European Review for Medical and Pharmacological Sciences 2021; 25: 7787-7798

Tailored tyrosine kinase inhibitor (TKI) treatment of chronic myeloid leukemia (CML) based on current evidence

R. CIFTCILER[1], I.C. HAZNEDAROGLU[2]

[1]Department of Hematology, Aksaray University Training and Research Hospital, Aksaray, Turkey
[2]Department of Hematology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Abstract.– Philadelphia(Ph*)/BCR-ABL1-positive chronic myeloid leukemia (CML) is a neoplastic hematologic disorder, which is a functionally curable chronic disease *via* using tyrosine kinase inhibitor (TKI) drugs. The life expectancy for the vast majority of chronic phase-CML patients is "normal", thanks to the unique effectiveness of the ABL-targeted TKIs of CML. The patients with CML receiving TKI could be expected to have a survival and 'quality of life' of the age- and sex-matched healthy people. Several TKI pathways may be selected for the first line CML treatment, including first-generation original/generic imatinib or second-generation TKIs, such as bosutinib, nilotinib, and dasatinib. Individual characteristics of the CML patients, TKI drug compliance, lifestyle preferences, comorbidities, distinct toxicity profile of the TKI drug, and physician-clinical center experience are among the critical factors to be taken into account while deciding on the proper first line TKI in the newly diagnosed CML patients. Identifying CML patients at a higher risk for the disease progression or TKI resistance is essential and could influence the choice of primary TKI. The optimized integrations of the best available evidence, individual patient characteristics, and physician clinical experience are required in order to select best TKI for the CML management. Pathobiological basis depending upon the prospective *in vivo* research data is also crucial during the follow-up as well.

Key Words:
Tyrosine kinase inhibitor, Imatinib, Nilotinib, Dasatinib, Bosutinib, Chronic myeloid leukemia.

Introduction

Philadelphia (Ph*)/BCR-ABL1-positive chronic myeloid leukemia (CML) is a clonal hematological neoplastic condition, a functionally curable chronic disease treated by tyrosine kinase inhibitor (TKI) drug administration[1]. CML accounts for about 15% of newly diagnosed adult cases of leukemia and 1-2 cases per 100,000 people[2]. Among the characteristics of the individual CML patient, disease comorbidities, molecular BCR-ABL1 profile, TKI drug compliance, lifestyle preferences and TKI drug off-target risk profile should be determined. Currently, persistent oral administration of a TKI drug is the initial treatment for CML[3].

The aim of the TKI therapy is to provide a life expectancy of normal duration to CML patients, compatible with their age and gender, as well as to provide a normal quality-of-life[1]. Research evidence TKI-class drugs include randomized clinical trials depicting essential data on the safety, efficacy, tolerability, toxicity, efficiency, possible long-term side effects and pharmaco-economical aspects of the drugs. The critical decision making for selecting TKI of the CML patient should be performed *via* the optimization of TKI availability, TKI reimbursability, TKI drug experience, therapeutic adherence, and molecular monitorization facilities for every single CML patient[1]. Moreover, the effectiveness of TKI treatment, TKI side effects, off-target drug complications, disease and drug-related long-term morbidities should be considered on patient basis within CML management.

Clinical response, the depth of the molecular response and the effect of TKI on the disease are the follow-up parameters, which shall be considered during long-term CML therapy. Most patients need life-long oral TKI drug maintenance therapy. On the other hand, the progression to accelerated phase/ blast crisis still occur in 5% to 7% of patients and remains a horrible challenge[4]. The aim of this review is to outline individual tailored TKI treatment of CML based on the best available evidence.

Corresponding Author: Rafiye Ciftciler, MD; email: rafiyesarigul@gmail.com

Materials and Methods

Up to June 2021, literature searches were performed using the internet search engines MEDLINE and EMBASE: (i) chronic myeloid leukemia; (ii) tyrosine kinase inhibitor; imatinib, dasatinib, nilotinib, ponatinib, bosutinib, radotinib. Only articles written in English and research conducted on people were included in the search. All abstracts were scanned. The studies that were found to be methodologically weak with restricted applicability and/or deficient presentation of the findings were excluded. Articles in full text were evaluated for eligibility and quality. The qualitative synthesis comprised the following studies (Figure 1).

Current Best Available Data

Current Efficacy Data of TKIs in CML

The first-line standard treatment of CML is administration of a TKI-class drug. Currently, there are imatinib, dasatinib, nilotinib and bosutinib for the first-line therapy, officially approved by the FDA and EMA[4]. Imatinib is successful in all stages of CML disease[4]. For most CML patients treated in the chronic phase (CP), treatment with imatinib resulted in a normal life expectancy[6-8].

Imatinib had a greatest impact on the CML treatment, allowing a large percentage of patients to achieve a deep molecular response on long-term medication[9]. Clinical trial evidence with second-generation TKIs shows that they have greater response rates than imatinib, with deeper and earlier responses. By 5 years, 42% of patients who got first-line dasatinib *vs.* 33 percent of patients who received imatinib in the DASISION study reached MR[4,5,10]. In an ENESTnd trial comparing first-line nilotinib with imatinib, 55% of patients who got nilotinib by 6 years reached MR[4,5], compared to 45% of those who received imatinib[11].

Second generation TKIs (2G-TKI) mainly consisted of dasatinib, nilotinib and bosutinib. 2G-TKIs were developed following the recognition of imatinib failure, intolerance, and ABL kinase domain (KD) resistance mutations that occur in 4.6% of chronic phase CML patients[12,13]. Five- and ten-year data of the randomized trials demonstrate that survival with 2G-TKI first-line is quite similar to imatinib[10,11,14]. 2G-TKI and ponatinib are effective against most KD resistance mutations, but with the advent of additional chromosomal abnormalities, other precipitating triggers, such as clonal evolution, may fail[4]. Radotinib is another 2G-TKI

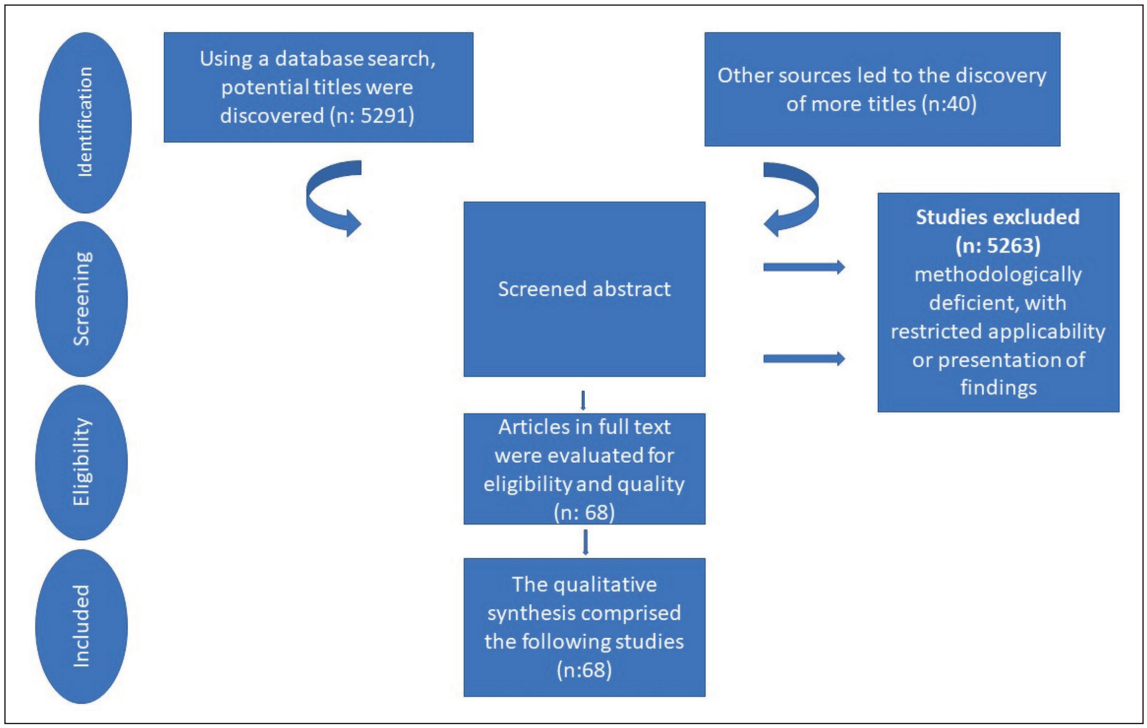

Figure 1. PRISMA flow diagram for the CML literature search focusing on TKI selection[5].

Table I. The concise summary depicting TKI (tyrosine kinase inhibitor) essentials in CML.

Imatinib	In the IRIS trial, imatinib, a first-generation TKI, was compared to a combination of recombinant interferon alpha (IFN) and low-dose cytarabine and demonstrated greater rates of cytogenetic and molecular responses[16]. Imatinib was quickly adopted as the first-line therapy for CML. The standard dose of imatinib is 400mg once daily.
Dasatinib	Dasatinib is a 2GTKI that is more powerful than imatinib and works against numerous BCR-ABL1 mutations that are resistant to imatinib15. Dasatinib is authorized for chronic phase CML at a dosage of 100 mg once day, and for advanced phase CML at a dose of 70 mg twice daily. Because dasatinib causes pleuro-pulmonary toxicity, respiratory failure and prior or concurrent pleuro-pulmonary or pericardial illnesses are severe contraindications to using it as first-line therapy[15].
Nilotinib	Several imatinib-resistant BCR-ABL1 mutations are inhibited by nilotinib, a 2GTKI that is more powerful than imatinib15. Nilotinib is prescribed at a dosage of 300 mg twice day in first-line therapy and 400 mg twice daily beyond that. The use of nilotinib as first-line therapy is strongly discouraged if you have a history of coronary heart disease, cerebrovascular accidents, or peripheral arterio-occlusive disease[15].
Bosutinib	The third 2GTKI that is more powerful than imatinib is bosutinib. Several BCR-ABL1 mutants are likewise inhibited by it. The first-line dosage is 400 mg once day, while the second-line dose is 500 mg once daily. Approximately 30% of individuals have transitory diarrhea, which can be a bothersome side effect1[5].
Radotinib	Radotinib is physically similar to nilotinib, and it has almost comparable efficacy against BCR-ABL1 mutations. Radotinib is a fourth 2GTKI that has not been approved by the FDA or the EMA[15].
Ponatinib	Ponatinib is a powerful third-generation TKI that outperforms all previous TKIs. Ponatinib is a drug that has been authorized for patients with the BCR-ABL1T315I mutation and CML who have failed two or more TKIs[17].

that has been approved first-line in South Korea although it has not been reviewed by the FDA or the EMA. Radotinib is somewhat similar to nilotinib in structure and has about the same activity profile[15]. In the absence of BCR-ABL1 KD-mutations for second-line therapy, there is no recommendation for any specific 2G-TKI.

All second-line TKIs are effective for disease-control but there are no 'head-to-head' studies comparing TKIs with each other. Second-line TKI selection criteria are almost entirely related to the individual patient characteristics as discussed in this review[15]. The concise summary depicting TKI (tyrosine kinase inhibitor) essentials in CML is shown in Table I.

Current Safety Data of TKIs in CML

The goal of the CML treatment with TKIs focuses on the effectiveness, particularly molecular response and clinical outcome without disease progression. On the other hand, TKI adverse events (AEs) are often reported as infrequent, small, tolerable, and manageable in numerous studies. Nowadays, the safety of TKI drugs is becoming increasingly important as treatment is life-long and multiple TKIs are commercially available[18]. Most patients receiving TKIs generally have early, often mild to moderate AEs that spontaneously resolve or are easily controlled by simple means. Reduction of treatment or short-term interruption can only be preferred if other methods are not available to achieve optimum control of AE.

Special attention should be paid to the comorbidities and drug-drug interactions. Safety issues unrelated to the TKIs may be unavoidable during such a life-long treatment[18]. Imatinib generics began to be utilized in CML patients, just after Novartis' Gleevec patent expired. Safety and efficacy should always be considered in the treatment with TKI in all CML patients within every step of clinical management. Several groups have reported the efficacy and safety of generic imatinib compared to the branded one. The response, survival rates and safety profiles in the patients treated with imatinib generics were quite similar to those treated with the branded imatinib[2].

Dose titration of TKI is as important as the TKI drug choice. In a randomized study[19] on dasatinib, 100 mg of dasatinib daily was noted to be as effective as 140 mg daily, with a better safety profile for pleuropulmonary complications. Cortes et al[10] demonstrated that bosutinib exhibited an acceptable safety profile for pulmonary and cardiovascular comorbidities. In patients with chronic phase imatinib-resistant or imatinib-intolerant CML, bosutinib is an efficient and tolerable alternative to TKI[10]. It is already reported that bosutinib, which may usually have gastrointestinal (GI) toxicity, is available first-line with a safety profile different from other 2GTKIs. Ponatinib is the only TKI with activity against the T315I mutant, but it is not used in the first line due to the potential serious vascular thrombotic complications, such as stroke and acute coronary syndrome[15].

Current Tolerability/Toxicity Data of TKIs in CML

While more than one TKI is currently available to treat CML, each of them has a different toxicity profile that should be considered when deciding on the individual tailored treatment. Most of the TKIs are generally well tolerated by the receiving CML patients under adequate clinical follow-up and supportive care. Since most of the patients take TKIs for a long time or indefinitely, observing the quality of life and improving chronic low-grade side effects are essential[15]. When a TKI is not tolerated, replacing it with another TKI can improve tolerability, but sometimes potentially more serious toxicity could be traced[20].

Imatinib has been shown to be effective at all clinic-biological stages of CML. The treatment with imatinib has resulted in a normal life expectancy in most patients treated in the chronic phase[6-8]. Clinical studies[18,21,22] with long-term follow-up have disclosed no serious toxicity after more than 20 years of human use. For the CML patients at high risk of developing pleural effusion, one of the TKIs other than dasatinib should be chosen[2]. Pulmonary arterial hypertension (PAH) is a rare but important complication of dasatinib[23]. Dasatinib also inhibits platelet function and may increase the risk of hemorrhagic complications in patients taking concomitant anticoagulants[24]. Nilotinib should be prescribed with caution in patients with diabetes or a history of pancreatitis[2]. Vasospastic and vaso-occlusive vascular events, such as ischemic heart disease, ischemic cerebrovascular events, and occlusive peripheral artery disease have been correlated with nilotinib[11].

Bosutinib has gastrointestinal, hepatic and renal side effects. Among the patients with such GI comorbidities, bosutinib should be avoided or used with caution[25]. Imatinib rarely causes uncomfortable side effects, such as mild to moderate weight gain, fatigue, peripheral and periorbital edema, bone and muscle aches, and nausea[2]. Patients under the age of 50 are expected to live for more than 30 years. The age of the patient also plays an important role in the treatment decision.

Current Pharmaco-Economical Data of TKIs in CML

CML studies include randomized clinical trials showing data on the safety, efficacy, tolerability, toxicity, possible long-term side effects, efficiency, and pharmaco-economics of TKIs. Low-risk or intermediate-risk disease patients are predicted to have an adequate response to imatinib, dasatinib, nilotinib, or bosutinib. TKI treatment economical toxicity and cost-effectiveness in the CML patients have become important issues for patients and social security associations. Since CML patients would use TKI for a long time, perhaps for life-long with an age- and sex-matched normal duration of life, the cost is an important variable while deciding on the primary TKI and switching to the alternative TKI within clinical backgrounds. In order to increase the rate of sustained deep molecular remission and to increase the rate of treatment-free remission, several studies[26-29] have examined the cost effectiveness of frontline treatments. As a result, generic imatinib is the cost-effective first-line treatment strategy for almost all chronic phase CML patients[21]. Until second generation TKI lose patent protection, cost effectiveness will maintain to be a significant matter in deciding first-line TKI because 80% of patients will never obtain a treatment free remission (TFR)[15].

Individual Patient Characteristics Subject to the Tailored TKI Treatment

CML Disease Risk

Sokal, Euro/Hasford, EUTOS or EUTOS long-term survival (ELTS) scoring systems are used to determine the risk of CML disease[1]. Optimum responses to imatinib, dasatinib, nilotinib or bosutinib are expected in CML patients with low-risk or intermediate-risk disease[2]. To choose a second generation TKI as first-line therapy for the patients with intermediate or high-risk disease based on Sokal or Hasford scores has been proven to be more beneficial[30-32]. Patients with higher risk disease have a lower chance to reach major molecular response and, particularly, higher risk of disease transformation to AP-CML or BP-CML[2]. Another preferred risk score for CML is the ELTS score, which has a higher accuracy in predicting death from CML than the Sokal score[33]. The key difference lies in the negative prognostic value of age, because TKI-treated patients (based on ELTS) have less effect than traditional chemotherapy-treated patients (based on Sokal). The Sokal score is more likely to allocate older patients than ELTS to intermediate and high-risk groups from the point of clinical prognostication[21].

Patient Age

In the Western countries, CML is diagnosed at an average age of 56 to 57 years[34,35]. Patients over the age of 70 make up more than 20% of CML patients. In the developing countries with a young

population, the median age is less than 50 years[36]. The annual incidence per 100,000 population varies by age and ranges from 1 to 2 depending on the age of the populations[4]. The age of the CML patient plays an important role in the key treatment decision. Patients under the age of 50 are expected to live more than about 30 years[2]. Thus, inducing a permanent complete molecular remission could potentially result in the discontinuation of TKI therapy. Second generation TKIs provide a significantly higher rate of complete molecular remission in comparison to imatinib. In elderly patients, where discontinuation of therapy is less important, the problem of possible discontinuation of care plays a less important position[2].

Patient Comorbidities

When selecting TKI for a patient with CML, comorbidities should be considered because there are certain contraindications for the use of a particular first-line TKI[37]. Previous or concomitant arteriovascular disease is highly contraindicated in the treatment of first-line nilotinib and second-line or third-line ponatinib[38-41]. For certain clinical states, no strong contraindications have been reported for imatinib or bosutinib. However, imatinib should be discontinued in the patients with severe renal impairment.

Pleural effusion is classically associated with dasatinib with a rate of 16-20% in different series. The Risk factors for developing pleural effusion with dasatinib include advanced age of the patient, twice daily 140 mg dosing, previous or concomitant heart/lung disease or autoimmune diseases, hypertension, hypercholesterolemia, and advanced phase CML[42]. Respiratory failure and prior or concomitant pleuro-pulmonary disorders in primary care are strong contraindications of dasatinib[21].

CML Disease Molecular Profile

Disease characteristics of a given CML patient include disease risk, comorbidities, molecular BCR-ABL1 profile, TKI drug compliance, lifestyle preferences, and drug off-target risk profile[1]. The diagnosis of CML must be proven by demonstrating the molecular abnormality of the BCR-ABL1 fusion[1]. The existence of t(9;22)(q34.1;q11.2) or BCR-ABL1 abnormality could be demonstrated by karyotype analysis, FISH, or PCR based methods. The real-time PCR technique is the most accurate and sensitive process. The method of IS-PCR is important and should be preferred for routine follow-up, particularly in assessing the level of molecular response to the treatment of TKI[43]. Previous research has revealed that p210 BCR-ABL is necessary for the uncontrolled proliferation and reduced apoptosis, both of which are the hallmarks of neoplastic CML cells[44,45]. BCR-ABL is a non-receptor tyrosine kinase that has the capacity to over-activate several cell survival pathways, including the AKT and JAK/STAT pathways[46]. There is evidence that the MYC pathway regulates the transcription of the BCR-ABL gene[47]. According to studies, the MYC oncogene is elevated in CML, which might cause to the disease's heightened aggressiveness and lack of responsiveness to therapy[48].

In the patients with CML, multiplex-PCR enables for the fast, specific, and simultaneous identification of the most common BCR-ABL variant transcripts. Likewise, b2a2 transcripts were more common than b3a2 transcripts[49]. Additionally, a CML phenomenon has been described with regard to the disease progression and treatment resistance related to the sFRP4 methylation[50].

Disease pathobiology can be complicated by cryptic, mutable variants of the Philadelphia chromosome and additional cytogenetic anomalies. For the diagnosis and follow-up of CML patients, Interphase fluorescent in situ hybridization (FISH), chromosome band analysis and PCR should be evaluated together[51].

Patient Compliance/Lifestyle

Individual characteristics of the CML patients, drug compliance and preferences, comorbidities, different toxicity profile of the drug, and physician-clinical center experience are among the factors to be taken into account when deciding on first line TKI in the newly diagnosed patients[3]. TKI doses (imatinib 300 *vs.* 400 *vs.* 600 mg; dasatinib 50 *vs.* 100 *vs.* 140 mg; nilotinib 600 *vs.* 800 mg; ponatinib 15 mg *vs.* 30 mg; bosutinib 300 mg *vs* 500 mg) should be adopted to the BCR-ABL1 levels and lifestyle that CML patients can tolerate side effects[1]. The resistance to imatinib and 2-GTKI may occur in first line treatment. In some of the CML patients, the TKI response failure may be associated with poor or intermittent adherence to the given therapy. Suspected incompliant CML patients shall be closely evaluated for the TKI drug adherence into the recommended dosage and schedule[15].

TKI Drug off-Target Risk Profile

With the production of TKIs that strongly interfered with the interaction between the BCR-ABL1 onco-protein and adenosine triphosphate, the CML therapeutic landscape changed drastically,

preventing the malignant clone's cellular proliferation. This quite "targeted" treatment strategy altered the natural history of CML, improving the 10-year survival rate from nearly 20% to 80%-90%[2,9,52]. The drug off-target complications, such as lung toxicity, cardiovascular toxicity, metabolic syndrome, bone toxicity, arterial occlusive events, pancreas/GI/ hepatic toxicity are well-described clinical limitations of the given TKI. Therefore, the dose of TKI (imatinib 400 *vs.* 600 mg; dasatinib 100 *vs.* 140 mg; nilotinib 600 *vs.* 800 mg) must also be tailored based on the tolerability and organ functions of the individual patient[3].

Advanced Phase CML Disease (AP/BC)

The chronic phase is usually the the initial phase of the CML disease. In two phases, disease progression is defined as the accelerated phase (AP) and blastic crises (BC). AP illness is characterized by blasts in the bone marrow or peripheral blood of 10%-19%. More than 20% of blasts in either the blood or in the bone marrow or at extra-medullary sites are the criterion for transformed BC. When diagnosed with CML, a bone marrow aspiration is required for morphological/cytogenetics analyses since the ratio of blastic cells, basophils, myelodysplasia, fibrosis and karyotype are all necessary to distinguish CP from advanced disease (AP/BC)[21]. In the advanced stages, especially in the BC, CML continues to be a clinic-biological problem. Moreover, multi-TKI resistance, BCR-ABL1 kinase domain mutation, or the emergence of additional chromosome abnormalities in Ph + cells warrant attention to the disease progression[53-55].

Pregnancy in CML

All TKIs are teratogenic and should not be used during pregnancy[56]. For women, the management of CML during pregnancy should be individualized. TKI treatment should be discontinued in the first trimester as soon as pregnancy is detected. Whether the pregnancy is continued, or treatment interrupted should be evaluated comprehensively[21]. Deep molecular remission, such as at least one-year of MR4.5 with TFR, is an ideal state for the female CML patients asking a baby without the risk of CML disease progression. Interruption of TKI treatment for the initiation of pregnancy process in a CML patient shall only be performed in tertiary CML research centers. Since TKI is secreted at low levels in breast milk, its use during breast-feeding is contraindicated[57]. It was observed that sperm quality and morphology did not change after treatment with TKI[58].

Allografting in CML

Despite the superiority of TKI drug therapy, allogeneic hematopoietic stem cell transplantation (Allo-SCT) continues to be included in the management of CML, particularly for the patients with resistant to multiple TKIs[59,60]. Transplantation should be seriously considered in the patients resistant to at least two 2G-TKIs. Those patients are unlikely to experience a sustained response to an alternative TKI and should be evaluated early for Allo-SCT[61]. The patient who progresses to AP/BC under TKI treatment is a strong candidate for emergency transplant. Conversion to CP should be attempted in the patients presenting with BC since returning to the CP increases the chances of allograft success[59]. Transplantation in BC without remission is a high-risk method and not advised[21].

Clinical Experiences of TKI Drugs in CML

TKI Drug Availability/Reimbursability

Clinical and physician experience for CML includes TKI availability, TKI reimbursability, drug experience, drug adherence, and BCR-ABL1 monitorization facilities. Generic imatinib has become a cost-effective initial treatment for CP and is available globally[21,29]. A generic medication is an appropriate alternative to a branded product if it meets the national consistency, bioavailability and efficacy requirements of a country involved. Recently, there has been an increased focus on the improving the 'quality-of-life' and avoiding long-term organ toxicities, and in particular on developing strategies to maximize the likelihood of stopping TKI therapy resulting in TFR. However, in countries with limited resources, due to the availability of more effective drugs and limited CML monitoring parameters, the goal of treatment is to continue to survive[36].

TKI Drug Clinical Experiences

Clinical experience includes TKI availability, TKI reimbursability, drug experience, adherence, and monitorization facilities. The critical decision regarding the management of CML patients should be made by optimizing these variables for each individual patient. Jain et al[62] examined patients with CP CML's long-term responses and outcomes and reported a comparison of four widely used TKI modalities. In this clinical experience, treatment with 800 mg imatinib or second generation TKIs dasatinib or nilotinib resulted in superior and

deeper responses than the standard dose imatinib maintained after 5 years of follow-up[62].

Physician Adherence to TKI Drugs

When deciding on first-line TKI for newly diagnosed CP-CML patients, the physician-clinical center experience is important as well as patient characteristics. Physician must consider TKI availability, TKI reimbursable, drug experience, adherence, monitorization facility when starting the treatment[1]. Physicians should be especially alert about the side effects of TKIs, and patients should be evaluated in this respect.

TKI Drug Monitorization Preferences

Blood cell counts and differential cell counts are required at least every 2 weeks until a complete hematological response is achieved. QPCR on blood cells expressed as BCR-ABL1% according to IS should be performed at least every 3 months even after MMR is obtained. The molecular response must be closely monitored to assess the suitability for discontinuation of therapy at follow-up[21]. Cytogenetics by chromosome banding analysis of bone marrow cell metaphases may be useful but not sensitive enough to track response alone. However, cytogenetics should be performed to detect atypical translocations, rare or atypical BCR-ABL1 transcripts that cannot be measured by qPCR, treatment failure / resistance to rule out additional chromosomal abnormalities, and progression to AP or BP. FISH follow-up may be required in patients with atypical transcripts[21].

Harmonization of Best Available Evidence, Individual Patient Characteristics and Physician Experiences for Selecting Best TKI for CML Management

A Typical Real-Life CML Patient

A 59-year-old male patient who was diagnosed with high Sokal risk CP CML, had a history of 8.5 pack years of smoking, obesity and hypertension treated with lisinopril. There was no diagnosis of diabetes, but high blood glucose was detected during his visits. His total cholesterol level was detected 232 mg/l. The goal of this patient is to determine the best option for TKI and to manage comorbidities. The development of arterio-occlusive events is probably the greatest risk for this patient. Compared to imatinib, the risk of cardiovascular events is significantly greater with 2G-TKIs (dasatinib and nilotinib). It was possible to treat patients with high-risk arterio-occlusive events (AOEs) preferentially with imatinib. However, with the risk and goals of the patient, this recommendation should be decided. Patients with higher Sokal risk scores are poorly responsive to imatinib, so 2GTKI, possibly bosutinib, may be preferable in this case[63]. There was a 27% risk of developing AOEs in patients with a history of hypertension and a 12% risk of developing AOEs in patients without hypertension who used ponatinib. Since the patient had hyperglycemia and hypercholesterolemia, nilotinib did not seem to be very appropriate. Grade 3-4 hyperglycemia occurred in 7% of the patients treated with nilotinib, while 0.4% of those treated with imatinib experienced hyperglycemia[38]. This patient has an elevated level of cholesterol. Imatinib can cure patients' lipid profiles, but nilotinib may worsen the lipid profile after treatment begins[64]. Since hypertension may increase the risk of developing pleural effusion, this patient may also increase the risk of developing pleural effusion with dasatinib[65]. Studies[66,67] have shown that imatinib, dasatinib and nilotinib are safe for patients with moderate renal dysfunction (or liver dysfunction) when administered at standard doses. The harmonization of the best available evidence for CML management is depicted in Figure 2.

Conclusions

Life expectancy for the vast majority of chronic phase-CML patients is "normal", thanks to the unique effectiveness of the ABL-targeted TKIs of CML. The patients with CML receiving TKI could be expected to have a survival and 'quality of life' of the age- and sex-matched healthy people. Numerous options are available for first-generation treatment selection, including first-generation imatinib and second-generation TKIs, bosutinib, dasatinib, and nilotinib. Identifying CML patients at higher risk for disease progression or resistance is important and influences the choice of primary TKI. To select the best TKI for CML management, it is necessary to harmonize the best available evidence, individual patient characteristics and physician experience. Gene expression profile, CML-leukemic stem cell, next-generation genomics, genetic polymorphisms, multi-drug resistance genes and existing BCR-ABL kinase domain mutations are the key subjects of novel studies in the field of CML[68]. Future perspectives

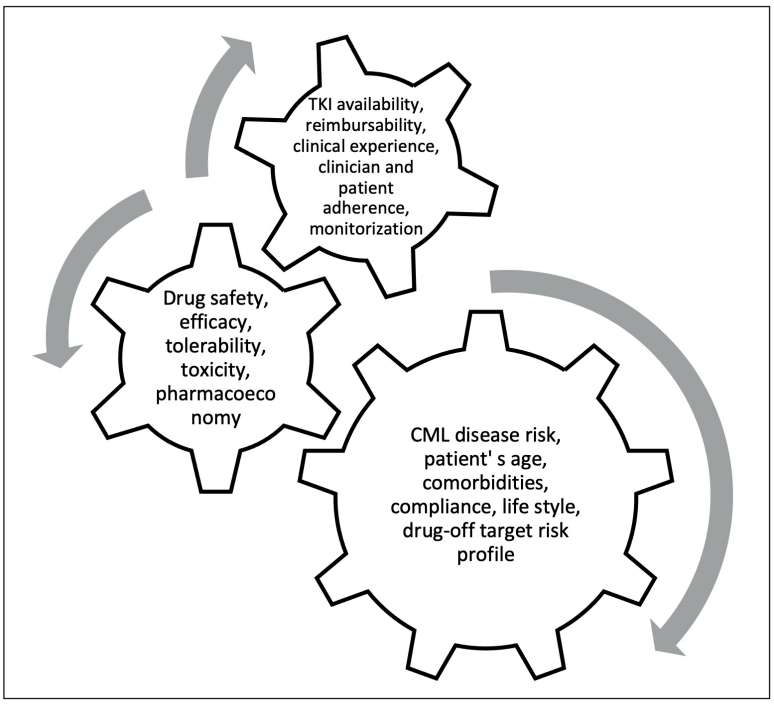

Figure 2. The harmonization of the best available evidence, individual patient characteristics and physician experiences for selecting the best TKI for CML management during the disease course. CML: Chronic myeloid leukemia, TKI: Tyrosine kinase inhibitor.

for the CML treatment will focus on the potential molecular treatment of CML-leukemic stem cell with the aim of achieving a durable non-detectable BCR-ABL1 transcripts and maintaining persistence after TKI therapy cessation. The prevalence of CML patients will continue to increase every year. Therefore, it is important to continue research to develop treatment options that increase durable CMR rates, if possible, TFR. Those aims could be achieved potent TKIs solely or in combination with other existing non-TKI drugs (Bcl-2 inhibitors, PEG-interferon alpha-2, omasetaxine, decitabine) or novel therapies, such as asciminib, which is the first-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor under intensive research[2].

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1) Haznedaroğlu IC, Kuzu I, İlhan O. WHO 2016 Definition of Chronic Myeloid Leukemia and Tyrosine Kinase Inhibitors. Turk J Haematol 2020; 37: 42-47.
2) Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. Am J Hematol 2020; 95: 691-709.
3) Haznedaroglu IC. Current concerns of undertreatment and overtreatment in chronic myeloid leukemia based on European LeukemiaNet 2013 recommendations. Expert Opin Pharmacother 2013; 14: 2005-2010.
4) Hehlmann R. Chronic myeloid leukemia in 2020. HemaSphere 2020; 4: e468.
5) Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, Barbour V, Barrowman N, Berlin JA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 7: e1000097.
6) Sasaki K, Strom SS, O'Brien S, Jabbour E, Ravandi F, Konopleva M, Borthakur G, Pemmaraju N, Daver N, Jain P. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. Lancet Haematol 2015; 2: e186-e193.
7) Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM-L: Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016; 34: 2851-2857.
8) Thielen N, Visser O, Ossenkoppele G, Janssen J. Chronic myeloid leukemia in the Netherlands: a population-based study on incidence, treatment, and survival in 3585 patients from 1989 to 2012. Eur J Haematol 2016; 97: 145-154.
9) Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, Baccarani M, Deininger MW, Cervantes F, Fujihara S, Ortmann CE, Menssen HD, Kantarjian H, O'Brien SG, Druker BJ, IRIS Investigators. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017; 376: 917-927.

10) Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, Shah NP, Chuah C, Casanova L, Bradley-Garelik B, Manos G, Hochhaus A. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol 2016; 34: 2333-2340.
11) Hughes TP, Saglio G, Larson RA, Kantarjian HM, Kim D-W, Issaragrisil S, Le Coutre P, Etienne G, Boquimpani C, Clark RE, Dubruille V, Flinn IW, Krzemien SK, Medras E, Zanichelli M, Bendit I, Cacciatore S, Titorenko K, Aimone P, Saglio G, Hochhaus A. Long-term outcomes in patients with chronic myeloid leukemia in chronic phase receiving frontline nilotinib versus imatinib: ENESTnd 10-year analysis. Leukemia 2021; 35: 440-453.
12) Hehlmann R, Lauseker M, Saußele S, Pfirrmann M, Krause S, Kolb HJ, Neubauer A, Hossfeld DK, Nerl C, Gratwohl A, Baerlocher GM, Heim D, Brümmendorf TH, Fabarius A, Haferlach C, Schlegelberger B, Müller MC, Jeromin S, Proetel U, Kohlbrenner K, Voskanyan A, Rinaldetti S, Seifarth W, Spieb B, Baalleisen L, Goebeler MC, Hänel M, Ho A, Dengler J, Falge C, Kanz L, Kremers S, Burchert A, Kneba M, Stegelmann F, Köhne CA, Lindemann HW, Waller CF, Pfreundschuh M, Spiekermann K, Berdel WE, Müller L, Edinger M, Mayer J, Beelen DW, Bentz M, Link H, Hertenstein B, Fuchs R, Wernli M, Schlegel F, Schlag R, Wit M, Trümper L, Hebart H, Hahn M, Thomalla J, Scheid C, P Schafhausen, Verbeek W, Eckart MJ, Gassmann W, Pezzutto A, Schenk M, Brossart P, Geer T, S Bildat , Schäfer E, Hochhaus A, Hasford J. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. Leukemia 2017; 31: 2398-2406.
13) Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, Sawyers CL. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001; 293: 876-880.
14) Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre PD, Etienne G, Dorlhiac-Llacer PE, Clark RE, Flin IW, Nakamae H, Donohue B, Deng W, Dalal D, Menssen HD, Kantarjian HM. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016; 30: 1044-1054.
15) Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, Clark RE, Cortes JE, Deininger MW, Guilhot F, Hansen HH, Hughes TP, Janssen JJWM, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Mayer J, Nicolini F, Niederwieser D, Pane F, Radich JP, Rea D, Richter J, Rosti G, Rousselot P, Saglio G, Saußele S, Soverini S, Steegmann JL, Turkina A, Zaritskey A. European Leukemia Net 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020; 34: 966-984.
16) O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ, IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003; 348: 994-1004.
17) Cortes JE, Kim DW, Pinilla-Ibarz JI, Le Coutre P, Paquette R, Chuah C, Nicolini F, Apperley J, Khoury H, Talpaz M, DiPersio J, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Müller MC, Passerini CG, Wong S, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H, PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome–positive leukemias. N Engl J Med 2013; 369: 1783-1796.
18) Steegmann JL, Baccarani M, Breccia M, Casado L, García-Gutiérrez V, Hochhaus A, Kim D, Kim T, Khoury H, Le Coutre P, Mayer J, Milojkovic D, Porkka K, Rea D, Rosti G, Saussele S, Hehlmann R, Clark RE. European Leukemia Net recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 2016; 30: 1648-1671.
19) Shah NP, Rousselot P, Schiffer C, Rea D, Cortes JE, Milone J, Mohamed H, Healey D, Kantarjian H, Hochhaus A, Saglio G. Dasatinib in imatinib-resistant or-intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol 2016; 91: 869-874.
20) Kim D-W, Saussele S, Williams LA, Mohamed H, Rong Y, Zyczynski T, Pinilla-Ibarz J, Abruzzese E. Outcomes of switching to dasatinib after imatinib-related low-grade adverse events in patients with chronic myeloid leukemia in chronic phase: the DASPERSE study. Ann Hematol 2018; 97: 1357-1367.
21) Hochhaus A, Baccarani M, Silver R, Schiffer C, Apperley J, Cervantes F, Clark R, Cortes J, Deininger M, Guilhot F, Hansen HH, Hughes TP, Janssen JJWM, Kantarjian HM, Kim DW, Larson LA, Lipton JH, Mahon FX, Mayer J, Nicolini F, Niederwieser D, Pane F, Radich JP, Rea D, Richter J, Rosti G, Rousselot P, Saglio G, Saußele S, Soverini S, Steegmann JL, Turkina A, Zaritskey A, Hehlmann R. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020; 34: 966-984.
22) Kalmanti L, Saußele S, Lauseker M, Müller M, Dietz C, Heinrich L, Hanfstein B, Proetel U, Fabarius A, Krause S, Rinaldetti S, Dengler J, Falge C, Leibundgut EO, Burchert A, Neubauer A, Kanz L, Stegelmann F , Pfreundschuh M, Spiekermann K, Scheid C, Pfirrmann M, Hochhaus A, Hasford J, Hehlmann R. Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study IV. Leukemia 2015; 29: 1123-1132.
23) Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubeau P, Girerd B, Natali D, Guignabert C, Perros F, O'Callaghan DS, Jaïs

X, Bitter PT, Zalcman G, Sitbon O, Simonneau G, Humbert M. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012; 125: 2128-2137.
24) Quintás-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor–induced platelet dysfunction in patients with chronic myeloid leukemia. Blood 2009; 114: 261-263.
25) Cortes JE, Gambacorti-Passerini C, Kim D-W, Kantarjian HM, Lipton JH, Lahoti A, Talpaz M, Matczak E, Barry E, Leip E, Brümmendorf TH, Khoury HJ. Effects of bosutinib treatment on renal function in patients with Philadelphia chromosome-positive leukemias. Clin Lymphoma Myeloma Leuk 2017;17: 684-695.
26) Andrews CN, Lipton J. The true value of second-generation TKIs as first-line therapy in chronic myeloid leukaemia. Lancet Haematol 2019; 6: e385-e386.
27) Yamamoto C, Nakashima H, Ikeda T, Kawaguchi S-i, Toda Y, Ito S, Mashima K, Nagayama T, Umino K, Minakata D, Nakano H, Morita K, Yamasaki R, Sugimoto M, Ishihara Y, Ashizawa M, Hatano K, Sato K, Oh I, Fujiwara SI, Ueda M, Ohmine K, Muroi K, Kanda Y. Analysis of the cost-effectiveness of treatment strategies for CML with incorporation of treatment discontinuation. Blood Adv 2019; 3: 3266-3277.
28) Shih YCT, Cortes JE, Kantarjian HM. Treatment value of second-generation BCR-ABL1 tyrosine kinase inhibitors compared with imatinib to achieve treatment-free remission in patients with chronic myeloid leukaemia: a modelling study. Lancet Haematol 2019; 6: e398-e408.
29) Padula WV, Larson RA, Dusetzina SB, Apperley JF, Hehlmann R, Baccarani M, Eigendorff E, Guilhot J, Guilhot F, Hehlmann R, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Saussele S, Schiffer CA, Silver TR, Simonsson B, Conti RM. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. J Natl Cancer Inst 2016; 108: djw003.
30) Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Garelik MB, Zhu C, Szatrowski T, Shapiro D, Baccarani M. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362: 2260-2270.
31) Saglio G, Kim D-W, Issaragrisil S, Le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM, ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362: 2251-2259.
32) Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim D-W, Dyagil I, Glushko N, Milojkovic D, le Coutre P, Gutierrez VG, Reilly L, Ellis AJ, Leip E, Bouxin NB, Hochhaus A, Brümmendorf TH. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol 2018; 36: 231.
33) Pfirrmann M, Baccarani M, Saußele S, Guilhot J, Cervantes F, Ossenkoppele G, Hoffmann V, Castagnetti F, Hasford J, Hehlmann R, Simonsson B. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016; 30: 48-56.
34) Hoffmann V, Baccarani M, Hasford J, Lindörfer D, Burgstaller S, Sertic D, Costeas P, Mayer J, Indrak K, Everaus H, Koskenvesa P, Guilhot J, Fritschle GS, Castagnetti F, Raimondo FD, Lejniece S, Griskevicius L, Thielen N, Sacha T, Hellmann A, Turkina G, Zaritskey A, Bogdanovic A, Sninska Z, Zupan I, Steegmann JL, Simonsson B, Clark RE, Covelli A, Guidi G, Hehlmann R. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. Leukemia 2015; 29: 1336-1343.
35) Hehlmann R, Cortes JE, Zyczynski T, Gambacorti-Passerini C, Goldberg SL, Mauro MJ, Michallet M, Simonsson B, Williams LA, Gajavelli S, De-Gutis I, Sen P, Paquette RL. Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY. Am J Hematol 2019; 94: 46-54.
36) Malhotra H, Radich J, Garcia-Gonzalez P. Meeting the needs of CML patients in resource-poor countries. Hematology 2019; 2019: 433-442.
37) Saussele S, Krauss M-P, Hehlmann R, Lauseker M, Proetel U, Kalmanti L, Hanfstein B, Fabarius A, Kraemer D, Berdel WE, Bentz M, Staib P, Wit M, Wernli M, Zettl F, Hebart HF, Hahn M, Heymanns J, Wolf IS, Schmitz N, Eckart MJ, Gassmann W , Bartholomäus A, Pezzutto A, Leibundgut EO, Heim D, Krause SW, Burchert A, Hofmann WK, Hasford J, Hochhaus A, Pfirrmann M, Müller MC. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. Blood 2015; 126: 42-49.
38) Hochhaus A, Saglio G, Hughes T, Larson R, Kim D, Issaragrisil S, Le Coutre P, Etienne G, Dorlhiac-Llacer P, Clark R, Flinn IW, Nakamae H, Donohue B, Deng W, Dalal D, Menssen HD, Kantarjian HM. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016; 30: 1044-1054.
39) Gugliotta G, Castagnetti F, Breccia M, Iurlo A, D'Adda M, Stagno F, Levato L, Martino B, Lunghi F, Tiribelli M, Cambrin GR, Abruzzese E, Rupoli S, Gozzini A, Pregno P, Salvucci M, Trabacchi E, Caocci G, Rosti G. Outcome of 472 chronic myeloid leukemia patients treated with frontline nilotinib: a GIMEMA CML WP analysis. Blood 2018; 132: 458-458.
40) Andrews C, Lipton J. The role of ponatinib in chronic myeloid leukemia in the era of treatment free remission. Leuk Lymphoma 2019; 60: 3099-3101.
41) Valent P, Hadzijusufovic E, Schernthaner GH, Wolf D, Rea D, le Coutre P. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. Blood 2015; 125: 901-906.

42) Hughes TP, Laneuville P, Rousselot P, Snyder DS, Rea D, Shah NP, Paar D, Abruzzese E, Hochhaus A, Lipton JH, Cortes JE. Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. Haematologica 2019; 104: 93-101.

43) Shanmuganathan N, Hughes TP. Molecular monitoring in CML: how deep? How often? How should it influence therapy? Hematology Am Soc Hematol Educ Program 2018; 2018: 168-176.

44) Cortez D, Reuther G, Pendergast AM. The Bcr-Abl tyrosine kinase activates mitogenic signaling pathways and stimulates G1-to-S phase transition in hematopoietic cells. Oncogene 1997; 15: 2333-2342.

45) Cortez D, Kadlec L, Pendergast AM. Structural and signaling requirements for BCR-ABL-mediated transformation and inhibition of apoptosis. Mol Cell Biol 1995; 15: 5531-5541.

46) Apperley JF. Part I: mechanisms of resistance to imatinib in chronic myeloid leukaemia. Lancet Oncol 2007; 8: 1018-1029.

47) Sharma N, Magistroni V, Piazza R, Citterio S, Mezzatesta C, Khandelwal P, Pirola A, Gambacorti-Passerini C. BCR/ABL1 and BCR are under the transcriptional control of the MYC oncogene. Mol Cancer 2015; 14: 1-11.

48) Gomez-Casares M, Garcia-Alegria E, Lopez-Jorge C, Ferrandiz N, Blanco R, Alvarez S, Vaqué J, Bretones G, Caraballo J, Sánchez-Bailón P, Delgado MD, Perez JM, Cigudosa CJ, León J. MYC antagonizes the differentiation induced by imatinib in chronic myeloid leukemia cells through downregulation of p27 KIP1. Oncogene 2013; 32: 2239-2246.

49) Kima D, Hien Y, Nikiéma M, Sanou F, Zoungrana C, Kafando E, Traoré Y. The Main Bcr-Abl Mrna Transcript Types And Hematological Features Of Newly Diagnosed Chronic Myeloid Leukemia In Burkina Faso. WCRJ 2020; 7: e1613.

50) Pehlivan M, Sirin N, Ozsan G, Yuce Z, Ogun Sercan H. Evaluation Of Secreted Frizzled-Related Protein-4 Methylation Profiles In Patients With Bcr/Abl Positive Chronic Myeloid Leukemia. WCRJ 2021; 8: e 1967.

51) Testoni N, Marzocchi G, Luatti S, Amabile M, Baldazzi C, Stacchini M, Nanni M, Rege-Cambrin G, Giugliano E, Giussani U, Abruzzese E, Kerim S, Grimoldi MG, Gozzetti A, Crescenzi B, Carcassi C, Bernasconi P, Cuneo A, Albano F, Fugazza G, Zaccaria A, Martinelli G, Pane F, Rosti G, Baccarani M. Chronic myeloid leukemia: a prospective comparison of interphase fluorescence in situ hybridization and chromosome banding analysis for the definition of complete cytogenetic response: a study of the GIMEMA CML WP. Blood 2009; 114: 4939-4943.

52) Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer 2012; 118: 3123-3127.

53) Fabarius A, Kalmanti L, Dietz CT, Lauseker M, Rinaldetti S, Haferlach C, Göhring G, Schlegelberger B, Jotterand M, Hanfstein B, Seifarth W, Hänel M, Köhne CH, Lindemann HW, Berdel WE, Staib P, Müller MC, Proetel U, Balleisen L, Goebeler ME, Dengler J, Falge C, Kanz L, Burchert A, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Spiekermann K, Brümmendorf TH, Edinger M, Hofmann WK, Pfirrmann M, Hasford J, Krause S, Hochhaus A, Saußele S, Hehlmann R, SAKK and the German CML Study Group. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. Ann Hematol 2015; 94: 2015-2024.

54) Wang W, Cortes JE, Tang G, Khoury JD, Wang S, Bueso-Ramos CE, DiGiuseppe JA, Chen Z, Kantarjian HM, Medeiros LJ. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood 2016; 127: 2742-2750.

55) Hehlmann R, Voskanyan A, Lauseker M, Pfirrmann M, Kalmanti L, Rinaldetti S, Kohlbrenner K, Haferlach C, Schlegelberger B, Fabarius A, Krause SW,Kolb HJ, Neubauer A, Hossfeld DK, Nerl C, Gratwohl A, Baerlocher GM, Burchert A, Brümmendorf TH, Hochhous A, Saussele S, Baccarani M. High-risk additional chromosomal abnormalities in CML herald death by blast crisis already at low blast levels. Blood 2019; 134: 666.

56) Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. Mediterr J Hematol Infect Dis 2014; 6: e2014028.

57) Chelysheva E, Aleshin S, Polushkina E, Shmakov R, Shokhin I, Chilov G, Turkina A. Breastfeeding in patients with chronic myeloid leukaemia: case series with measurements of drug concentrations in maternal milk and literature review. Mediterr J Hematol Infect Dis 2018; 10: e2018027.

58) Nicolini F-E, Alcazer V, Huguet F, Cony-Makhoul P, Heiblig M, Fort M-P, Morisset S, Guerci-Bresler A, Soula V, Sobh M, d'Estaing SG, Daudin M, Etienne G. CML patients show sperm alterations at diagnosis that are not improved with imatinib treatment. Leuk Res 2016; 48: 80.

59) Hehlmann R, Berger U, Pfirrmann M, Heimpel H, Hochhaus A, Hasford J, Kolb H-J, Lahaye T, Maywald O, Reiter A, Hossfeld DK, Huber C, Löffler H, Pralle H, Queisser W, Tobler A, Nerl C, Solenthaler M, Goebeler ME, Griesshammer M, Fischer T, Kremers S, Eimermacher H, Pfreundschuh M, Hirschmann WD, Lechner K, Wassmann B, Falge C, Kirchner HH, Gratwohl A. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood 2007; 109: 4686-4692.

60) Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, Kolb H-J, Ho AD, Falge C, Holler E, Schlimok G, Zander AR, Arnold R, Kanz L, Dengler R, Haferlach C, Schlegelberger B, Pfirrmann M, Müller MC, Schnittger S, Leitner A, Pletsch N, Hochhaus A, Hasford J, Hehlmann R, German CML Study Group. Allogeneic hematopoietic stem cell trans-

plantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010; 115: 1880-1885.
61) Gratwohl A, Pfirrmann M, Zander A, Kröger N, Beelen D, Novotny J, Nerl C, Scheid C, Spiekermann K, Mayer J. Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment. Leukemia 2016; 30: 562-569.
62) Jain P, Kantarjian H, Alattar ML, Jabbour E, Sasaki K, Gonzalez GN, Dellasala S, Pierce S, Verstovsek S, Wierda W, Borthakur G, Ravandi F, O'Brien S, Cortes J. Long-term molecular and cytogenetic response and survival outcomes with imatinib 400 mg, imatinib 800 mg, dasatinib, and nilotinib in patients with chronic-phase chronic myeloid leukaemia: retrospective analysis of patient data from five clinical trials. Lancet Haematol 2015; 2: e118-e128.
63) Cortes J. How to manage CML patients with comorbidities. Hematology Am Soc Hematol Educ Program 2020; 2020: 237-242.
64) Rea D, Mirault T, Cluzeau T, Gautier JF, Guilhot F, Dombret H, Messas E. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. Haematologica 2014; 99: 1197-1203.
65) Quintás-Cardama A, Kantarjian H, O'Brien S, Borthakur G, Bruzzi J, Munden R, Cortes J. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007; 25: 3908-3914.
66) Sasaki K, Lahoti A, Jabbour E, Jain P, Pierce S, Borthakur G, Daver N, Kadia T, Pemmaraju N, Ferrajoli A, O'Brien S, Kantarjian H, Cortes J. Clinical safety and efficacy of nilotinib or dasatinib in patients with newly diagnosed chronic-phase chronic myelogenous leukemia and pre-existing liver and/or renal dysfunction. Clin Lymphoma Myeloma Leuk 2016; 16: 152-162.
67) Tong WG, Kantarjian H, O'Brien S, Faderl S, Ravandi F, Borthakur G, Shan J, Pierce S, Rios MB, Cortes J. Imatinib front-line therapy is safe and effective in patients with chronic myelogenous leukemia with pre-existing liver and/or renal dysfunction. Cancer 2010; 116: 3152-3159.
68) White DL, Radich J, Soverini S, Saunders VA, Frede AK, Dang P, Cilloni D, Lin P, Mongay L, Woodman R, Manley P, Slader C, Kim DW, Pane F, Martinelli G, Saglio G, Hughes TP. Chronic phase chronic myeloid leukemia patients with low OCT-1 activity randomized to high-dose imatinib achieve better responses and have lower failure rates than those randomized to standard-dose imatinib. Haematologica 2012; 97: 907-914.