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Chronic myeloid leukemia, tyrosine kinase inhibitors and cardiovascular system

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Abstract. – OBJECTIVE: Cardiovascular system health becomes important with the extended survival of chronic myeloid leukemia (CML) patients. Cardiotoxicities are related to the second- and third-generation tyrosine kinase inhibitors (TKIs). The most frequent and important cardiovascular events are myocardial infarction, stroke and peripheral arterial disease, QT prolongation, pleural effusions, and both systemic and pulmonary hypertension. The aim of this paper is to review the interactions between administrated TKIs and the cardiovascular system during the clinical course of CML. Elucidation of TKI effects on the cardiovascular system is vital since the current goal of CML therapy is a cure that leads to normal age and gender-similar survival with a normal quality of life.

MATERIALS AND METHODS: Up to August 2022, literature searches were performed *via* the internet search engines MEDLINE, EMBASE, GOOGLE SCHOLAR: (i) chronic myeloid leukemia; (ii) tyrosine kinase inhibitor; (iii) cardiovascular system. Only articles in English and research including humans were included in the search.

RESULTS: Tailored TKI treatment with individual patient characteristics must account for CML disease risk, patient age, patient comorbidities, patient compliance, TKI drug off-target risk profile, accelerated or blastic phase CML disease, pregnancy and allografting in CML. The treatment-free survival, improving quality of life, limiting adverse events of TKIs, and the optimal dose and administration duration of TKIs are still a matter of controversy. Special attention should be paid to the comorbidities of CML patients and clinical TKI effects on CVS since the aim of CML treatment is a cure that leads to normal age and gender-similar survival with a "normal" quality of life. CVS is an important morbidity and mortality cause for adult patients. The discontinuation of TKI treatment in CML and the treatment-free remission of CML patients are very important in order to reduce the risk for cardiovascular adverse effects of TKIs. The frail CML patients and especially the patients who have cardiac comorbidities, should be carefully evaluated for TKI treatment, and hematopoietic stem cell transplantation (HSCT) should be the last choice in these risky CML patients.

CONCLUSIONS: The current CML treatment target is a cure that leads to normal age and gender-adjusted survival with a "normal" quality of life. Cardiovascular disorders are one of the major obstacles to reaching this target in CML patients. The treatment choices for CML patients must include a cardiovascular perspective.

Key Words:
Chronic myeloid leukemia, Tyrosine kinase inhibitors, Cardiovascular system.

Introduction

Chronic myeloid leukemia (CML) is related to the fusion of two genes: *BCR* (on chromosome 22) and *ABL1* (on chromosome 9), leading to the *BCR-ABL1* fusion gene. It derives from a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11), that forms an abnormal chromosome 22 called the Philadelphia (Ph) chromosome. CML is a functionally curable chronic disease with the use of tyrosine kinase inhibitors (TKIs)[1]. TKIs have been used for CML for many years efficiently and safely. TKIs bind to the tyrosine residue of kinases resulting in the inhibition of ATP, thus signaling mechanisms that are necessary for cell proliferation stops. Safety, efficacy, tolerability, toxicity, efficiency, adverse effects, and pharmaco-economical features of TKIs are very important for clinical decision-making for a CML patient[1]. Imatinib, as a first-generation TKI, is the preferred frontline treatment in patients with chronic myeloid leukemia. Cytogenetic and molecular treatment results[2] with imatinib have been very durable after 10-year follow-up; rare relapses in responding patients are seen after three to four years of follow-up. Nilotinib and dasatinib are potent second-generation TKIs and they are preferred in CML patients who had imatinib failure[3]. TKIs may lead to several adverse effects,

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including cardiovascular side effects[4]. TKIs such as imatinib mesylate, dasatinib, nilotinib, sunitinib, ponatinib, asciminib, sorafenib, and lapatinib may lead to cardiac toxicity[5]. Imatinib may lead to severe congestive heart failure due to myocyte contractile dysfunction presenting with peripheral edema, shortness of breath, and fatigue[6]. Heart failure has been described in the first years of imatinib use, but not confirmed in more recent studies[5]. Nilotinib has comparable cardiac adverse effects with imatinib, however, it is a more potent TKI than imatinib at the expense of more vascular adverse effects[7,8]. On the other hand, dasatinib is a second-generation TKI and is approved for treating chronic or accelerated phase CML in patients with resistance or intolerance to prior therapy with TKIs. Several cardiovascular sides effects, such as pleural effusion, pulmonary hypertension, and QTc prolongation, may be caused by dasatinib[9,10]. Generally, the cardiotoxicities are related to the second- and third-generation TKIs. The most worrying and important vascular events are myocardial infarction, stroke, and peripheral arterial disease[11]. Moreover, QT prolongation, pleural effusions, and both systemic and pulmonary hypertension may also be seen as adverse effects[11]. The aim of this paper is to review the interactions between administrated TKIs and the cardiovascular system during the clinical course of CML. Elucidation of TKI effects on the cardiovascular system is vital since the current goal of CML therapy is a cure resulting in normal age and gender-adjusted survival with a normal quality of life[12].

Materials and Methods

Up to August 2022, literature searches were performed *via* the internet search engines MEDLINE, EMBASE, GOOGLE SCHOLAR: (i) chronic myeloid leukemia; (ii) tyrosine kinase inhibitor; (iii) cardiovascular system. Only articles in English and research including humans were included in the search. All abstract was analyzed. The studies that have inappropriate methods, non-applicable or restricted results were excluded. Full-text articles were analyzed for quality and eligibility. We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method throughout this manuscript. The qualitative synthesis performed is depicted in the PRISMA flow diagram (Figure 1).

Results

The Aim of Chronic Myeloid Leukemia Treatment

The optimal goal of CML treatment is a cure that leads to normal age and gender-adjusted survival with a normal quality of life (QoL)[13-15]. Previous reports[13] indicate that the life expectancy of CML cases approaches the life expectancy of the general population. However, a few CML patients can achieve a cure[16]. CML patients who sustain a complete molecular response after imatinib discontinuation have evidence[16] of persistent leukemia by DNA polymerase chain reaction (PCR). The authors tried to understand why CML cannot be cured by TKIs[17]. The persistence of hematopoietic stem cells with *BCR-ABL1* despite TKI therapy causes this phenomenon. Novel drugs exploiting differences between CML and normal hematopoietic stem cells may be the key to achieving a cure for CML[17]. The intermediate objective is achieving near-normal age and gender-similar survival off TKI treatment, referred to as therapy-free remission (TFR)[18]. In order to achieve this goal, TKI treatment should be preferred individually. Various TKIs are found[19] to treat CML but the availability and cost of drugs change in each different country. Imatinib, nilotinib, dasatinib, and bosutinib are approved as frontline therapy and ponatinib and asciminib in the US for second and third-line CML treatment[20-22]. Imatinib is less potent and does not inhibit various *BCR-ABL1* mutations, many of which are sensitive to the other TKIs. On the other hand, *BCR-ABL1T315I* is inhibited only by ponatinib and asciminib[23,24]. Adverse events occur with all of the TKIs, but cardiovascular and pulmonary complications of TKIs differ. Imatinib is known as the safest TKIs among others[25]. When the benefits of TKIs are compared with their adverse effects, it is considered that the safety profiles are manageable. During TKI preference, the pharmacoeconomic and intolerance of drugs are also the other features that should be carefully considered for each patient[26-28]. Several algorithms and strategies were offered for the choice of TKIs regarding the initial and subsequent treatments of CML patients[29]. Some authors[29] suggested early responses predict better results in newly diagnosed CML patients. Imatinib and nilotinib were compared in the ENESTnd trial[30] for their long-term benefits and risks of frontline treatment of CML. Also, dasatinib and imatinib

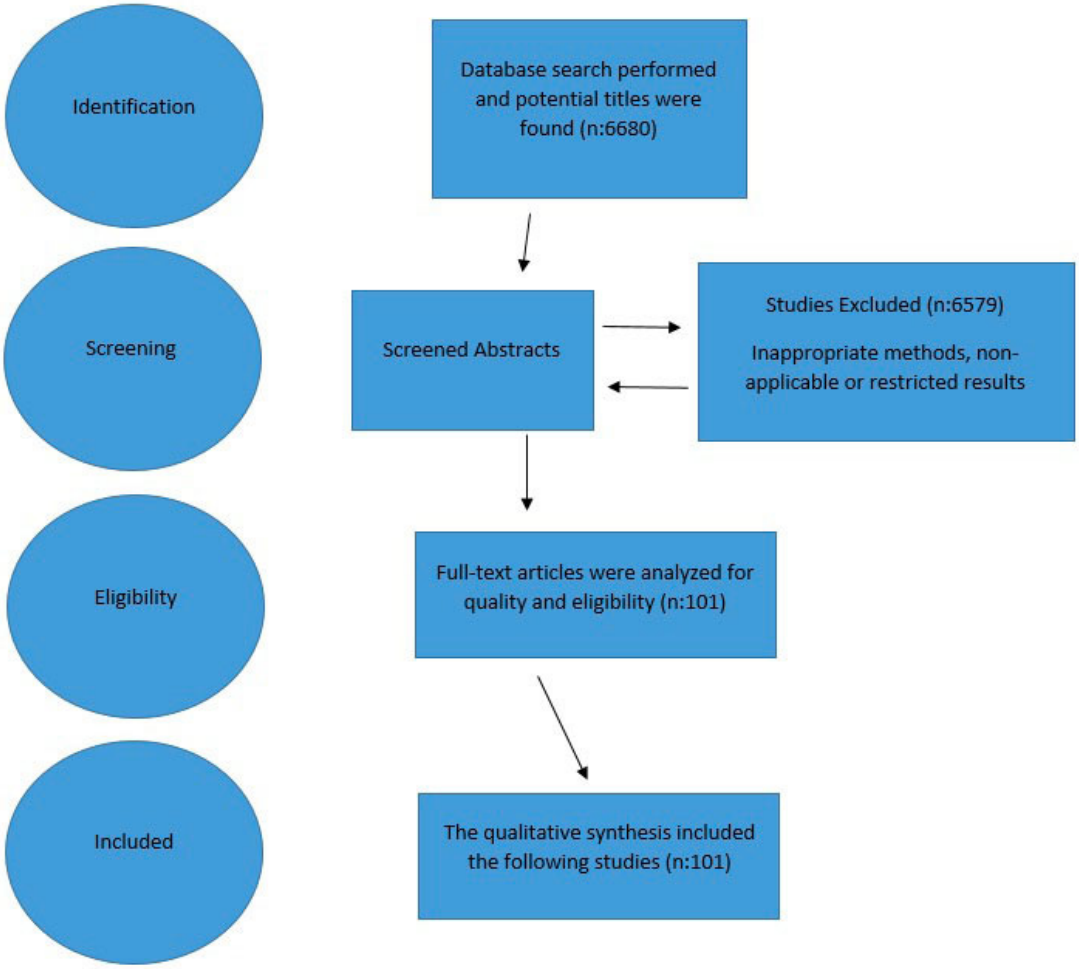

Figure 1. PRISMA flow diagram for the literature search on chronic myeloid leukemia, tyrosine kinase inhibitors and cardiovascular system.

were analyzed competitively in treatment-naive CML patients[31]. Nilotinib and dasatinib were compared in achieving a molecular response of 4.5 (MR4.5) for newly diagnosed CML[32]. The main problem is to find out the best frontline treatment option in CML therapy regarding faster, deeper molecular responses achievable with second-generation TKIs and switching from imatinib to second generation-TKIs if there is an inadequate response to imatinib[27,33]. These debates are ongoing because the major molecular response (MMR; *BCR-ABL1* ≤0.1% on the International Scale) is generally considered the best surrogate for survival in CML[2,34]. On the other hand, there is no evidence that supports the frontline use of a second generation-TKI being related to better progression-free survival (PFS), and probability of achieving TFR or survival[29,33]. The superiority of second-generation TKIs over imatinib in achieving faster and deeper molecular responses corresponds to a higher rate of TFR, and clinical cures are still unproven[28].

Tailored TKI treatment with individual patient characteristics must account for CML disease risk, patient age, patient comorbidities, patient compliance, TKI drug-off target risk profile, accelerated or blastic phase CML disease, pregnancy, and allografting in CML[35]. Choosing a second-generation TKI as a frontline treatment for CML patients with intermediate or high-risk diseases based on Sokal or Hasford scores has been proven[36,37] to be more advantageous. The age of CML patients is important in treatment decisions. In younger patients, inducing a permanent complete molecular remission may lead to the discontinuation of TKI therapy. Second-gen-

eration TKIs may be preferred in this situation since they have a higher rate of complete molecular remission in comparison to imatinib. On the other hand, discontinuation of TKI treatment is not an issue in elderly patients[38]. Patients' comorbidities and TKI adverse events should be carefully analyzed during the decision-making of TKI selection. Nilotinib and ponatinib are contraindicated in the CML treatment in the case of vascular disease[39,40]. Imatinib or bosutinib did not have important contraindications, however, in severe renal impaired patients, imatinib should not be preferred. Dasatinib is related to pleural effusion therefore, in patients with heart/lung diseases, it should not be preferred as the first choice[41]. TKI doses need to be adjusted to the *BCR-ABL1* levels and lifestyle so that CML patients can tolerate adverse effects[1]. The drug's adverse effects, such as lung and cardiovascular toxicity, metabolic syndrome, bone toxicity, vascular events, and gastrointestinal and hepatic toxicity, are the well-known clinical limitations of the given TKI. Therefore, TKI doses should be set up according to the tolerability and organ functions of each individual CML patient[42]. Pregnancy should be evaluated before the initiation of TKI treatment in CML patients because all TKIs are teratogenic[43]. During breastfeeding, TKIs are contraindicated because they are secreted at low levels in breast milk[44]. Hematopoietic stem cell transplantation is a treatment choice for patients who are resistant to at least two second-generation TKIs since those patients generally cannot achieve a sustained response to an alternative TKI[45].

ELN 2020 Recommendation for Tyrosine Kinase Inhibitor Therapy of Chronic Myeloid Leukemia

The frontline standard treatment of CML is a TKI-class drug. Imatinib, dasatinib, nilotinib, and bosutinib are approved for frontline treatment of CML patients by the Food and Drug Administration (FDA) and European Medicines Agency (EMA)[46]. Imatinib, the first-generation TKI was tested and analyzed in the IRIS trial[2], where it achieved higher cytogenetic and molecular responses compared with a combination of recombinant interferon alpha (IFNα) and low-dose cytarabine[47] and better progression-free and overall survival. Imatinib immediately became the first-line choice for the treatment of CML. Nearly all CML patients who were treated in the chronic phase with imatinib resulted in a normal life expectancy[48]. Generic imatinib is the cost-effective initial treatment in chronic phase CML[49]. Imatinib failure, intolerance, and *ABL* kinase domain (KD) resistance mutations lead to the development of second-generation TKIs which are dasatinib, nilotinib, bosutinib[34]. Second-generation TKIs have greater response rates than imatinib, with deeper and earlier treatment responses. According to the results of DASISION trial[9], 42% *vs*. 33% of patients who were given dasatinib and imatinib as the frontline treatment, respectively, achieved MR4.5 within 5 years. Likely, in the ENESTnd study[50], 55% *vs*. 45% of the patients achieved MR4.5 within 6 years and were given nilotinib and imatinib, respectively. Bosutinib is available for frontline treatment with a safety profile different from other second-generation TKIs[49]. Second-generation TKIs have no advantage in survival outcomes compared with imatinib, according to the data from 5- and 10-years analyses of randomized trials[9,51]. All second-line TKIs are effective in controlling disease. Nonetheless, prospective 'head-to-head' controlled trial comparing TKIs with each other is lacking. Ponatinib is a powerful third-generation TKI that is superior to all previous TKIs. Ponatinib is authorized for patients with the *BCR-ABL1T315I* mutation and CML who have failed two or more TKIs[52]. Radotinib is similar to nilotinib, and it has nearly similar efficacy in CML. Radotinib is a fourth-generation TKI that has not been approved by the FDA or the EMA[49]. Asciminib is a novel TKI that is approved for Ph+ CML in the chronic phase patients who were previously treated with more than one TKI, and the treatment of adults with Ph+ chronic phase CML with the T315I mutation[53].

CML treatment algorithms are continuously updated with success inviting to more ambitious goals. Five-year survival of CML patients is now approximately 80-90%[48]. CML patients who achieve a stable deep molecular response can discontinue TKI treatment, about one-half of whom achieve treatment-free remission[54,55]. The clinical benefit of treatment-free remission over lifelong TKI therapy is evident, but achieving this goal is not simple. Some CML patients prefer to continue TKI therapy for several reasons, such as the fear of leukemia recurrence[56]. There is debate on the optimal use of TKIs. The treatment-free survival, improving quality of life, limiting adverse events of TKIs, and the optimal dose and administration duration of TKIs are still a matter of controversy[57-60].

Discussion

Biological Basis of Tyrosine Kinase Inhibitor Effects on the Cardiovascular System in Chronic Myeloid Leukemia and the Interactions Between Bone Marrow and the Cardiovascular System

Intrinsic local renin-angiotensin-aldosterone system (RAS) exists in the bone marrow that controls both the physiological and pathological production of hematopoietic cells[61]. In a previous study[62] aiming to assess expressions of the RAS components, renin, angiotensinogen, and angiotensin-converting enzyme (ACE), during imatinib mesylate treatment of CML patients, it was found that *de novo* CML patients had increased ACE, angiotensinogen, and renin mRNA levels and these expression levels reduced after giving imatinib. The RAS activities were considerably changed according to the Sokal risk groups of CML patients, underlining the different biological activity of RAS in neoplastic disorders[62]. Hematopoietic RAS is related to neoplastic cell production, which may be controlled by TKIs such as imatinib mesylate[62]. Bone marrow has a progenitor that expresses renin during maturation and has a B-lymphocyte pedigree[63]. Deletion of *RBP-J* in the renin-expressing progenitors stimulates the precursor B-cell gene program and limits lymphocyte differentiation. Deletion of *RBP-J* in renin lineage cells results in stimulating cell cycle progression and augmented cell proliferation[63]. Bone marrow contains the *ACE, ACE2, AGT, AGTR1, AGTR2, MAS1, REN, ANPEP* and other important molecules of RAS[64]. Stimulation of the *MAS* receptor or *ACE2* increases the proliferation of CD34+ cells[65]. Vasoreparative effects of CD34 cells are controlled by the cardiovascular protective and deleterious arms of RAS[65]. The ACE2/Ang-(1-7)/MAS axis increases the vaso-protective activity of these cells. On the other hand, CD34 cell activity is stimulated by the ACE/Ang II/AT1 axis either directly or indirectly. Therefore, relative expression of the two axes of local RAS in CD34 cells may be a predictor of their vaso-reparative activity. On the contrary, an imbalance to the increased expression of the ACE/Ang II/AT1 axis may lead to dysfunction of CD34 cells, and this may be a predictor for increased risk for cardiovascular disease[65]. The bone marrow has various roles in tissue healing[66]. Bone marrow-derived stem cells have a role in tumorigenesis and metastases by releasing mesenchymal stem cells and endothelial progenitor cells. Cardiac stem cells have significant importance in improving cardiac function and they are replenished following myocardial injury by the stimulation and release of bone marrow-derived stem cells. Genotypic or phenotypic variances in bone marrow stem cells may result in the generation of inflammatory cells with different effects resulting in modifying end-organ functions[66]. Bone marrow may cause hypertension by stimulating the peripheral inflammatory cells and their extravasation into the brain. Moreover, bone marrow-originated cells have a role in neuroinflammation[67]. Local bone marrow RAS has effects on atherosclerosis as well. Ang II and Ang II type 1 receptor (AT1R), have important pro-inflammatory and pro-atherogenic effects on the vessel wall, leading to the progression of atherosclerosis[68]. Recent investigations[68] clarified that AT1R in bone marrow cells has a role in the pathogenesis of atherosclerosis.

Clinical Tyrosine Kinase Inhibitor Effects on Cardiovascular System in Chronic Myeloid Leukemia

The aim of CML treatment is a cure that leads to normal sex and age-adjusted survival with a normal quality of life, and CVS is an important cause of morbidity and mortality in adult patients. Direct inhibition of *ABL1* leads to myocardial dysfunction or damage to cardiomyocytes which presents as cardiac side effects of TKIs[6,69]. Moreover, mitochondrial dysfunction and stress in the endoplasmic reticulum play a role in the cardiotoxic effects of TKIs at a cellular level[4,5]. Dasatinib leads to substantial myocyte damage. However, imatinib and nilotinib exert mild to moderate or no damage to cardiomyocytes[70,71]. No serious toxicity has been found[49,72] with imatinib after more than 20 years of human use. The cardiac adverse effect of imatinib is severe congestive heart failure because of myocyte contractile dysfunction leading to peripheral edema, shortness of breath, and fatigue[5,6]. Dose titration of TKI is an important issue in adjusting the effective drug dosage without adverse effects. 100 mg of dasatinib daily was found[73] to be as effective as 140 mg daily, with a safer profile for pleuro-pulmonary adverse effects. Bosutinib had an acceptable safety profile for pulmonary and cardiovascular comorbidities[9]. In the BELA trial[74], cardiotoxicities, including heart failure, were compared between the patients receiving bosutinib and imatinib. Ponatinib may lead to serious vascular thrombotic complications, such as stroke and

acute coronary syndrome[49]. For CML patients at high risk of developing pleural effusion, dasatinib should not be preferred[38]. Pulmonary arterial hypertension is a rare but important adverse effect of dasatinib[75] and should be monitored because, if evidenced early, can be reversible. Dasatinib also may lead to pleural effusion, pulmonary hypertension, and QTc prolongation[9,10]. Nilotinib may lead to vasospastic and vaso-occlusive vascular events, such as ischemic heart disease, ischemic cerebrovascular events, and occlusive peripheral artery disease[50]. Nilotinib is similar to imatinib regarding cardiac side effects[8,37]. Also, nilotinib may lead to QT interval prolongation, hyperlipidemia and hyperglycemia[11]. Recent findings[76] suggest that dasatinib and nilotinib are not different from each other in terms of their effects on left ventricle systolic function, and their clinical use after imatinib failure is not related to overt heart failure syndrome. Ponatinib also has serious cardiac adverse events such as arterial vascular events, cerebrovascular disease/stroke, ischemic heart disease, venous thromboembolism, myocardial infarction, peripheral arterial disease, and systemic hypertension[11]. Asciminib is not related to serious cardiovascular adverse effects[77]. The cardiovascular effects of TKIs are summarized in Table I.

Molecular Response and Discontinuation of Tyrosine Kinase Inhibitor in Chronic Myeloid Leukemia

In order to discontinue TKI treatment, the deep molecular response should be achieved[78,79]. The proportion of patients achieving deep molecular response is approximately 20-70% with imatinib and 60-80% with second-generation TKIs[80]. Similarly, the 5-year rates of MR4.5 are nearly 5-35% with imatinib and 35-70% with second-generation TKIs. Second-generation TKIs are superior to imatinib in terms of MR4.5 and deep molecular response. In order to stop TKI treatment, experts[81-83] recommend >5 years of imatinib and >3-5 years of a second-generation TKI, with a response ≥molecular response of 4 (MR4) for ≥2 years. However, comprehensive data that support these suggestions are lacking[18]. Approximately 45% of patients who were given imatinib can achieve MR4 in three years. Supposing that they will sustain the MR4 response for another 2 years, 45% of these patients may be eligible to discontinue TKI treatment at ≥5 years. This ratio is around 50% in CML patients who were given second-generation TKIs. According to all these data[80], 10-25% of CML patients can discontinue TKI treatment, and discontinuation is predicted to be sustainable in 10% of all chronic phase CML patients.

The discontinuation of TKI treatment in CML and the treatment-free remission of CML patients is very important in order to reduce the risk for cardiovascular adverse effects of TKIs. The development of arterio-occlusive events is one of the main risks for CML patients. Cardiovascular events are considerably greater with second-generation TKIs compared to imatinib[35]. In patients who are at risk of developing arterio-occlusive events, imatinib should be preferred rather than second-generation TKIs. In the context of a higher ratio of MR4.5 achievement and deep molecular responses with second-generation TKIs, the discontinuation of TKIs should be considered in eligible patients in order to prevent morbidity from arterio-occlusive events.

Survival in Chronic Myeloid Leukemia

Life expectancy in CML cases approaches the life expectancy of the community[13]. During CML management, it is very important to consider the potential impact of cardiovascular disorders on the patients' survival and quality of life. The cardiovascular disease risk is increased among

Table I. Summary of cardiovascular effects of TKIs.

Imatinib	Severe congestive heart failure due to myocyte contractile malfunction resulting in peripheral oedema, dyspnea, and fatigue[6]
Nilotinib	Ischemic heart disease, ischemic cerebrovascular events, occlusive peripheral artery disease, QT interval prolongation, metabolic syndrome[12,51]
Dasatinib	Pleural effusion, pulmonary hypertension, and QTc prolongation[10]
Bosutinib	Hypertension, palpitations, oedema[75]
Ponatinib	Cerebrovascular disease/stroke, Ischemic heart disease, venous thromboembolism, myocardial infarction, peripheral arterial disease, systemic hypertension[12]
Asciminib	Hypertension, peripheral edema[78]

CML patients receiving TKI treatment[84,85]. There is an association between the increased incidence of cardiovascular disorders and the type, dose, and duration of TKIs[86]. Hypertension was the most frequent adverse event in CML patients who were given TKIs[86]. Particularly ponatinib is associated with cardiovascular or arteriothrombotic adverse events[86]. Survival rates of *de-novo* patients who were treated frontline with TKIs are >95% within the first and second years and >80% within the third, fifth, and tenth years in patients who had been given imatinib or a second-generation TKI as frontline treatment[34,87,88]. Along with the extended survival of CML patients, cardiovascular morbidities should be kept in mind since cardiovascular system disorders are frequently associated with mortality in elderly patients. In a previous study[89], the overall survival rate was found to be 80.5% at 10 years following CML diagnosis and TKI initiation. Cardiovascular complications were found[89] in 9.8% of CML patients. Hypertension was found[89] to be related to cardiovascular events during TKI treatment. TKI treatment contributed to the long-term survival of CML patients, but the incidence of cardiovascular disorders increased in these patients[89]. In CML patients, the cardiovascular death rate was found[90] to be similar in age and gender-matched patients without CML but a higher risk of cerebrovascular and peripheral arterial events was found in CML patients compared to non-CML patients. Therefore, only the cardiac evaluation is not enough for CML patients. CML patients should also be observed for possible cerebrovascular and peripheral arterial events during TKI treatment. In a study[91] that analyzed FDA Adverse Event Reporting System Database (FAERS), nilotinib was found to be especially related to cardiovascular events. Second-generation TKIs have cardiovascular risks that are greater than imatinib, and these risks must be balanced against the superior CML responses achieved by more potent TKIs[92].

Allografting in Chronic Myeloid Leukemia

Hematopoietic stem cell transplantation (HSCT) in CML was frequently used before TKI era. Among more than ten thousand allotransplant patients in 2020, less than two hundred of them were HSCT in CML patients, according to CIBMTR data[80]. 5-year survival is approximately 60% among chronic phase CML patients who underwent allo-HSCT from human leukocyte antigen (HLA)-identical siblings[80]. Fifteen-year leukemia-free survival is 83% in chronic phase CML patients who were transplanted from HLA-identical siblings[93]. Cumulative incidences of relapse are 7% in fifteen years of HSCT[93]. The relapse is not common after 5 years after transplantation[93]. However, these data include pre-TKI era patients. In the TKI era, according to the CIBMTR data[80], the five-year cumulative incidence of relapse is 18% and nearly all relapses are in the first year following HSCT. Leukemia recurrence is uncommon after allo-transplants for chronic phase CML patients[93]. CML patients who respond poorly to TKI therapy are more likely to undergo HSCT than good responders and HSCT is preferred generally in younger patients with good performance. Transplant procedures have advanced during the last few decades. The increased use of blood cells over bone marrow, the reduced intensity pre-transplant conditioning regimens, and the utilization of post-transplant cyclophosphamide and anti-lymphocyte globulin, which reduces the risks of graft-versus-host disease without increasing relapse risk are some of the developments of HSCT procedure in CML patients[94-96]. The innovations reduced transplant-related mortality by 20% and increased survival by 10%[97]. Although these results are promising for HSCT in CML patients, the risks of HSCT are still important. Some CML patients develop chronic graft-versus-host disease or other HSCT complications which compromise the quality of life and are sometimes fatal. Comorbidities of CML patients directly affect the outcome of HSCT. Cardiac diseases, coronary artery diseases, vessel coronary stenosis requiring medical treatment, stent, or coronary artery bypass graft are the cardiac comorbidities that are included in hematopoietic cell transplantation (HCT)-specific comorbidity index in order to assess the risk of HSCT[98]. Therefore, in CML patients with cardiovascular disease, the decision of HSCT should be carefully analyzed. The novel TKIs such as asciminib have the potential to postpone the need for HSCT in some resistant CML patients with an acceptable side effect profile since it has promising outcomes in chronic phase CML patients who are resistant/intolerant to two or more prior TKIs and patients with *T315I* mutation[77]. The elderly CML patients and especially the patients who have cardiac comorbidities, should be carefully evaluated for TKI treatment, and HSCT should be the last choice in these risky CML patients.

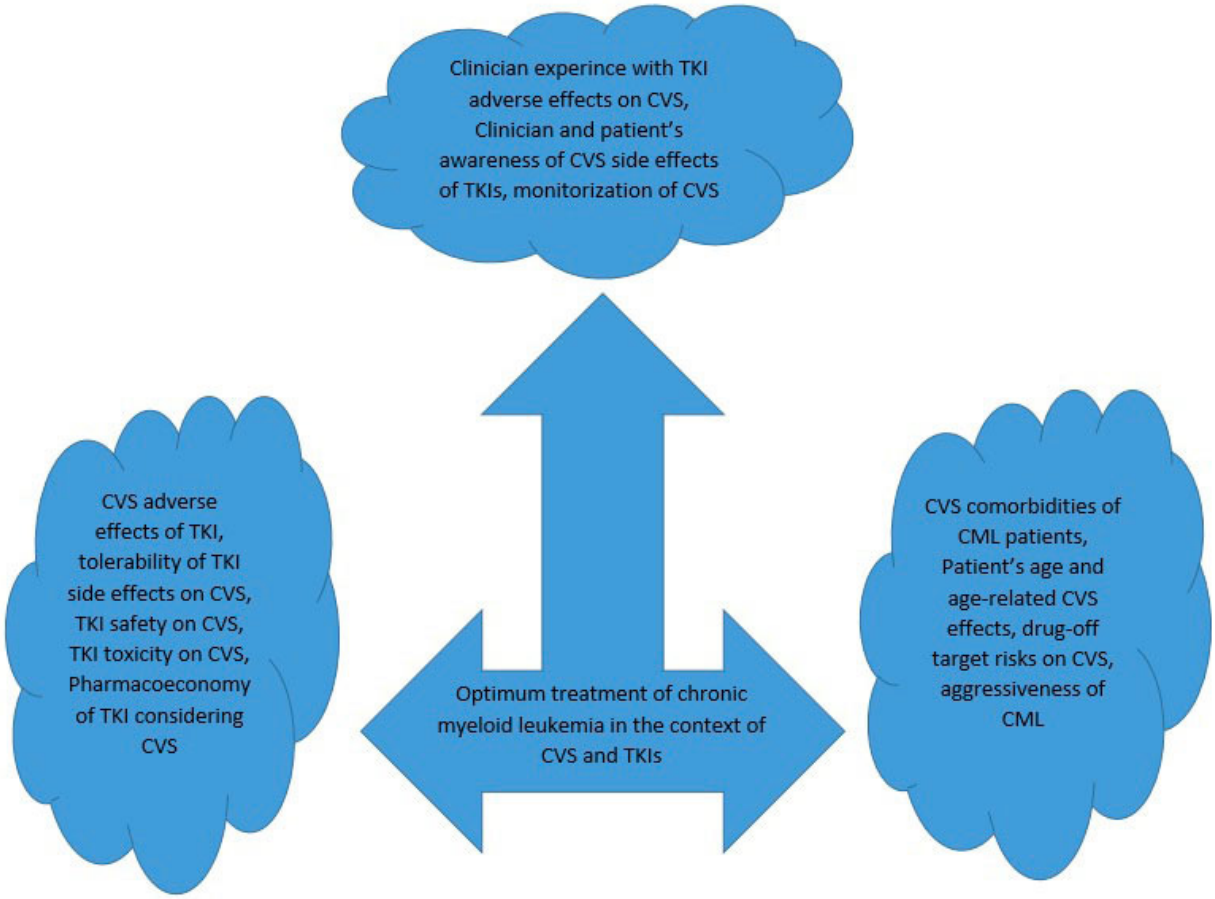

Figure 2. Optimum treatment of chronic myeloid leukemia in the context of CVS and TKIs. CML: chronic myeloid leukemia, TKI: tyrosine kinase inhibitor, CVS: cardiovascular system.

Conclusions

The clinical management of a CML patient should include three major considerations. Firstly, the TKI availability and reimbursability, clinician experience with TKI, clinician and patient adherence to TKI treatment, and monitorization should be carefully analyzed. Secondly, the TKI safety, efficacy, tolerability, toxicity, and pharmacoeconomy should be considered. Thirdly, CML disease risk, patients' age and comorbidities, patients' compliance and lifestyle, and drug-off target risk profile should be cautiously examined (Figure 2). The cardiovascular evaluation of CML patients is essential since the median age of CML diagnosis is 60 years[99]. The current target CML treatment is a cure that leads to normal age and gender-adjusted survival with a normal quality of life. Cardiovascular disorders are one of the major obstacles to reach this target in CML patients. The treatment choices for CML patients must include a cardiovascular perspective. HSCT should be the last choice for almost all CML patients in this era when novel TKIs are being developed. Asciminib may be used in CML patients who are resistant/intolerant to two or more prior TKIs with an acceptable side effect profile.

Authors' Contributions

UYM: Conceived and designed the analysis, collected the data, performed the analysis, wrote the paper
ICH: Conceived and designed the analysis, and critically review of the paper.

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Conflict of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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