phase CML patients, who are resistant to imatinib at a dose of 400 mg, should be treated with dasatinib (100 mg/day), nilotinib (800 mg/day) or bosutinib (500 mg/day).

Are there differences in the toxicity profiles of second-generation tyrosine kinase inhibitors (dasatinib and nilotinib)?

The difference in adverse effects between imatinib with nilotinib or dasatinib is expressed as the NNT; when these latter two drugs produce a reduction in the risk of adverse effects and the number needed to harm (NNH) when the risk of a particular adverse effect increases.

The use of nilotinib (at any dose) as first-line therapy of patients with newly diagnosed CML reduces the rates of nausea (NNT: 8), diarrhea (NNT: 7), vomiting (NNT: 6), muscle spasm (NNT: 6), edema (NNT: 11) and neutropenia (NNT: 3) when compared to imatinib. However, the rates of rash (NNH: 4), headache (NNH: 8), pruritus (NNH: 8) and alopecia (NNH: 11) are increased and there are increases in liver enzymes (NNH: 2), total bilirubin (NNH: 2) and glucose (NNH: 5)[43](A).

When nilotinib is given as second-line therapy in chronic phase CML patients, cardiotoxicity can occur with increases in the QT interval (QTc - 1% of cases) and thrombocytopenia (29% of cases)[65](B).

In a comparison of dasatinib and imatinib as first-line therapy for CML, the main non-hematological adverse effects including nausea (NNT: 9), myositis (NNT: 8) and water retention (NNT: 4) are reduced with dasatinib. However, there are increases in pleural effusion in 10% (NNH: 10), thrombocytopenia in 9% (NNH: 11) and cardiotoxicity in 0.4%[41](B).

As second-line therapy in chronic-phase CML patients, dasatinib produces increases in the rates of pleural effusion (NNH: 6), neutropenia (NNH: 5), thrombocytopenia (NNH: 2), dyspnea (NNH: 6) and headache (NNH: 7)[60](B).

Recommendation: With regards to most expected adverse effects using this class of medication, dasatinib and nilotinib have similar results but with slight differences in the degree. However, nilotinib seems to cause more hepatotoxicity and dasatinib causes more water retention (pleural effusion).

Does adherence to imatinib treatment have prognostic impact?

CML patients on imatinib treatment who have suboptimal response are less adherent to treatment (do not take the medication) than patients with optimal response. Patients treated for more than 12 months who have complete cytogenetic response also have better compliance than those with partial cytogenetic response. There is no difference in the hematologic response between adherent and non-adherent patients[69](B).

There is a direct correlation between adherence (≤ 90% or > 90%) of CML patients to imatinib treatment and the likelihood of major molecular response at 6 years (an increase in 66.1% of response in adherence > 90%). When adherence is less than 80% there is no molecular response. Patients who need to increase the dose of imatinib have 12.8% reduction in adherence[70](B).

In the treatment of CML with imatinib, ≤ 85% adherence increases the risk of loss of complete cytogenetic response by 34.9% (NNH: 3). No patients with adherence ≥ 95% lose cytogenetic response. Patients with adherence level ≤ 85% who never attained molecular response, have low adherence as a predictor of loss of cytogenetic response. Adherence of ≤ 85% reduces the disease-free survival by 37% (NNH: 3). Adherence rates of more than 85% confer a similar prognosis as patients who have major molecular response[71](B).

The 5-year disease-free survival in chronic phase CML patients who adhere to imatinib treatment is 16.9% higher than for non-adherent patients. Non-compliance reduces the possibility of complete cytogenetic response by 18% (NNH: 6). The greatest cause of cessation of imatinib treatment (29.6%) is related to noncompliance. Complete cytogenetic response is correlated to adherence to treatment, with a reduction in the response in noncompliant patients by 20%[72](B).

Recommendation: adherence to imatinib treatment is directly correlated to the probability of molecular and cytogenetic responses and disease-free survival.

Are prior cytogenetic response to imatinib and performance status prognostic factors for response to second-line tyrosine kinase inhibitors in imatinib-resistant patients?

The best cytogenetic response (0% positive Philadelphia chromosome) during treatment with imatinib is predictive of response to dasatinib and nilotinib, with an increase in cytogenetic response by 21% when compared to no cytogenetic response during treatment with imatinib, i.e. Philadelphia ≥ 95% [52](B).

The response to second-line TKI of Imatinib-resistant CML patients is associated with some other prognostic factors such as: 1. low-risk Sokal: 25.5% increase in cytogenetic response and 27.0% in disease-free survival; 2. percentage of positive Philadelphia chromosome at the beginning of treatment < 95%: 43.8% increase in the cytogenetic response and 27.3% in disease-free survival; 3. time to therapeutic failure of imatinib ≤ 6 months: 37.2% increase in cytogenetic response, 24.3% increase in overall survival rate and 13.8% increase in progression-free survival[52](B).

The prognosis of treatment using second-line TKIs (nilotinib or dasatinib) in Imatinib-resistant CML patients can be predicted by prior cytogenetic response (imatinib), giving an estimated 37% increase in disease-free survival at 3 years and in the cytogenetic response at 1 year. A performance status (European Cooperative Oncology Group - ECOG) of "0" at the beginning of treatment with second-line TKIs, predicts an 18% increase in disease-free survival and a 32% increase in overall survival at 3 years[73](B).

Other prognostic factors may be associated with response to treatment with nilotinib or dasatinib such as: age greater than 55 years with a 24% reduction in cytogenetic response at 1 year, a 20% reduction in disease-free survival at 3 years and a 6% reduction in overall survival at 3 years; ≥ 90% Philadelphia chromosome-positive metaphases at start of treatment with second-line TKIs with a 30% reduction in the cytogenetic response and a 21% reduction in disease-free survival[73](B).

Recommendation: Information related to cytogenetic response and performance status (ECOG) should be used to assess prognosis on starting second-line treatment with TKIs such as nilotinib or dasatinib in Imatinib-resistant CML patients. Additionally age and cytogenetic response prior to treatment with second-generation TKIs should be taken into account.

When is it necessary to make an analysis of BCR-ABL mutations in CML patients under treatment with tyrosine kinase inhibitors?

BCR-ABL mutations are associated to 100% resistance to imatinib treatment in accelerated-phase CML patients and in 79% of chronic-phase patients[74](C).

The presence of BCR-ABL mutations increases the risk by 52% of chronic-phase CML patients evolving to the accelerated or blast crisis phases within 9 months (NNH: 2). These mutations, especially P-loop mutations, also reduce the time free of disease progression and survival of these patients[75](B).

In the follow-up of CML, BCR-ABL mutations occur at different times in patients under treatment with imatinib and are correlated with lower survival rates. For patients in the early phase of the disease, mutations are associated with increases in transformation to the accelerated (32%) and blast crisis phases (16%) and a reduction in the complete cytogenetic response (24%). Regardless of the stage of the disease, mutations reduce hematologic response[76](B).

BCR-ABL mutations in CML patients under imatinib treatment predict, within about 20 months, loss of complete cytogenetic response and progression to the advanced stages of the disease[77](B).

Hematologic and cytogenetic responses are similar in patients with and without BCR-ABL mutations under treatment with second-generation TKIs (dasatinib and nilotinib). Moreover disease-free survival and overall survival are not significantly different between these two groups of patients[78](B).

In the four-year follow-up of chronic phase CML patients, the time from the beginning of imatinib treatment to the progression of the disease to the accelerated or blast crisis phases is worse in patients with mutations than those without mutations. The overall survival of patients without mutations and those with mutations is 51 and 10 months, respectively but this varies according to the type of mutation (P-loop type - 13 months and T315I - 9 months)[79](B).

Among chronic phase CML patients under nilotinib treatment, the two-year overall survival is reduced by 38% in the presence of BCR-ABL mutations. In addition, the presence of mutations is associated with a 34% reduction in the cytogenetic response[80](B).

T315I mutations occur more often in patients treated with dasatinib. The presence of mutations during nilotinib or dasatinib treatment is predictive of a worse prognosis in these patients[21](B).

Recommendation: BCR-ABL mutations should be investigated in CML patients resistant to TKIs (suboptimal response or failure) regardless of the stage, because their presence predicts the greater risk of resistance and shorter survival.

Does the diagnosis of mutations guide the choice of treatment in imatinib-resistant patients?

In imatinib-resistant CML patients, mutations can assist in the choice of second-generation TKIs (nilotinib or dasatinib). An evaluation of the sensitivity of mutations to inhibitors in *in vitro* studies (IC_{50}) defines three groups of sensitivity (low, intermediate and high concentrations) of the mutation to: dasatinib ($IC_{50} \leq 3$ nM, 3-60 nM and > 60 nM) and nilotinib ($IC_{50} \leq 50$ nM, 50-500 nM and > 500 nM) with the worst case scenario (resistance) corresponding to high concentrations[78](B).

Hematologic and cytogenetic responses at one year are significantly lower in patients with mutations and in the chronic phase, particularly for mutations with intermediate IC_{50} (25% and 25%, respectively) compared to low IC_{50} (96% and 54%, respectively). In the accelerated phase there is also a reduction in the cytogenetic response for mutations with 10% reduction in intermediate IC_{50} and 31% reduction in low IC_{50},[78](B). In the chronic phase, the disease-free survival and overall survival are lower in patients with mutations with high IC_{50} (0% and 75%, respectively), when compared with mutations with low IC_{50} (78% and 100%, respectively)[78](B). The T315I mutation is associated with high IC_{50} (resistance) but there is no difference comparing dasatinib and nilotinib[78](B).

Other specific mutations associated with high IC_{50} (resistance) in the chronic phase of CML treated with dasatinib are: T315I/A, F317L/I/V/C and V299L[81-83](B), and with nilotinib: T315I, Y253H, E255K/V and F359V/C[82,84](B). The G250E mutation also has an impact on resistance common in the two forms of treatment[83](B).

Mutations associated with resistance to dasatinib such as V299L, T315A and F317I may be sensitive to nilotinib, while the mutation V299L may be resistant to bosutinib[83-85](B).

Complete cytogenetic response subsequent to treatment using dasatinib or nilotinib is lower in patients with resistant mutations [mutations detected by sequencing that confer resistance to the inhibitor received (0%) - T315I, F359V/C, F317L, Y253H, E255V/K] compared to patients with other mutations (mutations detected by sequencing or spectrometry of masses sensitive to the inhibitor received) or without mutations (41% and 49%, respectively). The survival of chronic phase CML patients when resistant mutations are detected is 0% compared with 51% and 45% in patients with other mutations or without mutations, respectively[86](B).

Recommendation: the identification of mutations, especially resistant mutations, can assist in the choice of the TKI, allowing the definition of which therapeutic option will provide the best response.

How should monitoring of CML patients taking tyrosine kinase inhibitors be performed?

Reports state that monitoring of chronic-phase CML patients for BCR-ABL mutations during imatinib treatment can be achieved with PCR in peripheral blood (BCR-ABL/ABL ratio) correlating this with the result obtained through the usual cytogenetic study of bone marrow. This identifies responsive, partial responsive and unresponsive patients in respect to BCR-ABL/gene control of up to 0.08%, of 0.08% to 10% and of above 10%, respectively[87](B).

In a randomized trial, 1106 CML patients were treated with interferon or imatinib as first-line treatment. All patients who achieved cytogenetic remission performed qPCR for BCR-ABL mutations. The results were expressed in terms of the logarithmic reduction in relation to the median level of transcripts in 30 newly-diagnosed patients. Patients who achieved complete cytogenetic remission and at least a 3-log reduction in the level of transcripts, had progression-free survival of 100% at 24 months compared to 95% for those with complete cytogenetic remission and less than a 3-log reduction in the level of transcripts and 85% for patients without complete cytogenetic response[88](B).

Thus, this form of monitoring also allows you to identify the 2-year progression-free survival with the low values of transcripts[58,88](B).

Using samples from 38 international centers, one study validated the use of an international scale of BCR-ABL values that established 0.1% as a 3-log reduction[89](B).

It is possible to stratify patients by PCR during the 3 years follow-up as patients whose indexes reflect increases, stability or reduction, or even loss of cytogenetic response[53](B).

Plasma imatinib levels are significantly higher in patients with molecular and cytogenetic responses compared to patients without response. The level that differentiates the difference between molecular response and lack of response with the greatest accuracy (77% sensitivity and 71% specificity) is 1002 ng/mL[90](B).

The use of FISH to monitor CML patients on imatinib treatment enables the use of peripheral blood to identify cytogenetic response. A positive result points to the absence of cytogenetic response and a negative result identifies its presence. The association with PCR allows the molecular response to be monitored. In a study published by Reinhold et al., the estimated cytogenetic and molecular responses at 5 years were 81.7% and 67.1%, respectively[54](B). However, the comparison between the results of FISH using peripheral blood leukocytes and the cytogenetics of the bone marrow may not establish an appropriate correlation in the measurement of CML activity during imatinib treatment[91](B).

The existence or occurrence of mutations in CML patients under TKI treatment, when identified, enables an estimation of the prognosis and guides treatment. High-performance liquid chromatography (HPLC) is a practical and sensitive method to identify mutations to clinically monitor patients[92](B).

Some mutations can be identified by direct sequencing during the follow-up of patients including: T315T, T315I, F317L, V339L, M351T, E355G, Y253F and F359V; these are associated with different responses to available inhibitors. A 31% reduction in the overall survival of patients with mutations is identified in the 3-year follow-up[74](B).

Recommendation: The monitoring of CML patients treated with TKIs can be accomplished by bone marrow cytogenetics and qPCR for the BCR-ABL gene in peripheral blood, thereby allowing an estimation of prognosis and the definition of therapeutic strategies. Mutational analysis should be performed in patients with suboptimal response or loss of response to TKIs.

When should bone marrow transplantation be indicated for CML patients?

Imatinib may be used as treatment for relapse after allogeneic hematopoietic stem cell transplantation, the prevalence of which ranges from 40% to 70% at 5 months. In the chronic phase, the cytogenetic and hematologic response rates obtained and survival at 9 months are 58%, 84% and 100%, respectively[93,94] (B). Imatinib came to be used as first-line treatment in the chronic phase of CML demonstrating increased survival when used before bone marrow transplant[95](B).

Due to the lower cost, resistance to imatinib or advanced stages of the disease (accelerated and blast crisis phases), some series of cases of transplant in CML have been reported with comparative results or in association to imatinib, demonstrating similar disease-free survival, overall survival and cardiotoxicity[96](C).

The previous use (before transplantation) of imatinib in patients with advanced stages of CML, produces hematological response in 73% and cytogenetic response in 40% of patients, and 3 years after the transplant, 66.7% of patients have complete molecular response[97](C).

In a prospective study, Jiang et al. compared accelerated phase patients treated either with imatinib (n = 87) or allogeneic transplantations (n = 54). In this study, multivariate analysis established hemoglobin < 10.0 g/dL, blasts in peripheral blood ≤ 5% and disease duration of less than 12 months as independent risk factors for survival. High-risk (two risk factors or more) or intermediate-risk patients (one risk factor) had better overall survival and progression-free survival with allogeneic transplant. No difference was seen with low-risk patients[98](BII).

The mortality of CML patients on imatinib treatment associated to hematopoietic stem cell transplant is 9.7% and the relapse rate is 5.0% at one year[99](C).

Despite the new options in imatinib-resistant patients, such as dasatinib and nilotinib, non-comparative case series that associate TKIs and transplant are still being performed[100](C).

Data are still limited for the pediatric population, but the results with imatinib are similar to those seen in adults. Millot et al. published their experience in 44 children with newly diagnosed CML treated with imatinib. With a median follow-up of 31 months, the estimated progression-free survival at 36 months was 98%. The rates of complete cytogenetic response and major molecular response at 12 months were 61% and 31%, respectively. About 30% of the children discontinued the use of medication, mainly due to lack of effectiveness. There are adverse effects of TKIs on the growth of children and this aspect should be monitored[101](BII).

Moreover, researchers reported the results of a prospective study involving 200 CML children and adolescents treated by allogeneic transplantation according to donor availability. The probability of survival at five years was 87 ± 11% for matched related donors, 52 ± 9% for matched unrelated donors and 45 ± 16% for unmatched donors. The likelihood of relapse at 5 years was 20 ± 12%[102](BII).

Recommendation: Bone marrow transplantation is a therapeutic option to treat CML but it should be reserved for cases resistant to TKI treatment and patients in the advanced stages of the disease after an initial course of TKIs.

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Appendix 1

Search strategies and words used in to answer the clinical questions:

PICO 1

What are the diagnostic criteria for chronic myeloid leukemia?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic OR Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative) AND (classification OR criteria OR World Health Organization* OR standards*) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [MeSH:noexp] OR diagnosis,differential[MeSH :noexp] OR diagnosis[Subheading:noexp])

PICO 2

Is there any difference in the prognosis of CML patients with p210, e13a2(b2a2) and e14a2(b3a2) or (e1a2)p190 rearrangements?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND ((Fusion Proteins, bcr-abl AND genetics*) OR p210 OR e13a2 OR b2a2 OR e14a2 OR b3a2 OR p190 OR e1a2 OR Isoform*) AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])

PICO 3

At diagnosis, do the Philadelphia chromosome and the 9q deletion have prognostic significance?

((((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic)) AND (Fusion Proteins, bcr-abl OR BCR-ABL OR BCR/ABL OR 9q OR Philadelphia OR chromosome 9))) AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])

PICO 4

Do cytogenetic abnormalities in addition to the Philadelphia chromosome (Ph) at diagnosis have prognostic significance?
((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Fusion Proteins, bcr-abl OR BCR-ABL OR BCR/ABL OR 9q OR Philadelphia OR chromosome 9 OR cytogenetic OR additional chromosome abnormalities OR ACAs)) AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])

PICO 5

Are the criteria of the World Health Organization (WHO) comparable to other criteria to classify the CML phases (chronic, accelerated and blast crisis phases)?
((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (classification OR staging OR criteria) AND (World Health Organization OR WHO) AND ((sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp])) OR (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]) OR Investigative Techniques OR Comparative study)

PICO 6

Is it important to define risk to CML patients using the Sokal and Hasford scores?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Sokal OR Hasford) AND ((sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) OR (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])) OR (evaluation study OR comparative study OR epidemiologic methods))

PICO 7

Is imatinib better than second generation tyrosine kinase inhibitors as first-line treatment of chronic phase CML?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (nilotinib OR dasatinib) AND imatinib AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

PICO 8

Does the time between diagnosis and start of treatment with imatinib have prognostic importance?
(((((((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic)) AND Imatinib) AND Prognosis/narrow[filter])) OR ((((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia,

Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND Imatinib AND (Time factors OR early OR late OR delay*) AND Therapy/broad[filter])) OR ((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND Imatinib AND (Time factors OR early OR late) AND Prognosis/broad[filter]))))) OR (((((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic)) AND Imatinib)) AND therapy/narrow[filter])

PICO 9

Does the cytogenetic evaluation have an impact on prognosis?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Cytogenetic Analysis OR Cytogenetic*) AND ((sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) OR (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])) OR (evaluation study OR comparative study OR epidemiologic methods))

PICO 10

Does molecular evaluation by quantitative real time polymerase chain reaction (PCR) have an impact on prognosis?
((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Polymerase Chain Reaction OR PCR OR Nested PCR OR Anchored PCR) AND molecular AND (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]))

PICO 11

Can cytogenetics be replaced by quantitative PCR (qPCR) to monitor CML patients taking tyrosine kinase inhibitors who attained complete cytogenetic response?
((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Cytogenetic Analysis OR Cytogenetic*)) AND (Polymerase Chain Reaction OR PCR OR Nested PCR OR Anchored PCR OR DNA Mutational Analysis)

PICO 12

What is the treatment of choice for chronic-phase CML patients resistant to Imatinib 400 mg?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND imatinib AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND drug resistance

PICO 13

Are there differences in the toxicity profiles of second-generation tyrosine kinase inhibitors (dasatinib and nilotinib)?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (dasatinib) AND (nilotinib) AND (adverse effects OR complications OR safety OR toxicity) AND (Therapy/broad[filter] OR comparative study OR epidemiologic methods OR systematic[sb])

PICO 14

Does adherence to Imatinib treatment have prognostic impact?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND imatinib AND Prognosis AND (Adherence OR Compliance)

PICO 15

Are prior cytogenetic response with Imatinib and performance status prognostic factors for response to second-line tyrosine kinase inhibitors in patients resistant to Imatinib?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Cytogenetic Analysis OR Cytogenetic* OR performance status OR Karnofsky Performance Status) AND Imatinibe AND (Nilotinib OR Dasatinibe) AND ((sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract]OR diagnosis[MeSH:noexp]OR diagnostic*[MeSH:noexp] OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) OR (prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract])) OR (evaluation study OR comparative study OR epidemiologic methods))

PICO 16

When is it necessary to make an analysis of BCR-ABL mutations in CML patients under treatment with tyrosine kinase inhibitors?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Fusion Proteins, bcr-abl OR BCR-ABL OR BCR/ABL) AND (Protein Kinase Inhibitors OR crizotinib OR Cyclin-Dependent Kinase Inhibitor p15 OR Cyclin-Dependent Kinase Inhibitor p18 OR Cyclin-Dependent Kinase Inhibitor p19 OR Cyclin-Dependent Kinase Inhibitor p21 OR Cyclin-Dependent Kinase Inhibitor p27 OR Cyclin-Dependent Kinase Inhibitor p57 OR Cyclin-Dependent Kinase Inhibitor Proteins OR dasatinib OR erlotinib OR fasudil OR flavopiridol OR gefitinib OR Genistein OR imatinib OR lapatinib OR roscovitine OR sorafenib OR vatalanib)

PICO 17

Does the diagnosis of mutations guide the choice of treatment in imatinib-resistant patients?
((((Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic))) AND (((Fusion Proteins, bcr-abl)) OR (Mutation*))) AND (((nilotinib OR dasatinib)) OR (bone marrow transplantation))

PICO 18

How should monitoring of CML patients taking tyrosine kinase inhibitors be performed?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND (Protein Kinase Inhibitors OR Imatinib OR Nilotinib OR Dasatinib) AND (Blood Cell Count OR Cytogenetics OR Polymerase Chain Reaction OR Mutation* OR In Situ Hybridization, Fluorescence) AND monitor*

PICO 19

When should bone marrow transplantation be indicated for CML patients?
(Leukemia, Myelogenous, Chronic, BCR-ABL Positive OR Leukemia, Myeloid, Philadelphia-Positive OR Leukemia, Granulocytic, Chronic OR Myeloid Leukemia, Chronic OR Chronic Myeloid Leukemia OR Leukemia, Myelocytic, Chronic OR Chronic Myelocytic Leukemia OR Leukemia, Myelogenous, Chronic OR Myelogenous Leukemia, Ph1-Positive OR Leukemia, Myeloid, Ph1 Positive OR Myelogenous Leukemia, Chronic OR Myeloid Leukemia, Philadelphia-Positive OR Granulocytic Leukemia, Chronic) AND BONE MARROW TRANSPLANTATION AND (Therapy/broad[filter] OR Comparative study)