

# Turkey real-life data: demographic features, treatment results and effects of comorbidities in chronic myeloid leukemia

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**Aim:** This study aimed to identify patient characteristics, treatment patterns and outcomes and to evaluate the effects of presence of comorbidities at diagnosis in chronic phase (CP)-chronic myeloid leukemia (CML) patients in Turkey. **Materials & methods:** Hospital records between 2005 and 2018 were retrospectively reviewed. **Results:** Of 861 CP-CML patients included, 31% had at least one comorbidity at diagnosis. Sex, cardiovascular disease status at diagnosis and molecular (at least major) and cytogenetic (partial and complete) responses were the independent predictors of survival. **Conclusion:** The response rates of CP-CML patients to the tyrosine kinase inhibitors were satisfactory. In addition to tolerability and side effect profiles of drugs, comorbidity status of patients should also be considered in treatment choice in CML patients.

**Plain language summary:** This study aimed to identify patient characteristics, treatment patterns and outcomes and to evaluate the effects of presence of comorbidities at diagnosis in chronic phase (CP)-chronic myeloid leukemia (CML) patients in Turkey. Hospital records of patients between 2005 and 2018 were retrospectively reviewed. Of the included 861 CP-CML patients, 31% had at least one comorbidity at diagnosis. The survival of the patients was affected by sex, cardiovascular disease status at diagnosis, and molecular (at least major) and cytogenetic (partial and complete) responses. The response rates of CP-CML patients to the tyrosine kinase inhibitors were satisfactory. In addition to tolerability and side effect profiles of drugs, comorbidity status of patients should also be considered in treatment choice in CML patients.

First draft submitted: 21 May 2021; Accepted for publication: 9 June 2022; Published online: 30 June 2022

**Keywords:** chronic myeloid leukemia • co-medication use • comorbidity • cytogenetic response • hematologic response • molecular response • survival • tyrosine kinase inhibitors

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm; its incidence among adult population is 1–2/100,000 that accounts for 15% of newly diagnosed leukemia cases. CML is seen in three different phases, which are chronic phase, accelerated phase and blast phase, and is usually diagnosed at chronic phase [1]. In recent years, significant improvements have been achieved in the treatment of CML and tyrosine kinase inhibitors (TKIs) have been introduced into use as the targeted therapy approach based on abnormally expressed BCR-ABL protein in CML cells [1]. Along with the introduction of TKI treatment, the disease course of CML has changed and considerable improvements have been obtained in survival rates [2,3].

Imatinib mesylate is widely used as the first-line (front-line) treatment for CML. In addition, new-generation TKIs (dasatinib, nilotinib, bosutinib, radotinib and ponatinib) have also been introduced into use [4,5]. Patients' personal characteristics, lifestyle preferences, risk factors, comorbidities, concomitant medications, tolerability and toxicity profiles for TKIs as well as availability of TKIs, and experiences of physicians/clinics should be taken into account while making the first-line TKI choice [6,7]. The European LeukemiaNet (ELN) 2020 expert panel has recommended imatinib, nilotinib, dasatinib or bosutinib as the initial therapy for CML. Patient response to treatment, conditions for patient monitoring regarding intolerance/side effects, and patient comorbidities are also among the ELN recommendations for the decision of switching to a second- or further-line treatment [8]. The ELN response categories provide reliable prediction of outcomes in CML patients receiving TKIs [9].

In Turkey, imatinib is the only TKI included in the reimbursement for the first-line treatment of CML. Second-generation TKIs are used in further-line treatment. Dasatinib, nilotinib and bosutinib were approved in Turkey for the management of patients with CML in 2007, 2009 and 2019, respectively and have been included in the reimbursement list since 2008, 2009 and 2019, respectively. Ponatinib is not approved or in the reimbursement list in Turkey; however, it has been included in imported drug list since 2014, which is covered by national health insurance for patients with T315I mutation and/or not responding to other available TKIs. The present study aimed to identify demographic and clinical characteristics, to assess treatment patterns and outcomes, to determine survival rates and the effects of presence of comorbidities at diagnosis in chronic-phase (CP)-CML patients in Turkey.

## Materials & methods

The present study was designed as a national, multicenter, retrospective study. The hospital records of all patients diagnosed with CP-CML between January 2005 and January 2018 in 13 centers at different regions of Turkey were retrospectively reviewed. A total of 861 CP-CML patients were included in the analysis. The study was approved by the Clinical Research Ethics Committee of Erciyes University Medical Faculty (approval number: 96681246/, date: 10 July 2018) and was carried out in accordance with the legal and regulatory requirements, the principles of Good Clinical Practice, and Declaration of Helsinki.

Patients' data regarding demographic and clinical characteristics, treatments received and responses to treatments were retrieved from hospital files and recorded in data collection forms. The recorded data included age, sex, time of diagnosis, comorbidities at diagnosis, medications used for comorbidities at diagnosis, current treatment status (treatment-line) for CML, drug choice for each treatment-line, switching between generic drugs for each treatment-line, cumulative complete hematologic response, cytogenetic (partial and complete) response, molecular (at least major) response and response times, side effects and survival status. Response to treatment was assessed in accordance with the criteria described in the ELN 2013 guideline [10].

## Statistical analysis

Data analyses were performed using the Predictive Analytics Software (PASW) Statistics for Windows version 18 (SPSS Inc., IL, USA). Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard error, median, 25th percentile and 75th percentile for numerical variables. Normality of data was assessed using the visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Two group comparisons were performed using the Chi-square test for categorical variables when the Chi-square condition was met; otherwise, Fisher's exact test was used. For non-normally distributed numerical

**Table 1. Demographic and clinical characteristics of chronic-phase chronic myeloid leukemia patients included in the study.**

Characteristics	n	Values
Age, years	861	52 (40–64)
Age at diagnosis, years	861	48 (36–60)
Sex	861	
Female		427 (49.6)
Male		434 (50.4)
Follow-up duration, years	737	5.1 (2.9–8.1)
Number of comorbidities at diagnosis	830	
0		572 (68.9)
1		157 (18.9)
2		67 (8.1)
3		27 (3.3)
4		7 (0.8)
Comorbidity at diagnosis		
Cardiovascular diseases	841	117 (13.9)
Diabetes mellitus	823	87 (10.5)
Pulmonary diseases	840	28 (3.3)
Other	841	171 (20.3)
Co-medication use for comorbid conditions at diagnosis	182	139 (76.4)

Values are presented as n (%) or median (25th percentile–75th percentile), where appropriate.

variables, the Friedman test was used for multiple group comparisons and the Wilcoxon signed-rank test with Bonferroni correction was used for subgroup comparisons. Survival was calculated using the Kaplan-Meier method and the factors that were likely to affect survival were determined using the Cox regression analysis. The level of statistical significance was accepted as  $p < 0.05$ .

## Results

The study included 861 CP-CML patients (males, 50.4%) with a median age of 52 years. At the diagnosis, the median age was 48 years and 31% of the patients had at least one comorbidity. Of these patients, 13.9% had cardiovascular diseases at diagnosis, 10.5% had diabetes mellitus (DM) at diagnosis, and 76.4% were on co-medications for comorbid conditions at diagnosis. The median follow-up duration of the patients was 5.1 years. Demographic and clinical characteristics of the patients are summarized in [Table 1](#). Of all patients, 49.4% were on the first-line treatment for CML. The rates of cumulative complete hematologic, cytogenetic (partial and complete), and molecular (at least major) responses were 95.5%, 75.6% (354/468) and 78.1% (507/649), respectively and the median time to achieve hematologic, cytogenetic and molecular responses were determined as 2.3, 12 and 12 months, respectively. The information related to the treatments of CP-CML patients are summarized in [Table 2](#). When the TKI responses were compared between the patients with comorbidity receiving co-medications and those not receiving co-medications, no significant difference was obtained between the groups. The comparison of TKI responses between patients with co-medications and those without co-medications for comorbid conditions at diagnosis are presented in [Table 3](#).

Imatinib (97.6%) was the most frequently used drug by the patients as the first-line treatment. Switching between generic drugs was determined in 32.9% of the patients during the first-line treatment. The most common reasons for switching were problems related to drug supply, copayment and drug access (48.2%). Other reasons included side effects (11.4%) and absence/loss of response (9.6%). The rate of switching to a second-line treatment was 48.7% with the primary reason being absence/loss of response (60%). The most frequently used drug for the second-line treatment was dasatinib (57.3%) followed by nilotinib (40.7%). It was observed that 25.7% of the patients were switched to a third-line treatment and that the most common (50.9%) reason for switching was side effects. The most frequently used drug for the third-line treatment was nilotinib (59%) followed by dasatinib (34%). Of the patients, 2.9% were switched to the fourth-line treatment. The most common (75%) reason for switching to a fourth-line treatment was absence/loss of response. The most frequently used drug for the fourth-line

**Table 2. Information related to the treatments of chronic-phase chronic myeloid leukemia patients in the study.**

Information	n	Values
Current treatment status for CML	861	
First-line treatment		425 (49.4)
Second-line treatment		178 (20.7)
Third-line treatment		52 (6.0)
Fourth-line treatment		5 (0.6)
Others <sup>†</sup>		201 (23.3)
Cumulative complete hematologic response	663	633 (95.5)
Duration of hematologic response, months	591	2.3 (1.1–3)
Cytogenetic (partial and complete) response	468	354 (75.6)
Duration of cytogenetic response, months	317	12 (7.2–21.4)
Molecular (at least major) response	649	507 (78.1)
Duration of molecular response, months	351	12 (7.5–17)

Values are presented as n (%) or median (25–75th percentile), where appropriate.  
<sup>†</sup> Patients who were lost-to-follow-up or had missing data.  
 CML: Chronic myeloid leukemia.

**Table 3. Comparison of tyrosine kinase inhibitor responses between patients with co-medications and those without co-medications for comorbid conditions at diagnosis.**

Responses	Receiving co-medications		p-value
	Yes, n (%)	No, n (%)	
Cumulative complete hematologic response	132 (99.2)	22 (95.7)	–
Cytogenetic (partial and complete) response	78 (78.8)	16 (88.9)	0.520
Molecular(at least major) response	112 (85.5)	17 (73.9)	0.216

treatment was ponatinib. The characteristics of the patients according to the treatment lines are demonstrated in [Table 4](#).

It was determined that 55 (6.4%) patients died (due to unspecified reasons) and 680 (79%) patients were alive. Survival data of 14.6% of the patients were missing. The median survival was not achieved at the time of analysis. During the follow-ups, the mean survival was 13.6+ years (95% confidence interval [CI], 13.2–14.0). Accordingly, 1-year, 5-year, and 10-year survival rates of the patients were estimated as 99.2, 93.7 and 89.1%, respectively.

Effects of baseline demographic and clinical characteristics of the patients on survival are summarized in [Table 5](#). It was determined that survival was shorter in the patients with a cardiovascular disease at diagnosis than in those without. Moreover, patients with DM at diagnosis had shorter survival than in those without. However, there was no significant difference in the survival between the patients with co-medications for comorbid conditions and those without co-medications for comorbid conditions at diagnosis. Evaluation of the patients regarding their responses to treatments demonstrated that the mean survival was longer in those with cumulative complete hematologic, molecular (at least major) and cytogenetic (partial and complete) responses ([Table 5](#)). Comparison of the Kaplan-Meier survival estimates of the patients grouped according to being switched or not being switched to second-, third- or fourth-line treatments revealed that the survival did not significantly differ between the groups (data not shown).

The Cox regression analysis, which was performed to determine the independent predictor factors of increased survival rates in CP-CML patients, demonstrated that female sex, lack of cardiovascular disease at diagnosis, presence of molecular response and presence of cytogenetic response were independent predictors of extended survival. There was an unfavorable effect of presence of cardiovascular comorbidity on survival in the CP-CML patients (a hazard ratio [HR] of 5.6; 95% CI, 2.5–12.8). The independent predictors of survival in CP-CML patients are presented in [Table 6](#).

**Table 4. Characteristics of the patients according to the treatment lines used for chronic myeloid leukemia.**

Characteristics	Values
<b>Drugs used for the first-line treatment</b>	
Imatinib	661 (97.6)
Dasatinib	7 (1.0)
Nilotinib	3 (0.4)
Interferon	1 (0.1)
Switching between generic drugs during the first-line treatment (n = 504)	166 (32.9)
<b>Reasons for switching between generic drugs during the first-line treatment (n = 166)<sup>†</sup></b>	
Problems related to drug supply, copayment and drug access	80 (48.2)
Side effects	19 (11.4)
Absence/loss of response	16 (9.6)
None/unknown	51 (30.7)
Switching to the second-line treatment	310 (48.7)
Time to switching to the second-line treatment from diagnosis, months	17.5 (12–36)
<b>Reasons for switching to the second-line treatment (n = 310)</b>	
Absence/loss of response	186 (60.0)
Side effects	26 (8.4)
None/Unknown	69 (22.3)
Others	29 (9.4)
<b>Drugs used for the second-line treatment (n = 295)<sup>†</sup></b>	
Dasatinib	169 (57.3)
Nilotinib	120 (40.7)
Imatinib	3 (1.0)
Nilotinib and Dasatinib	2 (0.7)
Interferon	1 (0.3)
Side effects due to the second-line treatment (n = 225)	59 (26.2)
<b>Comorbidities during the second-line treatment</b>	
Diabetes mellitus (n = 272)	9 (3.3)
Pulmonary disease (n = 272)	28 (10.3)
Cardiac disease (n = 274)	20 (7.3)
Peripheral artery (n = 272)	4 (1.5)
Other diseases (n = 272)	44 (16.2)
Switching to the third-line treatment	106 (25.7)
Time to switching to the third-line treatment from diagnosis (months)	37.5 (22–63)
<b>Reasons for switching to the third-line treatment (n = 106)</b>	
Side effects	54 (50.9)
No response/loss of response	34 (32.1)
None/unknown	17 (16.0)
Others	1 (0.9)
<b>Drugs used for the third-line treatment (n = 100)<sup>†</sup></b>	
Nilotinib	59 (59.0)
Dasatinib	34 (34.0)
Imatinib	6 (6.0)
Ponatinib	1 (1.0)
Side effects due to the third-line treatment (n = 71)	14 (19.7)
<b>Comorbidities during the third-line treatment</b>	
Diabetes mellitus (n = 80)	8 (10.0)

Data are presented as n (%) or median (25–75th percentile), where appropriate.

<sup>†</sup> Among the patients switching between treatment lines, the ones with available data are presented.

**Table 4. Characteristics of the patients according to the treatment lines used for chronic myeloid leukemia (cont.).**

Characteristics	Values
Pulmonary disease (n = 60)	3 (5.0)
Cardiac disease (n = 80)	7 (8.8)
Peripheral artery disease (n = 78)	2 (2.6)
Other diseases developed (n = 80)	12 (15.0)
Switching to the fourth-line treatment	7 (2.9)
Time to switching to the fourth-line treatment from diagnosis (months)	60 (48–84)
Reasons for switching to the fourth-line treatment (n = 7)	
No response/loss of response	6 (85.7)
Side effects	1 (14.3)
Drugs used or the fourth-line treatment (n = 7)	
Ponatinib	3 (42.9)
Allogeneic transplantation	2 (28.6)
Bosutinib	1 (14.3)
Imatinib	1 (14.3)
Side effects due to the fourth-line treatment (n = 6)	1 (16.7)
Comorbidities during the fourth-line treatment	
Other diseases (n = 5)	1 (20.0)

Data are presented as n (%) or median (25–75th percentile), where appropriate.  
† Among the patients switching between treatment lines, the ones with available data are presented.

## Discussion

Along with the use of TKIs for the treatment of CML, the disease is no longer fatal and has become a manageable chronic disease for the majority of patients but not all. The life expectancy of CML patients has reached to a level close to that of normal population along with increased survival [11].

Imatinib is widely used as the first-line TKI treatment in CML patients. Bosutinib, nilotinib and dasatinib are also other options used as the first-line therapy based on their comparable efficacy and successful outcomes [12–15]. Studies from various countries have revealed that the rate of using imatinib as the first-line treatment is between 34 and 100% and cytogenetic and/or molecular response rates at different time points have been reported at varying rates ranging between 36 and 96% [16–19]. In a previous retrospective study from Turkey, it was observed that regardless of the phase, imatinib was used as the first-line treatment in all CML patients included in the study (n = 1,133; 94.9% of whom were CP patients) [19]. Moreover, it was reported that a complete hematologic response was achieved in 95.7% of the patients and a complete cytogenetic response was achieved in 63.8% of the patients [19]. In the present study, 49.4% of CP-CML patients were still on the first-line treatment and the most common drug used as the first-line treatment was imatinib (97.6%). The rate of imatinib use is compatible with the conditions of access to drugs in Turkey. Cumulative complete hematologic, cytogenetic (partial and complete), and molecular (at least major) responses were achieved in 95.5%, 75.6% (354/468), and 78.1% (507/649) of the patients, respectively and the median time to achieve these responses was 2.3, 12 and 12 months, respectively. Our results of response rates are consistent with the previously reported results in studies and the median time to achieve responses are within the range recommended by ELN guidelines [9,20]. It might seem inconsistent that the molecular (at least major) response rate was higher than the cytogenetic (partial and complete) response rate; however, this was due to the difference in the number of patients for which molecular (at least major) and cytogenetic (partial and complete) data were available.

In clinical practice, TKI treatment can be discontinued, interrupted, or switched to another TKI for various reasons. In a study based on the data from SIMPLICITY trial, Hehlmann *et al.* [21] reported the first-year and second-year switching rates to be 17.8 and 9.5%, respectively; the first-year and second-year interruption rates to be 16.4 and 4%, respectively; and the first-year and second-year discontinuation rates to be 21.8 and 10.2%, respectively in CML patients receiving TKI treatment. They determined that the most common reason for changing treatment was intolerance, followed by resistance to TKIs and that age and sex were the factors affecting intolerance [19]. In a retrospective study from Belgium, the most common reason for discontinuation/interruption of TKI treatment

**Table 5. Effects of patient-related characteristics on survival.**

Characteristics	Mean (years)	SE	95% CI	p-value
<b>Sex</b>				
Female	14.0	0.2	13.5–14.4	0.021
Male	12.5	0.2	12.0–13.0	
<b>Diabetes mellitus at diagnosis</b>				
Absent	13.8	0.2	13.4–14.1	0.026
Present	12.0	0.6	10.8–13.1	
<b>Cardiovascular disease at diagnosis</b>				
Absent	14.0	0.2	13.6–14.3	<0.001
Present	11.0	0.6	9.7–12.2	
<b>Pulmonary disease at diagnosis</b>				
Absent	13.6	0.2	13.3–14.0	0.981
Present	12.9	0.7	11.5–14.4	
<b>Other diseases at diagnosis</b>				
Absent	13.8	0.2	13.4–14.2	0.145
Present	12.3	0.4	11.5–13.2	
<b>Co-medication use for comorbid conditions at diagnosis</b>				
Absent	12.4	1.0	10.5–14.3	0.388
Present	11.8	0.5	10.8–12.8	
<b>Cumulative complete hematologic response</b>				
Absent	10.4	0.9	8.6–12.2	<0.001
Present	13.8	0.2	13.4–14.2	
<b>Molecular (at least major) response</b>				
Absent	10.1	0.5	9.2–11.1	<0.001
Present	14.2	0.2	13.8–14.5	
<b>Cytogenetic (partial and complete) response</b>				
Absent	10.3	0.5	9.3–11.3	<0.001
Present	14.0	0.2	13.6–14.5	

CI: Confidence interval; SE: Standard error.

**Table 6. Independent predictors of survival in chronic-phase chronic myeloid leukemia patients.**

Independent predictors	HR	95% CI		p-value
		Lower limit	Upper limit	
Sex (reference, female)	2.2	1.0	4.7	0.043
Cardiovascular disease at diagnosis	5.6	2.5	12.8	<0.001
Molecular(at least major) response	0.2	0.1	0.5	0.001
Cytogenetic (partial and complete) response	0.2	0.1	0.6	0.002

HR: Hazard ratio.

was side effect/intolerance (67%) and the other reasons included desire to become pregnant (9%) and attempt for achieving treatment-free remission (9%) [22]. In a study from Italy, it was reported that switching to another drug was required in 38% of the patients receiving imatinib as the first-line treatment with the primary reason being intolerance [23]. A retrospective study from Turkey reported switching to another drug in 29.3% of the patients receiving imatinib as the first-line treatment and the reasons for switching were reported as resistance/inadequate response in 90.8% of the patients and intolerance in 9.2% of the patients [19]. In the present study, rate of switching between generic drugs during the first-line treatment was 32.9%. The most common reasons for switching were problems related to drug supply, copayment and drug access (48.2%), side effects (11.4%), and absence/loss of response (9.6%). Switching to a generic due to efficacy reasons was performed in small number of patients due to clinical protocol of some centers when the generics were established firstly. However, after a regulation by hematology societies in Turkey, it has been no longer valid.



Studies have reported favorable outcomes with bosutinib, nilotinib or dasatinib for the second-line treatment in patients intolerant or resistant to imatinib [24–28]. In Turkey, imatinib is the only TKI included in reimbursement list for the first-line treatment of CML and the second-generation TKIs are used for further-line therapies. In the present study, the rate of switching to a second-line treatment was 48.7% with the primary reason being absence/loss of response (60%). The most frequently used drug for the second-line treatment was dasatinib (57.3%), followed by nilotinib (40.7%). The rate of patients continuing to the first-line treatment were found similar with the 8-year results of the IRIS study [29]. These results were also similar with the results of Turkey reported by Sahin *et al.* [19]. Bosutinib treatment was not accessible in our country during the time period of the present study.

There are many studies regarding second-line treatment choice after failure of first-line TKIs in CML patients and these studies can be a guide. Therefore, although choosing second-line treatment is relatively easy, third-line treatment choice has been reported to be complex and difficult due to lack of randomized studies on this topic. A physician in charge should choose an appropriate treatment based on country's resources, patient's response and tolerance to previous therapy, duration and depth of response, presence of comorbidities and presence of ABL1-kinase domain mutations [30].

Management of comorbidities and minimizing treatment-related toxicity have become the focus of interest as a consequence of disease control and prolonged survival achieved with the use of TKIs in CML patients [31]. Individualized treatment is recommended for CP-CML patients not only to improve survival but also to achieve the goal of a high quality of life. TKIs have different tolerability profiles and adverse events are specific to each drug. Presence of comorbidities and concomitant medication use have been suggested as the factors affecting tolerability of TKIs and occurrence of adverse events and thus treatment success [32,33]. Therefore, in order to optimize the treatment, in addition to factors related to CML, the factors needed to be considered for choice of TKIs include potency and toxicity profiles for each TKI as well as comorbidity status [32,34]. In brief, comprehensive assessment of comorbidities, primarily cardiovascular, metabolic and pulmonary diseases, is of importance for choice of TKIs [35–37]. Although CML is seen at any age, the median age at disease onset has been reported as 57–60 years according to the population-based data from Europe [38]. In USA, however, the median age at disease onset has been reported as 67 years [39]. Since CML is observed in advanced ages and its incidence increases with age, presence of comorbidities and concomitant medication use are expected situations. In the observational SIMPLICITY trial, 81% of the patients (median age 56.6 years) had comorbidities at baseline and it was reported that comorbidities were taken into account in treatment choice [17]. In a study based on real-life data in the United States, at least one comorbidity was determined in nearly 41% of the patients (median age, 56 years) who were initiated on TKI therapy [40]. In a study conducted in Italy, it was reported that 64% of the CML patients with the mean age of 70 years had at least one comorbidity [41]. In the EUTOS study, 55.5% of the patients with a median age of 56 years had at least one comorbidity [42]. The frequencies of comorbid diseases vary due to difference in the mean age of patient population in studies. In the present study, the median age at diagnosis was 48 years, which was lower than that reported in the aforementioned studies. Of the patients, 31% had at least one comorbidity at diagnosis and 76.4% were on medications for comorbid conditions at diagnosis. Our comorbidity rate was found lower than the previously shared results. This might be due to lower mean age of our patient group than other studies, or patients being undiagnosed despite having comorbidity at the baseline or lack of information in the records. The reason for the lower rate of medication use than the rate of comorbidity might be the presence of patients who did not use medication for the relevant disease. In the studies, among the comorbid diseases in CML patients, the frequency of cardiovascular diseases was reported as 17–45%, the frequency of DM was reported as 10–18% and the frequency of pulmonary diseases was reported as 9–18% [17,40–42]. In the present study, 13.9% of the patients had cardiovascular diseases at diagnosis, 10.5% of the patients had DM at diagnosis, and 3.3% of the patients had pulmonary diseases at diagnosis. The reason for the lower frequencies of cardiovascular and pulmonary diseases in our study as compared with those reported in the various studies might be due to, as mentioned above, our patient group being relatively young, presence of undiagnosed patients at baseline and lack of information. When planning the initial treatment for patients diagnosed with CML, it is important to make a more detailed evaluation in terms of the presence of comorbidities and to plan the necessary treatment accordingly.

In the present study, it was determined that survival was shorter in the patients with a cardiovascular disease at diagnosis than in those without a cardiovascular disease at diagnosis (11 vs 14 years;  $p < 0.001$ ). Moreover, those with DM at diagnosis had shorter survival than in those without DM at diagnosis (12 vs 13.8 years;  $p = 0.026$ ). However, there was no significant difference in the survival durations between the patients with co-medications for comorbid conditions and those without co-medications for comorbid conditions at diagnosis (11.8 vs 12.4 years;



$p = 0.388$ ). The severity of the disease was unknown in the patients with comorbidities receiving co-medications at diagnosis and those not receiving. It could be speculated that patients without co-medications for comorbid conditions at diagnosis had low disease severity and this did not affect overall survival. On the other hand, as in our analyses, comorbidities such as cardiovascular diseases and DM were shown to negatively affect overall survival. Therefore, CP-CML patient management should be performed holistically and necessary treatments should be applied for comorbidities. The Cox regression analysis also showed the unfavorable effect of presence of cardiovascular comorbidity on survival in the CP-CML patients (HR, 5.6; 95% CI, 2.5–12.8). Since the life expectancy of CML patients has now become close to that of the normal population, their comorbidity rates can increase to the rates in the normal population. This emphasizes once again that the presence of comorbidity should be well investigated.

In various studies, 1, 5 and 10-year overall survival rates in CML patients receiving treatment with TKIs have been reported as 97%, 90–94.5%, and 75%, respectively [16,18,43,44]. Consistent with these results, in the present study, the 1, 5 and 10-year survival rates in the CP-CML patients were estimated as 99.2, 93.7 and 89.1%, respectively. When the factors affecting the survival were evaluated, the mean survival was determined to be longer in females, in the patients without DM at diagnosis, in those without cardiovascular diseases at diagnosis, and in those not receiving any medication at diagnosis. Besides, the mean survival was also longer in the patients with cumulative complete hematologic, cytogenetic (partial and complete) and molecular (at least major) responses. The results of Cox regression analysis revealed that female sex, lack of cardiovascular disease status at diagnosis, and presence of molecular and cytogenetic responses were the independent predictors of extended survival. In the review by Hanfstein *et al.* [45], achieving cytogenetic or molecular response early (in 3–6 months) was stated to be associated with the long-term outcomes. Saussele *et al.* [46] reported that presence of comorbidity had negative effect on the overall survival. Our findings have also supported the results from these two studies.

It has been reported that long-term follow-up of CP-CML patients yields poorer survival rates than outcomes reported in short-term clinical studies and that long-term real-life data reflects many problems encountered by patients as CML is a chronic disease [44]. It has also stated that persistent decrease in event-free survival during long-term follow-up takes long time to have an effect on overall survival due to the chronic nature of the disease [44]. Continuous adherence to treatment has been determined as an important factor for optimum long-term outcomes [44]. Since the life expectancy of CML patients has been approximated to that of general population after introduction of TKIs into use, it has been suggested that new tools other than overall survival need to be considered to assess long-term outcomes [47].

The probability of missing data due to its retrospective design is one of the limitations of the present study. Nevertheless, when it is considered that some outcomes of clinical studies may not completely reflect the real life due to their rigid eligibility criteria, the outcomes of the present study are of great value as it evaluated the real-life data.

## Conclusion

In the present study which evaluated a large cohort of CML patients in Turkey, response rates to TKI treatments were considered satisfactory. Nevertheless, although they were relatively young, the rate of comorbidity in the patient population was determined to be considerable. The present study demonstrated that presence of comorbidity (particularly presence of a cardiovascular comorbidity) had unfavorable effects on survival. While choosing drug for TKI treatment in CML patients, comorbidity status of the patients should be taken into account in addition to tolerability and side effect profiles of drugs and treatment should be individualized accordingly. Treatment-related complications and adverse events could be minimized with good management of comorbidities and the patient outcomes would be improved.

## Future perspective

Since the life expectancy for CML patients is getting closer to the normal population, the importance of comorbidities in the treatment is increasing. However, data from different real world evidence studies have shown different comorbidity rates which can be a result of low focus on comorbidities. We believe that TKI decision will be made mostly by the safety profile of the molecules and types of comorbidities will be the main determinant. In addition to that, treatment-free remission is ultimate goal for all available patients with CML and comorbidities can have to be considered and taken seriously in order to achieve the requirements for treatment-free remission.

### Summary points

- A total of 861 CP-CML patients (males, 50.4%) with a median age of 52 years were included in the study. The median age of the patients at diagnosis was 48 years.
- The rate of the patients who were currently on first-line treatment was 49.4% and the rate of those who were switched between generic drugs during the first-line treatment was 32.9%. Problems related to drug supply, copayment and drug access (48.2%) were the most frequent reasons for switching.
- The rate of switching to a second-line treatment was 48.7%. The primary reason for switching to a second-line treatment was absence/loss of response (60%).
- The rates of cumulative complete hematologic, cytogenetic (partial and complete), and molecular (at least major) responses were 95.5%, 75.6% (354/468), and 78.1% (507/649), respectively. The median time to achieve hematologic, cytogenetic, and molecular responses was determined as 2.3, 12 and 12 months, respectively. The 1, 5 and 10-year survival rates were estimated as 99.2, 93.7 and 89.1%, respectively.
- The rate of the patients who had at least one comorbidity at diagnosis was 31%. At the time of the diagnosis, 13.9% of the patients had cardiovascular diseases, 10.5% of the patients had diabetes mellitus, and 76.4% of the patients were using medications for their comorbid conditions.
- The independent predictors of increased survival rates were found as female sex, lack of cardiovascular disease status at diagnosis and presence of molecular and cytogenetic responses.
- While deciding treatment, individualized treatments should be considered in CML patients taking the comorbidity status of these patients in addition to tolerability and side effect profiles of drugs.

### Author contributions

G Saydam made contributions to the design of the work and the acquisition, analysis and interpretation of data and drafted the manuscript and substantively revised it. A Unal, IC Haznedaroglu, A Hacıhanıfıoglu, O Mehtap, E Kurtoglu, M Gocer, M Turgut, E Kelkitli, MH Atay, N Guler, BU Koluman, M Sonmez, N Erkut, E Kaya, I Kuku, MA Erkurt, G Ozet, F Ceran, F Sahin, N Soyer, M Nalcaci, M Yilmaz, S Bozkurt, B Aver, B Ozdengulsun, E Ozbilgili, O Ilhan made contributions to the design of the study and acquisition of data. All authors read and approved the final manuscript.

### Financial & competing interests disclosure

This research was sponsored by Pfizer. G Saydam has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. A Unal has acted in advisory board of Novartis, AbbVie, Amgen 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. O Mehtap has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals, Takeda and Roche and has received speaker honorarium from Novartis, Takeda and Pfizer Pharmaceuticals. E Kurtoglu has acted in advisory board of Novartis, AbbVie, Deva Holding and Bristol Myers Squibb and has received speaker honorarium from Novartis and Bristol Myers Squibb. M Gocer has received speaker honorarium from Janssen Pharmaceutica. M Turgut has acted in advisory board of Novartis, Pfizer Pharmaceuticals and Bristol Myers Squibb and has received speaker honorarium from Novartis. N Guler has acted in advisory board of AbbVie and Deva Holding and has received speaker honorarium from AbbVie, Deva Holding, Novartis, Amgen, Pfizer Pharmaceuticals and Janssen Pharmaceutica. M Sonmez has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals, and Takeda and has received speaker honorarium from Novartis. E Kaya has acted in advisory board of Roche and has received speaker honorarium from Novartis, Janssen Pharmaceutica, AbbVie, Pfizer Pharmaceuticals and Arven Ilac. MA Erkurt has acted in advisory board of Johnson and AbbVie. G Ozet has acted in advisory board of Novartis, AbbVie and Deva Holding and has received speaker honorarium from Novartis and Janssen Pharmaceutica. F Ceran has received speaker honorarium from Novartis and Takeda. F Sahin has acted in advisory board of Pfizer Pharmaceuticals, Takeda, AbbVie, Novo Nordisk, Deva Holding and Sanofi. N Soyer has acted in advisory board of Novartis, AbbVie and Amgen. M Nalcaci has received speaker honorarium from Amgen and Pfizer Pharmaceuticals. M Yilmaz has acted in advisory board of Roche, AbbVie and Alexion Pharmaceuticals, has acted in clinical trials in Roche and Amgen, and has received honorarium from Janssen Pharmaceutica, Roche, Sanofi and Alexion Pharmaceuticals. O Ilhan has acted in advisory board of Novartis, AbbVie, Amgen, Pfizer Pharmaceuticals, Bristol Myers Squibb, Janssen Pharmaceutica, Deva Holding, Nobel Ilac and Roche. S Bozkurt, B Aver, B Ozdengulsun and E Ozbilgili are employees in Pfizer Pharmaceuticals. 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 for the manuscript was provided by Mine Nuyan Akkeci at OMEGA CRO, Ankara, Turkey and was funded by Pfizer.

### Ethical conduct of research

The authors state that the study was approved by the Clinical Research Ethics Committee of Erciyes University Medical Faculty (Approval number: 96681246/, date: 10 July 2018) and was carried out in accordance with the legal and regulatory requirements, the principles of Good Clinical Practice and Declaration of Helsinki.

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