Review

For reprint orders, please contact: reprints@futuremedicine.com

International Journal of Hematologic Oncology

The effect of comorbidities on the choice of tyrosine kinase inhibitors in patients with chronic myeloid leukemia

Guray Saydam*[,1], Ridvan Ali[2], Ahmet Muzaffer Demir[3], Ahmet Emre Eskazan[4], Birol Guvenc[5], Ibrahim Celalettin Haznedaroglu[6], Mehmet Ali Ozcan[7], Ozan Salim[8], Mehmet Sonmez[9], Ayse Tulin Tuglular[10], Mehmet Turgut[11], Ali Unal[12], Birkan Aver[13], Sirac Bozkurt[13], Begum Ozdengulsun[13] & Osman Ilhan[14]

[1]Department of Internal Diseases, Division of Hematology, Ege University Medical Faculty Hospital, İzmir, Turkey
[2]Department of Internal Diseases, Division of Hematology, Uludag University Medical Faculty Hospital, Bursa, Turkey
[3]Department of Internal Diseases, Division of Hematology, Trakya University Medical Faculty Hospital, Edirne, Turkey
[4]Department of Internal Diseases, Division of Hematology, Istanbul University Cerrahpaşa Faculty Hospital, İstanbul, Turkey
[5]Department of Internal Diseases, Division of Hematology, Cukurova University Medical Faculty Hospital, Adana, Turkey
[6]Department of Internal Diseases, Division of Hematology, Hacettepe University Medical Faculty Hospital, Ankara, Turkey
[7]Department of Internal Diseases, Division of Hematology, Dokuz Eylul University Medical Faculty Hospital, İzmir, Turkey
[8]Department of Internal Diseases, Division of Hematology, Akdeniz University Medical Faculty Hospital, Antalya, Turkey
[9]Department of Internal Diseases, Division of Hematology, Karadeniz Technical University Medical Faculty Hospital, Trabzon, Turkey
[10]Department of Internal Diseases, Division of Hematology, Marmara University Medical Faculty Hospital, İstanbul, Turkey
[11]Department of Internal Diseases, Division of Hematology, Ondokuz Mayıs University Medical Faculty Hospital, Samsun, Turkey
[12]Department of Internal Diseases, Division of Hematology, Erciyes University Medical Faculty Hospital, Kayseri, Turkey
[13]Medical Oncology Department, Pfizer Pharmaceuticals, Istanbul, Turkey
[14]Department of Internal Diseases, Division of Hematology, Ankara University Medical Faculty Hospital, Ankara, Turkey
*Author for correspondence: saydamguray@yahoo.com

Practice points

- Pre-existing comorbidities or the comorbidity-related polypharmacy, due to their toxicity profiles which may be different than that of concomitant tyrosine kinase inhibitors (TKI), may pose a risk in terms of patient safety.
- Due to the effect on survival and treatment choice in patients with chronic myeloid leukemia, it is important to consider comorbidities not only at baseline but at every stage of treatment and include Charlson Comorbidity Index, which is shown to be more useful in determining the prognosis in comorbid patients, into the clinical routine.
- Monitoring patients for toxicities, drug–drug interactions and discontinuing all unnecessary medicinal and nutritional supplements during TKI treatment would provide a positive contribution by reducing complications through early measures taken in a timely manner.
- The use of nilotinib should be avoided in patients with vascular risk factors and metabolic dysfunctions, and dasatinib in patients with pulmonary damage.
- Bosutinib may be the most ideal second generation TKI treatment alternative for patients with cardiac problems.
- It would be appropriate to prefer 2nd generation TKIs over ponatinib in patients with advanced cardiovascular comorbidities or those who develop specific mutations that may be sensitive to treatment with different 2nd generation TKIs.
- Comorbidity-related treatment discontinuation or change may make it difficult to achieve long-term disease control while moving toward the goal of treatment-free remission; therefore, treatments with TKIs should be planned and chosen accordingly.
- The use and superior efficacy of TKIs should be balanced against the potential risks.

Tyrosinekinase inhibitors (TKIs) approved for chronic myeloid leukemia known to have similar efficacies but different safety profiles. Therefore, the choice of patient-specific treatments is driven by factors such as tolerability and adverse event profile of TKIs. This review article examines the most up-to-date data and provides practical recommendations for clinical approaches. Nilotinib and ponatinib should be avoided in patients with cardiovascular risk factors, dasatinib in patients with lung damage and bosutinib and nilotinib in patients with liver disease. Considering that certain comorbidities predispose some patients to developing severe adverse events when receiving TKIs, the first- and second-line treatment of chronic myeloid leukemia should be tailored to each patient's individual condition.

Future Medicine

First draft submitted: 31 May 2021; Accepted for publication: 7 March 2022; Published online: 24 May 2022

Keywords: adverse event • chronic myeloid leukemia • comorbidity • drug toxicity • interactions (drug–drug) • safety • tolerability • tyrosine kinase inhibitor

In recent years, TKIs has significantly improved the survival of chronic myeloid leukemia (CML) patients, and most of them achieve a life expectancy similar to those of individuals without CML [1]. According to the indirect comparisons of the TKI studies, the first-generation TKI imatinib and second generation TKIs bosutinib, dasatinib and nilotinib have similar efficacy with different safety profiles [2–4]. Third-generation TKI ponatinib also has some safety concerns. Therefore, the choice of TKI treatments in CML has started to be driven by factors such as tolerability and adverse event profile of TKIs as well as disease phase and mutation profile [4,5].

Recent data suggest that TKI-related serious adverse events occur more frequently in patients with pre-existing risk factors or who are suffering from certain comorbidities [6]. Globally, elderly CML patients in chronic phase (CP) who receive TKI treatments increase in number and experience varying degrees of adverse effects during their treatment due to having one or more comorbid conditions. The underlying reason of this situation is the altered pharmacokinetic/pharmacodynamic status in these patients, which narrows the therapeutic window of antineoplastic agents. Therefore, comorbidities may also affect the treatment success and overall survival (OS) of CML patients in chronic phase CP even in the tyrosine kinase inhibitor (TKI) era [7–9]. Based on these data, current guidelines recommend that comorbidities and associated polypharmacy should be taken into account along with other parameters when choosing TKI treatments for CML patients [3,10,11].

This review article with expert opinions aims to investigate the presence of comorbidities and risk factors in CML patients and evaluates the impact of comorbidities on TKI treatment outcomes while considering toxicity and drug–drug interactions (DDI) of TKIs. This study also explores the most recent guidance papers on the choice of TKIs in CML patients with comorbidities and provides practical recommendations.

Materials & methods

The main literature search was performed in English by searching MEDLINE, EMBASE and PubMed databases for the 2010–2021 period in order to utilize the most recent data. Literature dating back to previous periods were reviewed only for the purpose of evaluating the historical evolution of epidemiological data and relevant treatments. TKI and/or chronic myelogenous leukemia were used as constant terms for the main literature search; with comorbidity, cardiovascular, vascular, cardiac, coronary, pulmonary and metabolic as sub terms in addition to further terms that included risk, disease, failure, safety, adverse event and side effect. The literature search was completed by including the terms that were frequently encountered during the initial search performed with the specified terms (peripheral vascular disease, ischemic heart disease, heart failure, myocardial infarction, venous thromboembolism, cerebrovascular events, hypertension and pulmonary hypertension, hyperglycemia, diabetes, obesity, hyperlipidemia and hypercholesterolemia, liver problems, gastrointestinal toxicity, renal pathology and ulcer) as main constant terms considering that they could provide more comprehensive information about the reviewed subject. Articles reporting preclinical data, and articles not directly related to comorbidities, toxicities and adverse events associated with TKIs used for CML were not included. The citations of references were reviewed when relevant and finally most recent related guidelines were also assessed.

Prevalence of comorbidities & evaluation of risk factors in CML patients

In a population-based registry study conducted in Europe which was designed to observe the characteristics and the epidemiology of CML patients from 20 countries, median age was reported as 56 years, 55.5% of patients had comorbidities, mainly cardiovascular (41.9%). While a single comorbidity was recorded in 28.7% of the patients, 15.3% were found to have two and 11.5% had three comorbidities. The most common comorbidities were hypertension (HT) (25.7%), other cardiovascular diseases (CVD) (17.2%) and diabetes mellitus (DM) (9.5%). The study also determined that 34.5% of all patients were at low risk and 24.7% were at high risk according to the Sokal risk scores [12]. Another study carried out in Italy investigated the effect of comorbidities on health-related quality of life in elderly patients (over 60 years of age) with CML and 64% of these patients were observed to have at least one comorbidity [13].

In an analysis by Jabbour and colleagues, which used data from patient insurance claims in the USA in 2015, reported that approximately 41% of the identified CML patients had at least one comorbid condition that may

Table 1. Comorbidities of the chronic phase-chronic myeloid leukemia patient populations in different countries.

Scope of the study	Region	Population size (n)	Median age (years)	Total CMs (%)	Most common CMs	Ref.
Population-based EUTOS registry	Europe	2904	56	55%	HT, CVD, diabetes, ND, CRF	[12]
Real-world Insurance Claims Database	USA	2296	56	41%	CVD, diabetes, PD, ART, PE	[14]
Multi-center retrospective study in Turkey	Turkey	861	52	31%	CVD, diabetes, PD†	[16]
The effect of comorbidities in elderly patients (aged 60 years and above)	Italy	174	70	64%	OA, VP, diabetes, PD, LP	[13]

†Data unspecified for other comorbidities.
ART: Arrhythmia; CM: Comorbidity; CP: Chronic phase; CRF: Chronic renal failure; CVD: Cardiovascular disease; HT: Hypertension; LP: Liver problems; ND: Neurological disease; OA: Osteoarthritis; PD: Pulmonary disease, PE: Pulmonary embolism; VP: Vascular pathology.

influence the choice of TKI treatment as recommended by NCCN guidelines [14]. This analysis on real-world data showed that the most prevalent comorbid condition was heart disease (23%), followed by DM (18%) and lung disease (13%). It was noted that the prevalence of comorbidities relevant to TKI treatment choice varied among patients of different age groups, genders and USA regions [14]. Another study conducted in USA reported that 18.7% of CML patients had CVD at baseline and that this figure increased to 33.0% during the 5-year follow-up period. The most common CVD conditions were observed to be myocardial infarction and atherosclerosis, prevalent in 10% of patients at baseline and increased to 16% during follow-up. The standardized prevalence rates of myocardial infarction, heart failure, atherosclerosis and stroke at 1 year in patients with CML were significantly higher by factors of 1.3–3.5-times ($p < .001$) when compared with the general US adult population [15]. Additionally, prevelance rates of hypertension, DM and obesity ($p < 0.001$) were also reported to be significantly higher (20–40%).

A recent retrospective study investigated the demographic and clinical characteristics of the CP-CML patient population in Turkey. The results revealed that these patients were younger (52 years) compared with the similar patient populations in Europe and USA, albeit 31% of them had varying numbers of comorbidities with a significant impact on OS (Table 1) [16]. Among these comorbidities, the most prevalent conditions were CVD (13.9%), DM (10.5%) and pulmonary diseases (3.3%) respectively [16].

A systematic analysis of epidemiological registries and trials of TKIs demonstrated that the median age at diagnosis of CML was between 60 and 65 years in most epidemiologic registries, while median age of the enrolled patients in majority of the TKI trials with newly diagnosed CML patients was significantly lower, around 50 years [17]. The prevalence of comorbidities in CML patients enrolled in these clinical studies was also relatively low if compared with an age-matched population [17]. Therefore, this analysis and real-world data of CML patients across different geographies revealed that CML patients within clinical trials are not representative of a significant part of CML patients observed in the daily practice [14,17].

Recommendation 1

Pre-existing comorbidities and comorbidity-related polypharmacy may pose a safety risk to CML patients receiving TKI treatments. Therefore, it is important to assess the presence and the severity of comorbidities at the time of initial CML diagnosis and routinely monitor patients on these issues during their long-term TKI treatments. Baseline screenings and routine monitoring of organ functions should be planned by hematologists along with relevant specialists where necessary.

The impact of comorbidities on prognosis

Several scoring systems such as Sokal, Hasford, EUTOS and ELTS have been proposed to predict prognosis in CML patients [18]. While Sokal and Hasford scoring systems can be used effectively to predict prognosis in CML patients, both are considered insufficient in evaluating comorbidities [18]. The Charlson Comorbidity Index (CCI) is a different method that is widely employed to estimate the 1-year mortality in patients with certain comorbid conditions [14]. CCI has been considered beneficial in predicting long-term prognosis of CML patients with or without comorbidities; furthermore, some studies have determined CCI to be more useful in evaluating elderly CML patients with other underlying diseases [18].

Participants of a CML treatment study were analyzed for comorbidities at diagnosis using the CCI [19]. A significant association between higher CCI scores and lower OS estimates was reported. The 8-year OS probabilities were 93.6, 89.4, 77.6 and 46.4% for patients with CCI 2, 3–4, 5–6 and 7+, respectively. This study demonstrated that comorbidities did not affect treatment success but had a negative effect on OS indicating that survival is

10.2217/ijh-2021-0010

determined more by comorbidities in patients with CML than CML itself. The authors suggested that the OS may not be an appropriate outcome measure for specific CML treatments and should be stratified by comorbidities in future CML studies [19].

Another study analyzed the potential correlation between baseline CCI and response rates of patients with CML in CP treated with second generation TKIs. The results did not show a significant difference between different risk categories based on CCI stratification with regard to the cumulative incidence of complete cytogenetic response (CCyR) and molecular response or in terms of discontinuation/dose reduction due to toxicity. However, a difference in OS was noted at a median follow-up of 2 years. OS was found to be 99% in those with CCI score 0 (95% CI; 89–100%; HR: 1.9), 92% in those with CCI 1–2 (95% CI; 88–95%; HR: 2.2), 89% in those with CCI 3–4 and only 76% in patients with CCI scores higher than 5 (95% CI; 72–83%; HR: 1.8) ($p = 0.01$). In a second analysis, which was not age-adjusted, CCI stratification appeared to maintain its prognostic role for OS [20].

Iurlo and colleagues retrospectively evaluated the effect of comorbidities and polypharmacy on achieving CCyR at 6 months in a group of elderly CML patients receiving treatment with imatinib and demonstrated that low CCyR was correlated with high CCI and polypharmacy. The vast majority of patients achieving CCyR were observed to have low CCI scores and were not receiving medication other than TKI treatment [21].

A retrospective registry study on treatment outcomes in Turkey showed longer OS in CML patients without DM ($p = 0.026$), without CVD ($p < 0.001$) and without concurrent treatment at the time of diagnosis ($p = 0.007$) [16]. In another retrospective study from Turkey that compared the efficacy and safety of imatinib between elderly (aged ≥60 years) and younger (aged <60 years) patients with CML, age at diagnosis and CCI were found to be associated with OS. Patients with CCI score ≥2 had a 3.8-times higher risk of death than patients with CCI score = 0 ($p = 0.033$) [22].

A study conducted in Italy investigated whether the presence and number of comorbidities led to decreased physical and cognitive health-related quality of life in elderly (aged 60 years and above) CML patients. Patients without comorbidities (Com0) were found to have significantly better scores in physical and cognitive health scales compared with those with one comorbidity (Com1) or two or more comorbidities (Com ≥2). In addition, a statistically significant difference (by at least twofold) was observed in all eight subscales of physical and cognitive functioning between the patients in the Com0 group and the Com ≥2 group [13].

In countries where imatinib is the only first-line treatment that can be used in CML patients (due to access conditions of TKI treatments) regardless of the prognosis score, the motivation to use these prognostic scores would be lower in hematologists since it will not make a difference in their treatment preference. For patients who are eligible to start a 2nd generation TKI as recommended by guidelines but have to start receiving imatinib treatment (due to drug access regulations) switching to a 2nd generation TKI should be considered when the disease control is not achieved at 3 months in line with the NCCN recommendations [3].

Recommendation 2

Despite the access barriers to treatments, scoring systems including CCI, which is shown to be more useful in determining the prognosis in comorbid patients, will continue to drive future treatment choices for CML patients who will receive long-term treatment. Therefore, it is important to include CCI in patients assessments. Comorbidities in CML patients should be investigated not only at baseline but at every stage of treatment due to their effect on survival and treatment choice in patients with CML. Comorbidities that may be associated with the common side effects of TKI treatments should also be borne.

Pharmacological properties, toxicity profile & DDIs of TKI treatments

The different pharmacological properties of TKIs are thought to be contributing to their toxicity profiles [23,24]. Detailed pharmacological properties of TKIs are summarized in Table 2 [2,23–26], and the most common side effects observed with TKIs in clinical studies are summarized in Table 3 [2,23–28].

The side effects of TKIs may pose risks to CML patients by triggering new or aggravating previous comorbidities (HT, CVD, DM and PD). HT appears to be relatively more common, especially in patients receiving ponatinib, in relation to its increased dose intensity, compared with other TKIs [12,14,15,29–31]. Compared with imatinib and dasatinib, nilotinib is associated with increased arterial thrombosis (more common with doses higher than 400 b.i.d.), where the risk of relevant complications also depends on the presence of previous cardiovascular risk factors [32–34]. While the risk of occlusive vascular events increases significantly with dasatinib, nilotinib and ponatinib compared with imatinib, such an increase was not observed with bosutinib [35]. Despite the use of nilotinib has been associated with increased fasting plasma glucose levels and other glucometabolic abnormalities,

Table 2. Pharmacological properties of tyrosine kinase inhibitors in chronic myeloid leukemia.

Pharmacological properties	First-generation TKI	Second-generation TKI				Third-generation TKI
		Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
Mechanism		Inhibits BCR-ABL tyrosine kinase by binding at the ATP-binding site	Competitively inhibits Src and ABL tyrosine kinases	Inhibits c-KIT, BCR-ABL and Src-family kinases, PDGFR-α and β and ephrin receptor kinase	Competitively binds to the ATP binding site of the inactive conformation of BCR-ABL tyrosine kinase	Designed to overcome the resistance of T315I mutation
Dosage	Chronic phase	400–800 mg/day	400–600 mg/day	100 mg mg/day	600 mg/day	45 mg/day
	Accelerated phase	600–800 mg/day	500–600 mg/day	140 mg mg/day	800 mg/day	45 mg/day
	Blastic phase	600–800 mg/day	500–600 mg/day	140 mg mg/day	Not indicated	45 mg/day
Absolute oral bioavailability		98%	23–64%†	14–34%†	50–82%	Not detected
Time to maximum concentration /Half-life (h)		2–4/18	4–6/22.5	0.5–6/3–5	3/17	6/24
Food intake	Fasting			✓	✓	✓
	with food	✓	✓	✓		✓
BBB penetration		<2%	<50%	<28%	<2%	NR
Major metabolism/elimination		CYP3A4/mostly with feces	CYP3A4/mostly with feces	CYP3A4/mostly with feces	CYP3A4/mostly with feces	CYP3A4/mostly with feces
Dose adjustment	Hepatic failure	Mild, moderate or severe failure: 400 mg/day If intolerable, the dose may be reduced	Mild, moderate or severe failure: 200 mg mg/day However, drug should be used with caution	Mild, moderate or severe failure: Standard dose However, drug should be used with caution	Mild, moderate or severe failure: Standard dose However, drug should be used with caution	Mild, moderate or severe failure: Standard dose However, drug should be used with caution
	Renal failure	Severe failure and ESRD: 400 mg/day If intolerable, the dose may be reduced.	Moderate: 400 mg/day in ≥2nd line 300 mg/day in 1st line Severe: 300 mg/day in ≥2nd line 200 mg/day in 1st line If intolerable, the dose may be reduced.	Mild, moderate or severe renal failure: Decrease in drug clearance is not expected	Mild, moderate or severe renal failure: Decrease in drug clearance is not expected	CrCl of <50 ml/min or ESRD: Caution is recommended
Important drug interactions	Increased exposure	CYP3A inhibitors, PPIs, quinolones, azoles, valproic acid, CSA	CYP3A inhibitors, azoles	CYP3A inhibitors, Beta blocker, ACE inhibitor, macrolide, azoles, CSA	CYP3A inhibitors, macrolides, valproic acid, azoles, CSA Drugs prolonging QT interval has additive effect	CYP3A inhibitors, Azole, protease inhibitor, macrolide
	Decreased exposure	CYP3A inducers (Dexamethasone, phenytoin, rifampicin, carbamazepine), lamivudine, metformin	CYP3A inducers (Phenytoin, rifampicin, carbamazepine), PPIs	CYP3A inducers (Dexamethasone, phenytoin, phenobarbital, carbamazepine), H-2 antagonists, PPIs, antacids	CYP3A inducers (Dexamethasone, phenytoin, phenobarbital, carbamazepine)	CYP3A inducers (Phenytoin, rifampicin, carbamazepine),
Fertility, pregnancy, and lactation		Contraception advised, Not recommended during pregnancy and breastfeeding	Contraception advised, Not recommended during pregnancy and breastfeeding	Contraception advised, Not recommended during pregnancy and breastfeeding	Contraception advised, Not recommended during pregnancy and breastfeeding	Contraception advised, Not recommended during pregnancy and breastfeeding
Use in elderly		No differences in safety and efficacy	No differences in safety and efficacy	No differences in safety and efficacy	No differences in safety and efficacy	More likely to experience adverse reactions

†Only animal studies.
BBB: Blood–brain barrier; CrCl: Creatinine clearance; CSA: Cyclosporine; ESRD: End stage renal disease; NR: Not reported; PPI: Proton pomp inhibitors.

hyperglycemia is not generally observed (<1%) with other TKIs [36–40]. Studies suggest that up to 30% of patients treated with dasatinib develop pleural effusion, and this complication may occur at any time during treatment. Although temporary drug interruption, diuretics and low-dose steroids can effectively be used to manage this

10.2217/ijh-2021-0010

Table 3. Key toxicities of tyrosine kinase inhibitors in chronic myeloid leukemia patients .

	Grade ¾ toxicities		Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
Non specific to drug†	Hematologic adverse events	*Anemia*	+++	+++	++++	++	++++
		Thrombocytopenia	++++	++++	++++	+++	++++
		Neutropenia	++++	++++	++++	+++	++++
	Fatigue		++	+	++	+	++
	Rash		++	+++	++	++	++
	Nausea		-	++	-	+	+
	Musculoskeletal/joint pain		++	+	++	++	++
	Headache		+	+	+	++	++
Specific to drug‡	ALT increased		++	++++	+	+++	++
	Diarrhea		++	++++	+	+	-
	Vomiting		-	++	-	-	-
	Abdominal pain		-	++	-	-	+++
	Edema		+++	+	+	+	+
	Pleural effusion		+	++	++++	+	+
	Lipase increased		+++	+++	-	+++	++++
	Pancreatitis		+	-	-	++	+++
	Hyperglycemia		-	-	-	+++	-
	Pulmonary hypertension		-	-	++	-	-
	Hemorrhage		+	-	+++	+	+
	Hypertension		+	++	-	-	++++
	Congestive heart failure		+	-	++	-	++

Grade 3/4 toxicity from the clinical trial data available for first-/second line use of the TKI in CP-CML: + ≤1% of the patients ++ = 1–5% +++ = 6–10%. ++++ = 11–50%. +++++ = 51–100%.
†Non specific to drug: common side effects of TKI treatment in CML patients.
‡Specific to drug: Side effects which are unique or more specific to some TKIs in CML patients.
CML: Chronic myeloid leukemia; TKI: Tyrosine kinase inhibitor.

complication, recurrent pleural effusion has been reported in the majority (up to 70%) of these patients upon resuming treatment with dasatinib [41–43].

The prevalence of fatigue and myalgia varied across large clinical trials of TKIs. While these trials were not designed to assess fatigue and myalgia, which may explain the wide range of prevalence rates, there was not a significant difference in prevalence between patients taking different TKIs [34,37,39,44]. In a cross-sectional survey study which assessed fatigue severity and fatigue predictors in 220 CML patients receiving TKI therapy and 110 gender- and age-matched controls, it was demonstrated that the majority of the CML patients receiving TKI therapy experienced severe fatigue and that severely fatigued patients have impaired quality of life [44]. Independent predictors of severe fatigue include were found to be; younger age, female gender, higher CCI, the use of comedication known to cause fatigue and physical inactivity. These findings highlighted the importance to set the reduction of fatigue as a treatment goal in CML care and the need for future studies to identify physical activity as a possible target to achieve this goal.

Potential teratogenicity of TKI is clearly a matter of concern. Congenital abnormalities on imatinib were mostly observed when it was used during organogenesis, no preclinical teratogenicity and no increased rate of birth abnormalities have been described in the full prescribing information for nilotinib and dasatinib has been noted to be harmful to the fetus in both early and late gestation. While imatinib and nilotinib's placental transfer is limited, dasatinib passes through placenta. The paucity of information regarding bosutinib as well as ponatinib discourages their use even after placental and organ formation [45–48]. Although there is only limited information about the effects of TKIs on human embryos, the possibility of placental insufficiency, low birth weight, premature birth, perinatal morbidity and mortality should be taken into account while making a decision between terminating the pregnancy or discontinue TKI treatment [49].

While numerous studies and reviews have been published on the DDIs of conventional chemotherapeutic agents, studies investigating the drug interactions specific to TKIs appear to be limited with regard to CML

patient profiles [50–53]. Drug interactions between TKIs and other prescribed drugs have been shown to reduce treatment efficacy and increase the rate of side effects in various oncology patient cohorts [53]. Keller and colleagues reported that potential DDIs were identified in 244 of the 356 patients included in their study, with 109 (44.7%) considered in the severe category [52]. In this study, the most common mechanisms leading to subtherapeutic and supratherapeutic concentrations were reduced absorption of the TKI due to concomitant gastric acid-suppressive therapy and interactions with the CYP3A4 enzyme, respectively. Other reported clinical outcomes were QTc prolongation (n = 53, 48.6%), decreased TKI concentration (n = 53, 48.6%) and increased TKI concentration (n = 3, 2.8%) [52]. In another study, 94.8% (251) of 265 patients were receiving various prescribed drugs in addition to TKI treatment [54]. In this study, where the interaction rate of TKIs with other prescribed drugs was 54.2%, the nature of the interaction was described as a decrease in TKI level in 39.7% of the patients and an increase in TKI level in 30.1%. In addition, it was reported that 77.1% of these patients had been warned on the increased risk of QT prolongation [54]. In a retrospective multicenter study that aimed to investigate the frequency and real clinical consequences of DDI between TKI and concurrent medications in CML, it was reported that 60% of the study population had at least one potential DDI (n = 105). The most common drug classes involved in DDIs were proton pump inhibitors and statins. Most of the AEs attributed to DDIs were mild and the most common were diarrhea, vomiting, edema, cramps and transaminitis. Nilotinib and dasatinib showed a tendency toward a higher risk of DDI compared with imatinib [55].

Recommendation 3

All non essential medicinal products and nutritional supplements in CML patients should be discontinued and the drugs that need to be continued but carry a risk of interacting with TKI treatments should be closely monitored. Such considerations would especially be important when choosing the second generation TKIs as well as during the treatment period with these drugs. Another important notion is the fact that TKIs may have potentially teratogenic properties. Patients who got pregnant during TKI treatment should be advised to make a decision between terminating the pregnancy or discontinue TKI treatment, after being thoroughly informed about the risks of treatment interruption throughout pregnancy. Additonally, patients diagnosed with CML during their pregnancies should also be informed on the chance of progression without TKI treatment.

Practical approaches in choosing TKI treatments

In a study that investigated the cardiovascular, metabolic and pulmonary toxicities of TKIs in patients with CML, Medeirosa and colleagues looked in to the current evidence for monitoring, evaluating and managing such complications. They concluded that all patients receiving TKI agents for CML should be monitored for signs and symptoms of toxicity throughout therapy. They also reported that proactive assessment, early detection of adverse events and prompt management of toxicities can minimize treatment-limiting complications and improve outcomes in patients with CML [30].

In 2020, Jabbour and Kantarjian systematically assessed how CML patients should be evaluated regarding their comorbidities before choosing a TKI treatment [56]. They stated that dasatinib should not be be used in patients with a risk of developing pleural effusion (with pre-existing lung damage) and/or who were previously diagnosed with pulmonary arterial hypertension. In addition, they claimed that patients receiving dasatinib concurrently with anticoagulants may be at a higher risk of hemorrhagic complications. In this review, it is recommended to avoid nilotinib or prescribe this agent with caution in patients with DM or a history of pancreatitis. Patient's serum potassium and magnesium levels should be brought to an adequate range prior to determining their QT interval or before starting a treatment with nilotinib. Authors also recommended to avoid or limit the use nilotinib in patients with risk factors such as DM, coronary artery disease or cerebrovascular disease. Bosutinib and imatinib were noted as the safest TKIs in terms of cardiovascular events. Bosutinib should not be preferred or should be used with caution in patients with gastrointestinal, hepatic and renal comorbidities and bosutinib should be avoided in patients with inflammatory bowel disease or renal dysfunction [56].

European LeukemiaNet 2020 recommendations on CML treatments also underline the importance of comorbidity assessment in CML patients before choosing a TKI treatment. These recommendations state that previous or concurrent arteriovascular diseases indicate a major contraindication for first-line nilotinib and second/third-line ponatinib, nilotinib may also elevate serum cholesterol levels which can be associated with later arterial occlusions. Respiratory failure, previous or concurrent pleural-pulmonary disease are outlined as major contraindications for first-line initiation of dasatinib. Dasatinib may affect platelet function; thereby, can be a predisposing factor for bleeding despite the disproportionate platelet count. It has been noted that patients with significant renal failure

10.2217/ijh-2021-0010

should not use imatinib and diarrhea is common particularly with bosutinib, while no other significant comorbidity or major contraindication has been identified for bosutinib and imatinib. It has also been stated that hepatotoxicity may occur with any TKI, especially with bosutinib and nilotinib but mostly in the form of elevated transaminase levels rather than more serious evidence of drug-induced liver damage. Finally, history of pancreatitis is also specified as a contraindication for the use of nilotinib, therefore it is recommended to use other TKIs in patients with a history of pancreatitis [10].

The British Society for Hematology guideline, which is the most recently updated guideline for the diagnosis and management of CML recommends a baseline evaluation including electrocardiography, lipid profile, fasting glucose level or HbA1c, CVD risks, hepatitis B and C screening before the initiation of treatment (Grade 2B). It recommends second generation TKIs in patients with a high or intermediate ELTS or Sokal score (Grade 2B) or in those who may wish to attempt early treatment discontinuation (e.g., female patients who wish to become pregnant)(Grade 2B) and evaluating comorbidities before choosing a 2nd generation TKI (Grade 2B) [11].

Similar statements have also been included in the 2021 version of NCCN guidelines with additional sections on DDIs (between TKIs and concurrent medication) and on the management of TKI-related side effects. While concurrent use of histamine 2 receptor antagonists or proton pump inhibitors with bosutinib, nilotinib and dasatinib cause a drop in these TKIs' serum concentrations, NCCN 2021 guideline recommends to administer histamine 2 receptor antagonists $\geq$2 h after bosutinib and dasatinib, $\geq$2 h after or $\geq$10 h before taking nilotinib when patients can not avoid using these TKIs. It is also recommended to use antacids at least 2 h before or after taking each of three TKIs. It has been stated that investigating TKI-related side effects and planning appropriate follow-up visits for the adequate and proper management of these side effects may be beneficial in terms of improving treatment persistence. In addition, switching to an alternative TKI in patients with acute grade 3/4 non hematological toxicities or in those with low-grade, chronic and persistent adverse events that cannot be managed with appropriate supportive care measures was noted as usefull [3].

Recommendation 4

Comorbidity status, concomitant drug usage, cardiovascular, metabolic and pulmonary risk factors should be interrogated in CML patients both at diagnosis and during the treatment period. Monitoring patients for the possible toxicities related to TKI treatments can reduce complications through early measures taken in a timely manner. The use of nilotinib should be avoided in patients with vascular risk factors and metabolic dysfunctions and dasatinib should not be used in patients with pulmonary damage. Bosutinib is the most suitable second generation TKI treatment alternative for patients with cardiac problems. Finally, it would be more appropriate to prefer 2nd generation TKIs over ponatinib in patients with advanced cardiovascular comorbidities or those who develop specific mutations that may be sensitive to different 2nd generation TKIs (Figure 1) [11,26,30,57] .

Discussion

The comorbidities of CML patients have been observed to have a greater effect on OS than the conventional CML specific factors [58]. Taking into account that CML patients may receive treatment for several years and there may be further risk factors likely to cause comorbidities over time, it is clear that risk estimation would be important even in younger patients without comorbidities. Therefore, parameters for assessing the risk, detecting comorbidities and detecting TKI related adverse events should be considered not only at the time of initiating first-generation imatinib therapy, but also before initiating second-generation agents and at all stages throughout CML treatment. CCI, which has been shown to be more useful in determining the prognosis particularly in comorbid patients, should also be included in the clinical routine in addition to risk assessment scores such as Sokal, Hasford and EUTOS.

Considering the average age of CML patients and the potential accompanying comorbidities at the beginning of or during their long-term treatment, it may be inevitable to use other medicines concurrently with TKIs. All medicinal products and nutritional supplements that are not necessary for CML patients should be discontinued and patients should be informed about the potential risks of alternative therapies. Drugs that carry a risk of interacting with TKI treatments but need to be used should be monitored closely.

There are two possible scenarios on the timing of the pregnancy that will affect TKI treatment management; CML diagnosed during pregnancy or pregnancy during CML treatment. Overall, for CML diagnosed during pregnancy, such decisions, including choosing termination or continuation of pregnancy, should be judged individually. In

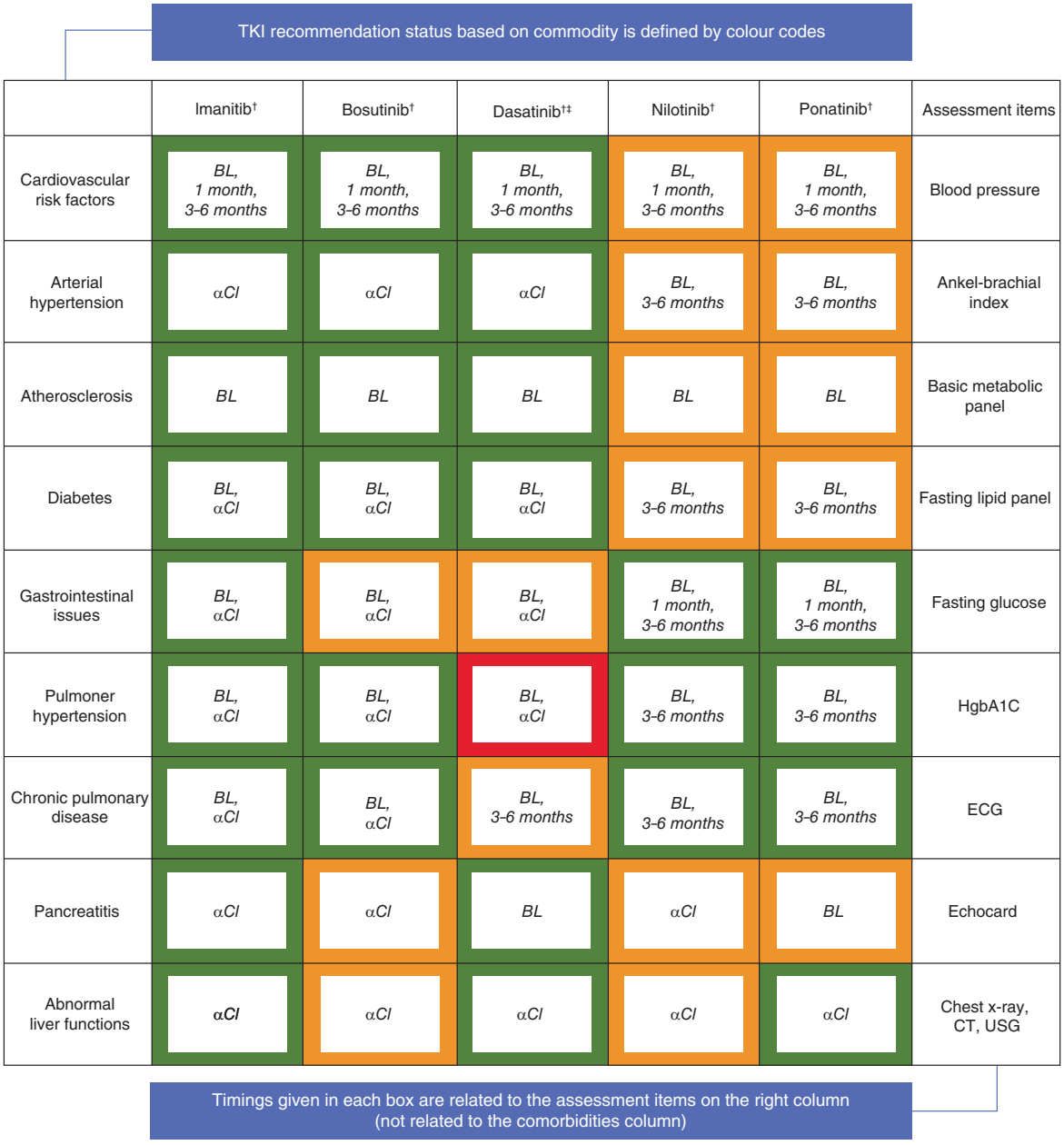

Figure 1. Tyrosine kinase inhibitors: Follow-up assessment recommendations and preference level based on comorbidities. Selecting TKIs based on existing comorbidities and assessment recommendations for cardiopulmonary-metabolic diseases.
TKI: Tyrosine kinase inhibitor.

the event of pregnancy while receiving TKI treatments, patients should be advised to make a decision between terminating the pregnancy or discontinue TKI treatment immediately.

Determining the comorbidity-related risks that are present at the time of decision making for TKI treatments or that may develop during TKI treatment in CML patients is important with regard to treatment choices among 2nd/3rd generation TKIs. In summary, assuming that all related TKIs are available, nilotinib and ponatinib should be avoided in patients with cardiovascular risk factors, dasatinib in patients with lung damage, and bosutinib and nilotinib in patients with liver disease. Considering that certain comorbidities predispose some patients to developing severe adverse events when receiving treatment with TKIs, the first- and second-line treatment of CML should be tailored to each patient's individual condition [5]. In this regard, the use and superior efficacy of TKIs

10.2217/ijh-2021-0010

should be balanced against the potential risks. Finally, since not all TKIs are available worldwide, TKI choice could be limited by geographical and/or socio-economical reasons.

Conclusion

In this review, we aimed to highlight the importance of comorbidity- and drug-related risks of TKI treatment in clinical practice. Raising awareness on this subject may help to reduce the complications associated with comorbidities, the prevalence of drug–drug interactions, alleviate drug toxicities and contribute to the effective management of CML patients. The recommendations given in this study are undoubtedly no further than interpretations of available evidence and the current clinical guidelines. We believe that monitoring parameters to assess comorbidities should be included in the future studies and the data generated by these studies should be used to provide evidence-based recommendations.

Future perspective

With the development of TKI drugs, most CML patients in CP already have a life expectancy close to that of the general population. On the other hand, the comorbidities of CML patients have been observed to have a greater effect on OS than the conventional CML specific factors. Taking into account that CML patients may receive treatment for several years and there may be further risk factors likely to cause comorbidities over time, it is clear that risk estimation would be important even in younger patients without comorbidities.

Additionally, it should be kept in mind that comorbidity-related treatment discontinuation or change may make it difficult to achieve long-term disease control while moving toward the goal of treatment-free remission; therefore, these treatments should be planned and chosen accordingly.

We believe that monitoring parameters for comorbidities should be included in the future observational studies and the data on these parameters should be evaluated to provide evidence-based recommendations.

Author contributions

G Saydam made contributions to the design of the work, acted as a moderator during face-to-face discussions, interpretated the collected inputs from other authors and drafted the manuscript and substantively revised it. All other authors contributed to the face-to-face discussions, provided input and revised and approved the final manuscript.

Financial & competing interests disclosure

All authors received an honorarium from Pfizer in connection with the development of this study.

G Saydam has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. R Ali has acted in advisory board of Novartis, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis, Amgen and Pfizer Pharmaceuticals. AM Demir has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. AE Eskazan has acted in advisory board of Novartis and Pfizer Pharmaceuticals, and has received speaker honorarium from Pfizer Pharmaceuticals, Bristol Myers Squibb and Novartis. B Guvenc has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. IC Haznedaroglu has acted in advisory board of Novartis, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. MA Ozcan has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals, and Bristol Myers Squibb and has received speaker honorarium from Novartis. O Salim has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb. M Sonmez has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Takeda and has received speaker honorarium from Novartis. M Turgut has acted in advisory board of Novartis, Pfizer Pharmaceuticals, and Bristol Myers Squibb and has received speaker honorarium from Novartis. ATT has acted in advisory board of Novartis, AbbVie, Pfizer Pharmaceuticals, and Takeda and has received speaker honorarium from these companies. A Unal has acted in advisory board of Novartis, AbbVie, Amgen, and Bristol Myers Squibb and has received speaker honorarium from Novartis. S Bozkurt, B Aver and B Ozdengulsun are employees in Pfizer Pharmaceuticals. O İlhan has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals, Bristol Myers Squibb, Janssen Pharmaceutical, Deva Holding, Nobel Ilac and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical Writing support was provided by Ayşe Özlem Yılmaz and submission assistance was provided by İlknur Kehlibar at Remedium Consulting Group and was funded by Pfizer.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Pfirrmann M, Baccarani M, Saussele S *et al.* Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia* 30(1), 48–56 (2016).
2. Jabbour E. Chronic myeloid leukemia: first-line drug of choice. *Am. J. Hematol.* 91(1), 59–66 (2016).
3. Deininger MW, Shah NP, Altman JK *et al.* Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl Compr. Canc. Netw.* 18(10), 1385–1415 (2020).

• **According to this guideline the selection of first-line tyrosine kinase inhibitors (TKI) therapy (bosutinib, dasatinib, imatinib or nilotinib) in a given patient should be based on the risk score, toxicity pro-file of TKI, patient's age, ability to tolerate therapy and the presence of comorbid conditions.**

4. Muresan B, Mamolo C, Cappelleri JC, Shapiro M. Matching-adjusted indirect treatment comparison of bosutinib, dasatinib, nilotinib and ponatinib on survival for second line chronic phase chronic myeloid leukemia patients. *Blood* 128(22), 3095(2016).
5. Valent P, Hadzijusufovic E, Schernthaner GH *et al.* Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood* 125(6), 901–906 (2015).
6. Valent P. Severe adverse events associated with the use of second line BCR/ABL tyrosine kinase inhibitors: preferential occurrence in patients with comorbidities. *Haematologica* 96(10), 1395–1397 (2011).
7. Ono T, Takahashi N, Kizaki M *et al.* Prognostic effect of comorbidities in patients with chronic myeloid leukemia treated with a tyrosine kinase inhibitor. *Cancer Sci.* 111(10), 3714–3725 (2020).
8. Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. *Lancet Oncol.* 12(13), 1249–1257 (2011).
9. Given B, Given CW. Cancer treatment in older adults: implications for psychosocial research. *J. Am. Geriatr. Soc.* 57(s2), 283–285 (2009).
10. Hochhaus A, Baccarani M, Silver RT *et al.* European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* 34(4), 966–984 (2020).

• **This European Leukemia Net expert panel article states that all TKIs have toxicities which may cause clinically relevant complications. According to the experts on this panel, these must be considered when selecting a TKI for a patient with comorbidities, because some are contraindications for using a specific TKI first-line.**

11. Smith G, Apperley J, Milojkovic D *et al.* A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. *Br. J. Haematol.* 191, 171–193 (2020).
12. Hoffmann VS, Baccarani M, Hasford J *et al.* The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. *Leukemia* 29(6), 1336–1343 (2015).
13. Efficace F, Rosti G, Breccia M *et al.* The impact of comorbidity on health-related quality of life in elderly patients with chronic myeloid leukemia. *Ann. Hematol.* 95(2), 211–219 (2016).
14. Jabbour E, Makenbaeva D, Lingohr-Smith M, Lin J. Use of real-world claim databases to assess prevalence of comorbid conditions relevant to the treatment of chronic myelogenous leukemia based on National Comprehensive Network Treatment Guidelines. *Clin. Lymphoma Myeloma Leuk.* 15(12), 797–802 (2015).
15. Countinho AD, Makenbaeva D, Farrelly E, Lenihan D *et al.* Elevated cardiovascular disease risk in patients with chronic myelogenous leukemia seen in community-based oncology practices in the United States. *Clin. Lymphoma Myeloma Leuk.* 17(10), 676–683 (2017).
16. Saydam G, Unal A, Kurtoglu E *et al.* Demographic/clinical features and treatment outcomes of chronic phase chronic myeloid leukemia patients in Turkey: real-world data. Presented at: *24th Congress of the European Hematology Association (EHA).* Amsterdam, The Netherlands (13–16 June 2019).
17. Gugliotta G, Castagnetti F, Fogli M, Cavo M, Baccarini M, Rosti G. Impact of comorbidities on the treatment of chronic myeloid leukemia with tyrosine-kinase inhibitors. *Expert Rev. Hematol.* 6(5), 563–574 (2013).
18. Uemura M, Imataki O, Kawachi Y *et al.* Charlson comorbidity index predicts poor outcome in CML patients treated with tyrosine kinase inhibitor. *Int. J. Hematol.* 104(5), 621–627 (2016).
19. Saußele S, Krauß MP, Hehlmann R *et al.* Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. *Blood* 126(1), 42–49 (2015).
20. Breccia M, Molica M, Colafigli G *et al.* Correlation between Charlson comorbidity index and outcome in patients with chronic phase chronic myeloid leukemia treated with second generation tyrosine kinase inhibitors upfront. *Leuk. Lymphoma* 56(7), 2206–2207 (2015).

21. Iurlo A, Ubertis AB, Artusoa S *et al.* Comorbidities and polypharmacy impact on complete cytogenetic response in chronic myeloid leukaemia elderly patients. *Eur. J. Intern. Med.* 25(1), 63–66 (2014).

•• **In this study, chronic myeloid leukemia patients, previously treated with more than 3 drugs that interact with TKI metabolism, it was necessary to reduce TKI daily dose, as polypharmaco-therapy influenced TKI therapeutic success. In the majority of patients who obtained complete cytogenetic response, they scored low on the Charlson Comorbidity Index and did not take any other drugs other than TKI.**

22. Eşkazan AE, Özmen D, Öztaş M *et al.* Efficacy and safety of imatinib treatment in elderly patients with chronic myeloid leukemia: real-life data and a single-center experience. *Clin. Lymphoma Myeloma Leuk.*https://doi.org/10.1016/j.clml.2021.04.005 (2021) (In Press).

23. Pophali PA, Patnaik MM. The role of new tyrosine kinase inhibitors in chronic myeloid leukemia. *Cancer J.* 22(1), 40–50 (2016).

•• **This Mayo clinic review underlines that although there is no doubt on TKI's efficacy, especially in patients with kinase domain mutations, their safety profiles are somewhat controversial and continue to evolve.**

24. García-Gutiérrez V, Boluda JCH. Tyrosine kinase inhibitors available for chronic myeloid leukemia: efficacy and safety. *Front. Oncol.* 9, 2–10 (2019).

25. Pushpam D, Bakhshi S. Pharmacology of tyrosine kinase inhibitors in chronic myeloid leukemia; a clinician's perspective. *DARU J. Pharm. Sci.* 28, 371–385 (2020).

26. Manouchehri A, Kanu E, Mauro MJ, Aday AW, Lindner JR, Moslehi J. Tyrosine kinase inhibitors in leukemia and cardiovascular events from mechanism to patient care. *Arterioscler. Thromb. Vasc. Biol.* 40(2), 301–308 (2020).

27. Apperley JF. Chronic myeloid leukaemia. *Lancet Lond. Engl.* 385, 1447–1459 (2015).

28. Caldemeyer L, Dugan M, Edwards J *et al.* Long-term side effects of tyrosine kinase inhibitors in chronic myeloid leukemia. *Curr.. Hematol. Malig. Rep.* 11, 71–79 (2016).

29. Breccia M, Pregno P, Spallarossa P *et al.* Identification, prevention and management of cardiovascular risk in chronic myeloid leukaemia patient's candidate to ponatinib: an expert opinion. *Ann. Hematol.* 96(4), 549–558 (2017).

• **As observed by this study, the experience in patients treated with second generation TKIs shows that the Charlson Comorbidity Index can predict overall survival also in this subset of patients.**

30. Medeiros BC, Possick J, Fradley M. Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: strategies for monitoring, detecting, and managing. *Blood Rev.* 32(4), 289–299 (2018).

31. Dorer DJ, Knickerbocker RK, Baccarani M *et al.* Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. *Leuk. Res.* 48, 84–91 (2016).

32. Alhawiti N, Burbury KL, Kwa FA *et al.* The tyrosine kinase inhibitor, nilotinib potentiates a prothrombotic state. *Thromb. Res.* 145, 54–64 (2016).

33. Hadzijusufovic E, Albrecht-Schgoer K, Huber K *et al.* Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia* 31(11), 2388–2397 (2017).

34. Saglio G, Kim DW, Issaragrisil S *et al.* Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N. Engl. J. Med.* 362(24), 2251–2259 (2010).

35. Douxfils J, Haguet H, Mullier F *et al.* Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. *JAMA Oncol.* 2(5), 625–632 (2016).

36. Kantarjian HM, Hochhaus A, Saglio G *et al.* Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the Phase III randomised ENESTnd trial. *Lancet Oncol.* 12(9), 841–851 (2011).

37. Kantarjian H, Shah NP, Hochhaus A *et al.* Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N. Engl. J. Med.* 362(24), 2260–2270 (2010).

38. Sacha T. Imatinib in Chronic Myeloid Leukemia: An Overview. *Mediterr. J. Hematol. Infect. Dis.* 6(1), e2014007 (2014).

39. Cortes JE, Gambacorti-Passerini C, Deininger MW *et al.* Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial bosutinib. *J. Clin. Oncol.* 36(3), 231–237 (2018).

40. Iurlo A, Orsi E, Cattaneo D *et al.* Effects of first- and second-generation tyrosine kinase inhibitor therapy on glucose and lipid metabolism in chronic myeloid leukemia patients: a real clinical problem? *Oncotarget* 6(32), 33944–33951 (2015).

41. Cortes JE, Jimenez CA, Mauro MJ *et al.* Pleural effusion in dasatinib-treated patients with chronic myeloid leukemia in chronic phase: identification and management. *Clin. Lymphoma Myeloma Leuk.* 17(2), 78–82 (2017).

42. Hughes TP, Laneuville P, Rousselot P *et al.* Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia. *Haematologica* 104(1), 93–101 (2019).

43. Rousselot P, Mollica L, Guerci-Bresler A *et al.* Dasatinib daily dose optimization based on residual drug levels resulted in reduced risk of pleural effusions and high molecular response rates: final results of the randomized OPTIM DASATINIB trial. *Haematologica* 99, 237–238 (2014).

44. Janssen L, Blijlevens NMA, Drissen MMCM *et al.* Fatigue in chronic myeloid leukemia patients on tyrosine kinase inhibitor therapy: predictors and the relationship with physical activity. *Haematologica* 106(7), 1876–1882 (2021).
45. Pye SM, Cortes J, Ault P *et al.* The effects of imatinib on pregnancy outcome. *Blood* 111, 5505–5508 (2008).
46. Russel MA, Carpenter MW, Akhtar MS *et al.* Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. *J. Perinatol.* 27, 241–243 (2007).
47. Jovelet C, Seck A, Mir O *et al.* Variation in transplacental transfer of tyrosine kinase inhibitors in the human perfused cotyledon model. *Ann. Oncol.* 26, 1500–1504 (2015).
48. Chelysheva E, Turkina A, Polushkina E *et al.* Placental transfer of tyrosine kinase inhibitors used for chronic myeloid leukemia treatment. *Leuk. Lymphoma* 59, 733–738 (2018).
49. Abruzzese E, Mauro M, Apperley J *et al.* Tyrosine kinase inhibitors and pregnancy in chronic myeloid leukemia: opinion, evidence, and recommendations. *Ther. Adv. Hematol.* 11, 2040620720966120 (2020).
50. van Leeuwen RWF, van Gelder T, Mathijssen RHJ, Jansman FGA. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. *Lancet Oncol.* 15(8), e315–e326 (2014).
51. Bowlin SJ, Xia F, Wang W *et al.* Twelve-month frequency of drug-metabolizing enzyme and transporter-based drug–drug interaction potential in patients receiving oral enzyme-targeted kinase inhibitor antineoplastic agents. *Mayo Clin. Proc.* 88(2), 139–148 (2013).
52. Keller KL, Franquiz MJ, Duffy AP, Trovato JA. Drug-drug interactions in patients receiving tyrosine kinase inhibitors. *J. Oncol. Pharm. Pract.* 24(2), 110–115 (2018).
53. Gay C, Toulet D, Le Corre P. Pharmacokinetic drug–drug interactions of tyrosine kinase inhibitors: a focus on cytochrome P450, transporters, and acid suppression therapy. *Hematol. Oncol.* 35(3), 259–280 (2017).
54. Ergun Y, Ozdemir NY, Toptas S *et al.* Drug-drug interactions in patient using tyrosine kinase inhibitors: a multicenter retrospective study. *JBUON* 24(4), 1719–1726 (2019).
55. Osorio S, Escudero-Vilaplana V, Gómez-Centurión I *et al.* CML Spanish Group (GELMC). Drug–to–drug interactions of tyrosine kinase inhibitors in chronic myeloid leukemia patients. Is it a real problem? *Ann. Hematol.* 97(11), 2089–2098 (2018).
56. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *Am. J. Hematol.* 95, 691–709 (2020).

- **Highlights the evidence supporting the use of each of the available TKIs, including how to select an agent under various circumstances and phases of the disease.**

57. Isfort S, Brümmendorf TH. Bosutinib in chronic myeloid leukemia: patient selection and perspectives. *J. Blood Med.* 9, 43–50 (2018).
58. Ross DM, Arthur C, Burbury K *et al.* Chronic myeloid leukaemia and tyrosine kinase inhibitor therapy: assessment and management of cardiovascular risk factors. *Intern. Med. J.* 48(Suppl. 2), 5–13 (2018).

10.2217/ijh-2021-0010