ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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REAL LIFE DATA OF CHRONIC MYELOID LEUKEMIA PATIENTS IN ISPARTA

ISPARTA'DAKİ KRONİK MYELOİD LÖSEMİ HASTALARININ GERÇEK YAŞAM VERİLERİ

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Öz

Amaç
Kronik myeloid lösemi (KML), 100.000 yetişkinde 1-2 vaka insidansı olan myeloproliferatif bir neoplazmdır. KML' nin patogenezinin merkezi, kromozom 9 üzerindeki Abelson murin lösemi (ABL1) geni ile, kromozom 22 üzerindeki kırılma noktası bölgesi (BCR) geninin füzyonudur. KML tedavisi, tirozin kinaz inhibitörlerinin (TKİ) bulunması ile değişmiştir. Bu hedeflenmiş yaklaşım, KML' nin doğal seyrini değiştirmiş ve 10 yıllık sağ kalım oranını yaklaşık %80-90'lara çıkarmıştır. TKİ ile tedavi altında olan "gerçek hayat" KML hastalarımızda etkin tedavi yönetiminin yapılıp yapılmadığı, tedavi yanıt oranları ve sağ kalım verilerinin güncel literatür ile benzer olup olmadığının araştırılması amaçlanmıştır.

Gereç ve Yöntem
Süleyman Demirel Üniversitesi Tıp Fakültesi Hematoloji Bilim Dalı'nda 2000-2018 yılları arasında KML tanısı alan 58 KML hastası çalışmaya alınmıştır. Bu çalışmada hastaların klinik, laboratuvar ve demografik özellikleri, tedavi seçenekleri, yan etkileri ve yanıtları değerlendirildi. Sokal, Hasford ve Eutos risk puanlama sistemi ve Dünya Sağlık Örgütü kriterleri ile risk değerlendirmesi ve evrelemesi uygulandı. European Leukemia Network'ün kriterlerine göre hematolojik, sitogenetik ve moleküler yanıtı belirledik.

Bulgular
Çalışmamızda literatürle benzer yaş ortalaması, erkek/kadın oranı saptandı. Çalışmamızda yaş dağılımının (p=0,001) Charlson komorbidite İndeksi' nin (p=0,005) ve Charlson komorbidite-yaş İndeksi' nin (p=0,000) genel sağkalıma istatistiksel olarak anlamlı etki ettiği görülmüştür. Çalışmamızda yaş dağılımının (p = 0.029), Charlson komorbidite yaş İndeksi (p = 0,001) ve 12. ayda Major Moleküler Yanıt (MMY) alınmasının (p = 0,028) hastalıksız sağkalıma istatistiksel olarak anlamlı etki ettiği görülmüştür. Çalışmamızda sadece 12. Ayda MMY (p=0,006) progresyonsuz sağkalıma istatistiksel olarak anlamlı etki ettiği görülmüştür. Hastalarda retiküler lif derecesinin genel sağkalım, hastalıksız sağkalım ve progresyonsuz sağkalıma önemli ölçüde etki etmediği saptanmıştır.

Sonuç
Bu sonuçlar, KML'nin genellikle mevcut tedavilerle iyi yönetildiğini ve ölümlerin diğer tıbbi problemler nedeniyle daha sık meydana geldiğini göstermektedir. KML'de, Charlson indekslerinin genel sağ kalım ve hastalıksız sağ kalımla anlamlı derecede ilişkili olduğu gösterilmiştir.

Anahtar Kelimeler: Charlson komorbidite indeksi, Charlson komorbidite-yaş indeksi, Gerçek yaşam verileri, Kronik Myeloid Lösemi, Prognoz

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Abstract

Objective
Chronic myeloid leukemia is a myeloproliferative neoplasm with an incidence of 1–2 cases per 100 000 adults. Central to the pathogenesis of CML, is the fusion of the Abelson murine leukemia (ABL1) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22. The therapeutic landscape changed dramatically with the development of the tyrosine kinase inhibitors (TKIs). This "targeted" approach altered the natural history of CML, improving the 10-year survival rate to 80-90%. This study aims to investigate the effective management of TKI treatment and overall survival in "real-life" CML patients and to discuss the results with current literature.

Material and Method
Fifty-eight patients who were diagnosed as CML between 2000 and 2018 in Suleyman Demirel University Hematology Department were evaluated. Patients' clinical and laboratory characteristics, clinical and demographical features, treatment options, side effects and responses were evaluated in this study. Risk assessment and staging applied with World Health Organization criteria and Sokal Hasford and Eutos risk scoring system. We determined hematological, cytogenetic and molecular response according to European Leukemia Network criteria.

Results
The average age, male / female ratio and survival rates were found similar to those in literature. The age distribution (p = 0,001) and Charlson comorbidity index (p = 0.005) and Charlson comorbidity-age index (p = 0,000) had a statistically significant effect on overall survival. Age distribution (p = 0,029), Charlson comorbidity age index (p = 0,001) and major molecular response at 12 months (p = 0,028) were found to have a significant effect on disease-free survival. Major molecular response at 12 months (p = 0,006) also had a statistically significant effect on progression-free survival. Reticular fiber grade did not significantly affect overall survival, disease-free survival and progression-free survival of patients.

Conclusion
These results suggest that CML is generally well managed with existing treatment options and that death occur more frequently due to other medical problems. In CML, Charlson indices have been shown to be significantly associated with overall survival and disease-free survival.

Keywords: Charlson comorbidity index, Charlson comorbidity-age index, Chronic Myeloid Leukemia, Real life data, Prognosis

Introduction

Chronic Myeloid Leukemia (CML) is a clonal hematopoietic malignancy characterized by the Philadelphia chromosome formed by the fusion of Abelson's murine leukemia (ABL1) on chromosome 9 and the cut point on chromosome 22 (1). This fusion gene product has tyrosine kinase activity and ensures proliferation of clonal myeloid leukocytes (2). The incidence of CML is reported to be 1-2/100,000 per year (3). Today, although the molecular pathogenesis of CML is well understood, the etiology of gene translocation is not well known; radiation and some chemical carcinogens are blamed.

CML has three stages: chronic (85%), accelerated (10%), and blastic stage (5%). About 50% of patients diagnosed with CML are asymptomatic and are usually diagnosed during routine physical examination or blood tests; symptoms include fatigue, weight loss, malaise, early satiety, and left upper quadrant fullness or pain and are mostly due to anemia and splenomegaly (2).

Untreated chronic phase CML patients usually progressed to the blastic stage within 5 years and died. The most important reason for this was the presence of nonspecific and ineffective agents such as busulfan, hydroxyurea and interferon-alpha (IFN-a) in the treatment until 2000. Of these drugs, partial cytogenetic remission was achieved only in IFN-a, but its use was limited due to its low efficacy and serious side effects (2). Allogeneic stem cell transplantation is curative but carries serious morbidity and mortality risks. The treatment of CML has changed with the discovery of tyrosine kinase inhibitors (TKIs) and these agents inhibit the proliferation of the malignant clone by blocking the interaction between BCR-ABL1 oncoprotein and adenosine triphosphate. This targeted approach changed the natural course of CML and increased the 10-year survival rate to approximately 80-90% (4). Today, a major or complete molecular response is targeted in patients receiving TKI therapy, and BCR-ABL level is monitored with peripheral blood every six months in patients who achieve these responses. Many studies have been conducted on the effectiveness of TKIs; however, the

comparison of data between studies on real-life data and drug follow-up studies is still up to date. Our aim is to present a study that reveals real-life data of CML patients in and around Isparta.

Material and Method

A total of 58 patients aged 18 years and over, who were followed up for 6 months or more with the diagnosis of CML in the Department of Hematology of the Suleyman Demirel University between 2000 and 2018, were included in the study. Data were obtained from retrospective file and hospital records system.

Charlson comorbidity index was used to define and grade comorbidity. According to this index, comorbid diseases are scored according to their severity. Comorbidities were given a score of 1, 2, 3, and 4, respectively, from mild to severe disease, and comorbidity was graded according to the weighted score obtained by summing the scores of comorbid diseases. According to this grading, patients were divided into four grades as 0, 1-2, 3-4, 5 and above. The effect of Charlson comorbidity index and Charlson comorbidity-age index on prognosis was examined.

The response of the patients to the treatment and the side effects developed under the treatment were evaluated. The reason for the transition to the second TKI, and if the patient passed away, the time and whether it was related to CML were recorded. The effects of comorbidity score according to gender, age, Charlson-age index, presence of splenomegaly, major molecular response (MMR) at 12 months, Sokal risk score and bone marrow reticulin fiber grade on the prognosis were evaluated.

Progression-free survival (PS) was defined as the time from the date of first diagnosis to the loss of hematological, cytogenetic and MMR, and/or the time to progression to advanced CML. Overall Survival, was defined as the time from the first diagnosis to the last date of scanning the files (March 2019) for surviving patients. For patients who died, it was defined as the time from the date of first diagnosis to death. Disease-free survival was defined as patients except who died for reasons other than CML. Major molecular response was determined as ≤0.1 copies of BCR-ABL according to the International Scale. The criteria of the European Leukemia Network were used for the definition of complete hematological response at the 3rd month of treatment.

Statistical analyzes were performed using IBM SPSS Statistics 22.0. Continuous data and discrete data were recorded for descriptive statistics. While Kaplan-Meier survival analysis was used for univariate analyzes in survival statistics, Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware tests were used to compare survival at different levels. Cox-Hazard Regression Chi-square analysis was used for multivariate analyses. In comparisons, values with $p < 0.05$ were considered statistically significant.

The approval of the Ethics Committee of the Faculty of Medicine of Suleyman Demirel University, dated 16.01.2019 and numbered 17, was obtained for the study. Informed consent was obtained from all the participants, and all study steps were performed in accordance with Declaration of Helsinki.

Results

Of the total patients included in the study, 32 (55%) were male and 26 (45%) were female. The male / female ratio was found to be 1.23. The age distribution of the patients ranged from 18 to 89, with a mean age of 52 years. The mean age of men was 51.8 years, and the mean age of women was 53.6 years.

Additional diseases were as follows; hypertension in 14 (24%), diabetes mellitus in 11 (18%), coronary artery disease in 9 (15%), chronic obstructive pulmonary disease in 7 (12%) patients. disease, 3 (5%) chronic kidney failure, 2 (3%) peptic ulcer, 1 (1.7%) congestive heart failure, and 1 (1.7%) colon cancer. No additional disease was found in 29 of 58 patients (50%). According to the Charlson comorbidity age index, the grade was found to be 0 in 19 patients (33%), a score of 1-2 in 19 patients (33%), a score of 3-4 in 15 patients (26%), and a score of 5 and above in 5 patients (8%).

Symptoms at diagnosis were found in 27 (56%) of 58 patients; fatigue in 13 (27%), anorexia in 2 (18%), abdominal pain in 7 (15%), abdominal bloating and fullness in 8 (12%), weight loss in 4 (5%), infection in 9 (3%), and itching in 1 (1.7%). The complaints of 10 patients at the time of diagnosis were unknown.

It was unknown whether 5 patients had splenomegaly and/or hepatomegaly at the time of diagnosis, out of a total of 58 patients. Of 53 patients, 20 (38%) had splenomegaly and 7 (13%) had hepatomegaly. There were 5 patients with both splenomegaly and hepatomegaly.

Median laboratory counts on admission were hemoglobin 11.5 g/dl (6.7-15.4), leukocyte count

119.000/mm^3 (11.500-438,000), neutrophil count 108,000/mm^3 (5.400-386,000), platelet count 453,000/mm^3 (138,000- 1,324.000) (Table 1).

The Sokal risk score at the time of diagnosis was low in 14 patients (36%), moderate in 14 patients (36%), and high in 10 patients (27%). The Sokal risk score in 20 patients was unknown. MMR was evaluated at 12 months in 66.7% of those with a low Socal risk score, 70% of those with a medium risk score, and 75% of those with a high-risk score. When the relationship between Sokal risk score and MMR removal at 12 months was examined, no statistically significant difference was found (P= 0.924). In addition, 21.4% progression (loss of molecular response) was found in patients with low Sokal risk score, 14.3% in those with medium risk, and 40% in those with high risk. In our study, it was observed that MMY did not have a statistically significant effect on progression-free survival at 12 months (P= 0.758).

When the bone marrow reticular fiber grade at diagnosis was evaluated, 11 patients were Grade 0 (24%), 12 patients were Grade 1 (27%), 12 patients were Grade 2 (27%), 9 patients were Grade 3 (20%), and 1 patient was Grade in (% 2). The degree of reticular fiber at diagnosis was unknown in 13 of the patients.

In 10 patients, we could not evaluate the status of hematological response at three months. Complete hematological response was obtained in 47 (98%) of the remaining 48 patients in 3 months. Due to insufficient data, 12 patients could not be evaluated for MMR. Thirty-six (78%) of the remaining 46 patients had MMR at 12 months.

Eighteen (31%) of 58 patients were switched to second line TKI; 8 of them had side effects, 4 were not responding to 1st-line TKI (Imatinib) treatment, and 6 were switched due to the development of MMR loss.

Side effects developed in 15 (25.8%) of patients under imatinib treatment. While hematological side effects developed in 8 of the patients who developed side effects, 6 of them developed hematological side

Table 1 Laboratory values of patients

	Patients	Minimum	Maximum	Mean	Standard deviation
Age	58	18	89	52	15,718
Follow-up (month)	58	6	264	88	62
FISH %	47	35	100	88,53	15,13323
Hgb	53	6,7	15,4	11,5	1,86384
Leukocyte	53	11,5	438,5	119	95,17162
Platelet	53	138	1324	453	265,24756
Neutrophil(%)	49	8	97	85,1	13,03928
Lymphocyte (%)	48	1,1	34,	7,2	5,12252
Neutrophil	48	5,4	386,8	108,1	88,29488
Lymphocyte	48	1,8	31,2	7,0	5,97923
Eosinophile %	48	,00	7,3	1,74	1,81694
Basophile %	48	,00	45,7	2,23	6,63963
Eosinophile	48	,00	28,5	3,21	6,04201
Basophile	48	,00	30,6	1,80	4,59326
Uric acid	44	2,70	14,2	7,12	2,21612
Ldh	51	266	1943	900	446,12976
Creatinine	52	,50	1,69	1,0033	,25180

Hgb: Hemoglobin, LDH: Lactate Dehydrogenase

Table 2 Association of factors and survival

	Overall survival (p)	Progression-free survival (p)	Disease-free survival(p)
Age	**0,000**	0,980	**0,029**
Gender	0,086	0,431	0,30
CCAI	**0,001**	0,419	**0,001**
CCI	**0,005**	0,424	0,214
Splenomegaly	0,939	0,193	0,266
MMR at 12 months	0,183	**0,007**	**0,028**
Sokal	0,759	0,758	0,191
Reticulin fiber	0,686	0,984	0,620

MMR: Major molecular response, CCAI: Charlson comorbidity-age index, CCI: Charlson comorbidity index

effects requiring drug change (3 patients with severe anemia, 2 patients with moderate anemia and 1 patient with grade 2 thrombocytopenia and mild anemia). It was observed that 3 of the patients developed rash, 2 of the patients developed renal dysfunction and other side effects under imatinib treatment.

Under dasatinib treatment, side effects developed in 6 (55%) of 11. Of these, 3 (27%) had pleural effusion, 2 (18%) had hematological, 2 (18%) had gastrointestinal system side effects. 2 patients who developed side effects were excluded from evaluation due to insufficient follow-up data.

Since 1 out of 10 patients who were switched to nilotinib treatment dropped out of our follow-up, side effects could not be evaluated. Side effects did not develop in 5 (56%) of 9 patients under nilotinib treatment. Other side effects were rash in 2 patients (22%), Qtc prolongation in 1 patient (11%), cerebrovascular accident in 1 patient (11%), and elevated liver function test in 1 patient (11%). Due to these side effects, Nilotinib was discontinued in 2 patients and switched to Dasatinib.

The mean follow-up time was 88 months (6-264), and the mean overall survival was 87 months (40-183). In the follow-up, 11 of the patients (19%) died, while three of these patients (5%) died due to blastic stage CML. In our study, overall survival was found to be 81%.

In our study, it was observed that age distribution (p=0.001), Charlson comorbidity Index (p=0.005) and Charlson comorbidity-age Index (p=0.000) had a significant effect on overall survival; while, gender (p=0.086), splenomegaly at diagnosis (p=0.939), Sokal risk score (p=0.759), bone marrow reticulin fiber grade at diagnosis (p=0.686), and MMR loss at 12 months (p=0.183), had no significant effect on overall survival (Table 2). Sokal score were obtained in 38 of 58 patients. In patients with low, moderate, and high Sokal risk scores, overall survival was 92.9%, 78.6%, and 80%, respectively. 3 of 58 patients died due to blastic stage CML. Disease-free survival was found to be 95%.

In our study, it was observed that age distribution (p = 0.029), Charlson comorbidity age Index (p = 0.001) and reaching MMR at 12 months (p = 0.028) had a statistically significant effect on disease-free survival. Gender (p=0.30), CCI (p=0.214) splenomegaly at diagnosis (p=0.266), Socal risk score (p=0.191) and bone marrow reticulin fiber grade at diagnosis (p=0.620) were found to have no significant effect on disease-free survival.

In our study, the mean duration of PS was 73 months (9-183). Progression developed in 13 (22%) of the patients during the follow-up, and 3 of these patients died due to blastic stage CML.

In our study, only MMR at 12 months (p=0.006) was found to have a statistically significant effect on PS.

Discussion

CML is seen with an incidence of 0,4-1,75 per 100,000 adults (5). It constitutes approximately 15% of newly diagnosed leukemia cases in adults

(6). The average age at diagnosis in Europe varies between 60 and 65, but the age at diagnosis is lower in countries with younger populations. The prevalence of CML is increasing gradually due to the prolongation of survival achieved with targeted therapy (7). All the cases evaluated in this study were patients diagnosed in the chronic phase. The clinical course and treatment response of CML cases are not homogeneous. There are differences in laboratory parameters and degrees of myelofibrosis between patients. For example, while thrombocytosis or myelofibrosis is evident in some patients, it is absent or minimal in others. Similarly, erythrocyte values vary. The pathogenetic mechanisms for these differences have not been elucidated, but mutations are thought to play an important role. In addition, while cytogenetic and molecular response to tyrosine kinase inhibitors continues in some patients, there is a loss of response in others, which causes significant changes in the follow-up and treatment of patients and heterogeneity in studies.

Of the 58 patients included in the study, 32 (55%) were male and 26 (45%) were female. The male / female ratio was found to be 1.23. The age distribution of the patients ranged from 18 to 89, with a mean age of 52 years. The mean age of men was 51.8 years, and the mean age of women was 53.6 years. In the IRIS study, in which 1106 patients were examined and imatinib and interferon alpha + low dose cytarabine treatment were compared, the ratio of male patients was 61.7% in the imatinib arm, the rate of female patients was 38.3%, the mean age was 50 years, and the ratio of male patients in the arm using the interferon alpha + cytarabine combination was 61.7%. It was reported that the rate of female patients was 56.1, 43.9%, and the mean age was 51 (8). In the study conducted by Radich et al. in 246 patients with chronic phase CML, the mean age was 50 years in the arm receiving imatinib at diagnosis, the age range was 19-89 years, and the mean age was 47 years in the arm that received dasatinib. In the same study, the rate of male patients in the arm receiving imatinib was 59%, and the rate of female patients was 41% (9). In our study, the mean age and male/female ratio were similar to those in the literature.

In our study, splenomegaly was observed in 20 patients (38%) and hepatomegaly was observed in 7 patients (17%) on physical examination. Splenomegaly is the most common physical examination finding detected in 40-50% of cases. Hepatomegaly is less common (<10%) (2). In the study conducted by Radich et al. in 246 patients with chronic phase CML, splenomegaly was observed at diagnosis at a rate of 44% in the arm receiving imatinib and 51% in the arm receiving dasatinib. In the same study, hepatomegaly rates were reported as 3% and 5%, respectively (10). Palpable splenomegaly is a common physical examination finding in patients with CML and is the most common physical examination finding in our study, consistent with the literature.

In our study, treatment with a second-generation tyrosine kinase inhibitor was continued in 18 patients (31%) after imatinib treatment (8 nilotinib, 10 dasatinib). When the reasons for switching to second generation drugs were examined; second-generation therapy was initiated due to loss of response (secondary resistance) in 6 patients using imatinib, primary resistance in 4 patients), and intolerance in 8 patients. Radich et al. switched to second-generation drug in 34 patients (28% of all study population) (9). In the study conducted by Sahin et al. in 1133 patients, the rate of switching to second generation tyrosine kinase inhibitor was 29.3%. Resistance (90.8 %) was the primary cause of switching and 9.2% had a transition after intolerance (10). In the study of Eskazan et al. in which they compared original and generic Imatinib treatments; the conversion rates to second-generation treatment were 11% and 15%, for the original and generic treatment, respectively (11). In our study, similar to the literature, the most common reason for treatment change was side effects. In a study comparing imatinib and dasatinib treatment responses in 253 patients with chronic phase CML, hematological side effects were reported as the most common adverse event in both treatment arms. It has been reported that edema, nausea, and muscle pain, which are non-hematological side effects, were observed more frequently in the arm receiving imatinib, and pleural effusion was observed more frequently in the dasatinib group (9). In Sahin's study, gastrointestinal system side effects were the most common (13.24%); cytopenia was the second in more than one series (10.75%) (10). In the study of Eskazan et al., non-hematological side effects were also higher (11). In our patients, cytopenia was the most common side effect. In contrary to literature, rash and elevated creatinine were the most common non-hematologic side effects in our patients; it may be attributed to the low number of our patients.

Pleural effusion was more common with dasatinib compared to imatinib (19% vs. <1%). Other side effects of dasatinib are myelosuppression (20%) and rarely pulmonary hypertension (1-2%) (12). Similar to the literature, pleural effusion and myelosuppression were also observed in our study with patients using Dasatinib. In ENESTnd study, the most frequently reported adverse events were hematological. Among

the non-hematological effects, rash was higher in the nilotinib treatment arm, while adverse effects such as nausea, vomiting, edema, and muscle spasm were higher in the imatinib treatment arm (2). The fact that the side effects of second-generation tyrosine kinase inhibitors were different from the literature in our patients may be attributed to the small number of patients using these drugs.

Disease-free survival was found to be 95 % in our study. In the 8-year data of IRIS, which is the main and baseline study of imatinib, overall survival was 85%, but when non-CML-related causes were excluded, the survival rate increased to 93% (8, 13). The data of our study was quite compatible with the literature in this respect.

As the risk of death from CML decreases, the prognostic impact of comorbidities has gained greater importance. In one study, the estimated overall survival at eight years decreased with the increase in comorbidity measured by the Charlson Comorbidity Index (CCI) (14). Overall survival estimates were 94%, 89%, 78%, and 46% for patients with CCI 2.3 to 4.5, 5 to 6, and ≥7, respectively. In our study, age distribution (p=0.001), Charlson comorbidity Index (p=0.005) and Charlson comorbidity-age Index (CCAI) (p=0.000) were found to have a statistically significant effect on overall survival. GS estimates were found to be 100, 84, 73 20% in patients with CCAI of 0.1 -2, 3-4, ≥5. These results suggest that CML is well managed with current treatments and deaths occurred more frequently due to other medical problems.

In our study, gender (p=0.086), splenomegaly at diagnosis (p=0.939), Socal risk score (p=0.759), bone marrow reticulin fiber grade at the time of diagnosis (p=0.686) and MMR loss at 12 months (p=0.183) had no significant effect on survival. In the literature, a significant difference was found with patients at MMR 12 months (p<0.001). Jabbour et al., found no significant difference between MMR at the 12th month versus 18th (15). In our study, while reaching MMR at 12 months did not have a significant effect on overall survival, it had a significant effect on PS and disease-free survival.

Lakshmaiah et al., found that the estimated five-year overall survival was 95%, 95%, and 81% for the low, intermediate, and high-risk Sokal groups, respectively, and the difference was not significant (p = 0.89) (16). In studies conducted before TKI, it was observed that survival increased in low-risk patients and that survival decreased as the risk increased, however, there were data indicating that the Sokal risk score did not have a significant effect in studies conducted after TKI treatment (17). Our results were compatible with literature.

In our study, overall survival according to reticular fiber grade was 90.9% in grade 0 patients, 75% in grade 1, 75% in grade 2, 77.8% in grade 3 and 100% in grade 4. In the study of Kantarjian et al.; grade 3-4 fibrosis was detected in 67% of CML patients at diagnosis; however, no significant correlation was found between overall survival and reticular fiber grade in follow-up of imatinib treatment (18). It was thought that the significant decrease in survival parallel to the increase in reticular fiber grade in pre-TKI period disappeared with TKI treatment.

In conclusion, age distribution and Charlson comorbidity age Index had a significant effect on disease-free survival while reaching MMR at 12 months had significantly increased PS and disease-free survival. In CML patients, considering the patient's comorbid conditions, careful molecular monitoring and switching to second generation TKIs in case of side effects development were key points for follow-up of CML patients. Prospective and “real life” studies are needed to validate our results.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The approval of the Ethics Committee of the Faculty of Medicine of Suleyman Demirel University, dated 16.01.2019 and numbered 17, was obtained for the study. All study steps were performed in accordance with Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
MA: Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

DÖ: Formal analysis; Investigation; Project administration; Resources; Supervision; Validation; Writing-review & editing; Writing-original draft.

EGA: Conceptualization; Investigation; Methodology; Validation; Writing-original draft.

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