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Outcome of COVID-19 in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors

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Abstract

Introduction: In this study, we aim to report the outcome of COVID-19 in chronic myeloid leukemia (CML) patients receiving tyrosine kinase inhibitor (TKI).

Method: The data of 16 laboratory-confirmed COVID-19 patients with CML receiving TKI and age, gender, and comorbid disease matched COVID-19 patients without cancer at a 3/1 ratio (n = 48), diagnosed between March 11, 2020 and May 22, 2020 and included in the Republic of Turkey, Ministry of Health database, were analyzed retrospectively.

Results: The rates of intensive care unit (ICU) admission, and mechanical ventilation (MV) support were lower in CML patients compared to the control group, however, these differences did not achieve statistical significance ($p = 0.1$, and $p = 0.2$, respectively). The length of hospital stay was shorter in CML patients compared with the control group; however, it was not statistically significant ($p = 0.8$). The case fatality rate (CFR) in COVID-19 patients with CML was 6.3%, and it was 12.8% in the control group. Although the CFR in CML patients with COVID-19 was lower compared to the control group, this difference did not achieve statistical significance ($p = 0.5$). When CML patients were divided into 3 groups according to the TKI, no significant difference was observed regarding the rate of ICU admission, MV support, CFR, the length of stay in both hospital and ICU (all $p > 0.05$).

Conclusion: This study highlights that large scale prospective and randomized studies should be conducted in order to investigate the role of TKIs in the treatment of COVID-19.

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Introduction

At the end of 2019, a group of pneumonia cases of unknown origin started to be observed in China.[1] After the genetic analysis of the virus, it was understood that these pneumonia cases were caused by the 2019 Novel Coronavirus (2019-nCoV).[2] The phylogenetic analysis also revealed that the Severe Acute Respiratory Syndrome (SARS) Cov (SARS-CoV) and the Middle East Respiratory Syndrome (MERS) CoV (MERS-CoV) were close to 2019-nCoV about 79% and 50%, respectively.[3,4] The disease caused by 2019-nCoV was named as COVID-19, by the World Health Organization (WHO).[5] On the same day, 2019-nCoV was named as SARS-CoV-2.[6] As of 18 May 2020, in the worldwide, there have been 4.619.477 COVID-19 cases, including 311.847 deaths, as reported to WHO.[5]

COVID-19 currently does not have licensed vaccines or therapeutics. Given the large number of untreated patients, seeking a remedy in a short period is essential. In this regard, it is important to note that tyrosine kinase inhibitors (TKIs) have previously been shown to be effective against other CoVs. In a previous study, imatinib mesylate and dasatinib were found to be active against both MERS-CoV and SARS-CoV, and nilotinib was found to be active against SARS-CoV.[7] In recent studies, it was shown that on the surface of the CoVs, there are spike proteins that binds to angiotensin-converting enzyme-2 (ACE-2) receptor of the host cells. ACE-2 receptors are found in many tissues such as lower respiratory tract, heart, lungs, kidneys, and gastrointestinal tract. The complex of virus spike protein and host's ACE-2 receptor is proteolytically processed leading to proteolysis of ACE-2 and activation of the spike protein, which provides the entry of virus into the host cell.[8,9]

The entry of the virus into the host cell initiates the host's immune response.[10] Imatinib inhibits the activity of some tyrosine kinases, such as the BCR-ABL1 fusion oncoprotein, c-kit, platelet derived growth factor receptor (PDGFR), and the native ABL1 kinase.[11,12] In vitro activity of tyrosine kinase inhibitors (TKIs) against RNA viruses such as coxsackie virus, hepatitis C virus, or Ebola virus were demonstrated.[13–16] In addition, studies in murine models, revealed that imatinib may inhibit IL-6 and other pro-inflammatory cytokines.[17,18] Imatinib has also been shown to improve pulmonary endothelial barrier dysfunction and edema observed in acute lung injury and sepsis.[19,20] In most patients with chronic myeloid leukemia (CML), TKIs can achieve long-term control of the disease; thus, they are the initial treatment of choice for almost all newly diagnosed patients with CML. In this study, we aim to report the outcome of COVID-19 in CML patients who were receiving TKI treatment at the time of COVID-19 diagnosis in Turkey.

Materials and methods

Patients

The data of laboratory-confirmed COVID-19 patients diagnosed between March 11, 2020 and May 22, 2020 included in the Republic of Turkey, Ministry of Health database, were analyzed retrospectively. The research was in accordance with 1964 Helsinki declaration and ethical approval was obtained from Ministry of Health, Turkey. As of 22 May 2020, in Turkey, there have been 154.500 confirmed cases of COVID-19. There were 28 COVID-19 infected CML patients in the database. We included only 16 of them whose data were fully available in the database. An age, gender, and comorbid diseases matched laboratory-confirmed COVID-19 patients without cancer at a 3/1 ratio was also included in the study for comparison.

Laboratory analysis

Real-time reverse transcriptase-polymerase chain reaction (PCR) tests for SARS-CoV-2 RNA were performed using nasopharyngeal swabs. Total nucleic acid extraction of nasopharyngeal swabs of viral isolates was performed using a biospeedy and coyote extraction system (Bioeksen ltd and Coyote Bioscience ltd.). Real-time PCR (RT-PCR) assays for SARS-CoV-2 RNA detection were performed using Biospeedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey), Direct Detect SARS-Cov2 Detection Kit (Coyote Bioscience Co Ltd, China), Probe RT-PCR kit in a Light Cycler 960 real-time PCR system (Roche, Basel, Switzerland), CFX96 Touch Real-Time PCR Detection System

(Bio-Rad, California, USA), and Rotor-Gene Q (Qiagene, Hilden, Germany).

Statistical analysis

IBM SPSS v26 software was used for data analysis. Variables assessed for normal distribution with graphics, Shapiro-Wilk and Kolmogorov-Smirnov tests. Descriptive statistics were utilized to summarize data. Categorical data were presented as a ratio, and numerical data were presented as median. Chi-square test and Fisher's exact test were applied to investigate categorical variables between groups. Kruskal Wallis and Mann Whitney U test were applied to assess duration in hospital and duration in intensive care unit (ICU). A two-sided p-value ≤ 0.05 was considered statistically significant.

Results

Patients

Out of 16 CML patients with COVID-19, 10 were female and 6 were male, and median age was 51 years. The characteristics of the CML patients with COVID-19 are given in Table 1. Hypertension was the most common comorbid disease observed in both groups (43.8%). The characteristics of the CML patients with COVID-19 and the control group are given in Table 2.

Outcome

The rates of intensive care unit (ICU) admission and mechanical ventilation (MV) support were lower in CML patients compared with the control group; however, these differences did not achieve statistical significance ($p = 0.1$, and $p = 0.2$, respectively). The length of hospital stay was shorter in CML patients compared with the control group; however, this difference did not achieve statistical significance ($p = 0.8$). The case fatality rate (CFR) in CML patients with COVID-19 was 6.3% and it was 12.8% in the control group. Although the CFR in CML patients with COVID-19 was lower compared with the control group, this difference did not achieve statistical significance ($p = 0.5$) (Table 3). At the time of COVID-19 diagnosis, 9 CML patients were using imatinib whereas 4 patients were using dasatinib and 3 patients were using nilotinib. When CML patients were divided into 3 groups according to the TKI type, no significant difference was observed regarding the rate of ICU admission, MV support, CFR and length of stay in hospital and ICU (Table 4).

Discussion

Currently, there is no licensed therapeutics for COVID-19. In this context, the treatments investigated in other CoV infections and those found to be effective, should be tested in the current pandemic. TKIs were evaluated in SARS-CoV and MERS-CoV infections and imatinib and dasatinib were demonstrated to be effective both in SARS-CoV and MERS-CoV whereas nilotinib was found to be effective in SARS-CoV.[7] Novel medical research programs should be directed towards drug development that can stop the entrance of the virus to the host cells, and the replication of the virus in the host cells, or the prevention of the oversecretion of inflammatory cytokines in order to avoid organ

Table 1. The characteristics of the CML patients with COVID-19.

Patients	Gender	Age	TKI	Comorbidity
Patient 1	Male	27	Imatinib	None
Patient 2	Female	34	Imatinib	None
Patient 3	Male	37	Imatinib	None
Patient 4	Male	44	Imatinib	COPD
Patient 5	Female	47	Nilotinib	COPD
Patient 6	Female	47	Imatinib	None
Patient 7	Male	50	Dasatinib	None
Patient 8	Female	50	Imatinib	DM, HT
Patient 9	Female	52	Dasatinib	HT
Patient 10	Female	52	Nilotinib	CAD
Patient 11	Male	53	Imatinib	CKD
Patient 12	Male	60	Imatinib	DM, HT, CAD, CKD
Patient 13	Female	62	Imatinib	HT, CAD, COPD
Patient 14	Female	66	Dasatinib	DM, HT, CAD
Patient 15	Female	80	Dasatinib	HT, CAD, CVD, COPD
Patient 16	Female	87	Nilotinib	HT

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CKD: chronic renal disease; CVD: cerebrovascular disease; DM: diabetes mellitus; TKI: tyrosine kinase inhibitors; HT: hypertension.

Table 2. The characteristics of the CML patients with COVID-19 and control group.

Characteristics	CML (N = 16)	Control group (N = 48)	P value
Gender			
Female, n (%)	10 (62.5%)	31 (64,6%)	0,9
Male, n (%)	6 (37,5%)	17 (35,4%)	
Age (years)	51 (27–87)	56 (20–87)	0.4
Comorbidity			
Hypertension	7 (43,8%)	21 (43,8%)	1
Diabetes mellitus	3 (18,8%)	10 (20,8%)	1
Cardiovascular diseases	5 (31,3%)	12 (25%)	0,8
Respiratory system diseases	4 (25%)	11 (22,9%)	1
Chronic renal diseases	2 (12,5%)	3 (6,3%)	0,6
Cerebrovascular diseases	1 (%6,3)	2 (%4,2)	1
Additional treatment, n (%)			
Favipiravir	4 (25%)	14 (29,2%)	1
Oseltamivir	9 (56,3%)	20 (41,7%)	0,4
Lopinavir/ritonavir	1 (6,3%)	0	0,2
Hydroxychloroquine	13 (81,3%)	33 (68,8%)	0,5
High dose Vitamin C	1 (6,3%)	6 (12,5%)	0,7

CML: chronic myeloid leukemia.

Table 3. The outcome of CML patients with COVID-19 and control group.

	CML	Control Group	P value
ICU admission, n (%)	1 (%6,3)	11 (22,9%)	0,1
MV, n (%)	1 (%6,3)	10 (20,8%)	0,2
Duration in hospital, days	9 (2–18)	18 (4–46)	0,8
CFR, n (%)	1 (6,3%)	6 (12,8%)	0,5

CFR: case fatality rate; CML: chronic myeloid leukemia; ICU: intensive care unit; MV: mechanical ventilation.

damage.[21,22] Previous studies suggested that the ABL pathway may have a role in the replication of a variety of virus families, because of this, ABL pathway inhibitors of this pathway have the potential to be antivirals. Researchers demonstrated that Abl1 tyrosine kinase has a role in budding or release of poxviruses and the Ebola virus. Researchers have also shown that c-Abl1 kinase signaling mechanisms play a crucial role in CoV replication.[7] Previous studies showed that in the early phases of CoV infection, imatinib prevents virion fusion with the endosome and impending release into the cytoplasm, thus blocking viral entry and viral replication by Abl-mediated cytoskeletal rearrangement. In a subsequent stage of the infection, the expression of Abl2 protein, inhibited by both imatinib and dasatinib, facilitates replication of SARS-CoV and MERS-CoV.[23]

ACE-2 has a protective role against acute lung injury.[24,25] When the spike protein of SARS-CoV-2 binds, ACE-2 is downregulated, leading to an increase in angiotensin II and an increased pulmonary vascular permeability, pulmonary edema, and reduced lung function.[26,27] In addition to inhibiting the BCR-Abl fusion protein, imatinib also inhibits some other kinases including c-Abl, Abl-related gene, c-kit, and platelet-derived growth factor receptor (PDGFR), involved in regulating vascular permeability. Therefore, theoretically imatinib may have a role in attenuating inflammation and restoring vascular integrity in inflammatory vascular leak syndromes.[28] In an animal model of acute lung injury, imatinib significantly decreased bronchoalveolar lavage proteins and total cells therefore attenuated vascular leak.[29] Previous studies revealed the role of targeting Abl kinases to regulate vascular permeability, in which imatinib therapy was associated with rapid resolution of pulmonary and systemic vascular leak.[30,31] TKIs including imatinib, nintedanib, dasatinib, nilotinib, sorafenib, and saracatinib, have been studied for their anti-inflammatory effect and potential use in pulmonary diseases.[32] However, there is very limited data about the course of COVID-19 in CML patients receiving TKIs. In a case study, it was reported that 29 years old female CML patient who achieved major molecular response under dasatinib treatment and was continuing full-dose dasatinib therapy was diagnosed with COVID-19 and treated with antibiotics (amoxicillin and clavulanic acid). After four days, the fever cleared, and after two weeks, two separate consecutive swab tests were negative. During this time, she continued treatment with dasatinib at the same dose.[33]

In our study, we investigated the clinical effect of TKIs on the outcome of COVID-19 patients by

Table 4. The characteristics and outcome of the CML patients with COVID-19 patients according to the TKI they received.

Characteristics	CML-imatinib (n = 9)	CML-nilotinib (n = 3)	CML-dasatinib (n = 4)	P value
Gender				
Male	5 (55,5%)	0	1 (25%)	0,2
Female	4 (45,5%)	3 (100%)	3 (75%)	
Age (years)	46 (27–62)	52 (47–87)	53 (50–80)	0,2
Comorbidity				
Hypertension	3 (33,3%)	1 (33,3%)	3 (75%)	0,7
Diabetes mellitus	2 (22,2%)	0	1 (25%)	0,4
Cardiovascular diseases	2 (22,2%)	1 (33,3%)	2 (50%)	0,6
Respiratory system diseases	2 (22,2%)	1 (33,3%)	1 (25%)	0,9
Chronic renal diseases	2 (22,2%)	0	0	0,4
Cerebrovascular diseases	0	0	1 (25%)	0,2
Additional treatment, n (%)				
Favipiravir	3 (33,3%)	1 (33,3%)	0	0,4
Oseltamivir	5 (55,5%)	2 (66,6%)	2 (50%)	0,9
Lopinavir/ritonavir	0	1 (33,3%)	0	0,1
Hydroxychloroquine	8 (88,8%)	2 (66,6%)	3 (75%)	0,7
High dose Vitamin C	1 (11,1%)	0	0	0,7
ICU admission, n (%)	0	0	1 (25%)	0,2
MV, n (%)	0	0	1 (25%)	0,2
Duration in hospital, days	8 (6–18)	12,5 (12–3)	5,5 (2–9)	0,4
Duration in ICU, days	0	0	1 (25%)	0,2
CFR, n (%)	0	0	1 (25%)	0,2

CFR: case fatality rate; CML: chronic myeloid leukemia; ICU: intensive care unit; MV: mechanical ventilation.

comparing to an age, gender, and comorbidity matched control group. The main findings of the current study were that: (i) compared with the control group, the rates of ICU admission and MV support were lower and length of hospital stay was shorter in patients receiving TKI, however none of them achieved statistically significance. (ii) The CFR in patients receiving TKI was 6,3% and it was 12,8% in the control group. Although the CFR in patients receiving TKI was lower than the control group, this difference did not achieve statistically significance.

There are some limitations of our study. The study has a retrospective design and has limited number of patients. The superior side of our study is that the control group was composed of age, gender and comorbidity matched patients however in most of the ongoing studies, control groups are not comorbidity matched.

Neither chronic phase CML nor BCR-ABL tyrosine kinase inhibitors cause a clinically significant immune suppression, and there is no data suggesting that chronic phase CML patients are at higher risk of infection by SARS-CoV-2 compared to the general population.[34] Our study shows that the clinical course of COVID-19 is not worse in CML patients who are receiving TKIs than control group. Moreover, the rates of ICU admission and MV support, CFR were lower and length of hospital stay was shorter in CML patients receiving TKI compared to the age, gender and comorbidity matched control group but these differences were not statistically significant. Our study highlights that to find out whether the TKIs are associated with a better course of COVID-19 or not, large scale prospective and randomized studies should be conducted.

Abbreviations

CAD, coronary artery disease; CFR, case fatality rate; CKD, chronic renal disease; CML, chronic myeloid leukemia; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HT, hypertension; ICU, intensive care unit; MV, mechanical ventilation; TKI, Tyrosine Kinase Inhibitors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

This study was approved by the Ministry of Health, Turkey.

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