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Research

SARS-CoV-2 Infection in Patients with Chronic Myeloid Leukemia: A Multicenter Retrospective Study

Kronik Miyeloid Lösemi Hastalarında SARS-CoV-2 Enfeksiyonu: Çok Merkezli Retrospektif Bir Çalışma

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ABSTRACT

Objective: Coronavirus disease-2019 (COVID-19) infection is more severe and mortality is more common in patients with malignancy.

Methods: We evaluated the clinical course of COVID-19 infection in patients with chronic myeloid leukemia. 327 patients with chronic myeloid leukemia were analyzed and 21 cases with COVID-19 infection were included in this study. The complaints at the time of admission, laboratory and clinical findings, drugs used for treating COVID-19 infection of these patients were examined.

Results: The mean age of 21 patients was 45±15.85 years; 8 (38.1%) of the cases were male and 13 (61.9%) were female. All of these cases had chronic phase chronic myeloid leukemia. The most common complaints at the time of admission to hospital were weakness (66.7%), muscle and/or joint pain (57.1%), sore throat (42.9%). Four (19%) cases had pulmonary involvement and 4 (19%) cases were hospitalized. None of our patients needed intensive care unit admission and mechanical ventilation support. No cases died from COVID-19 infection.

Conclusion: The chronic myeloid leukemia patients with COVID-19 infection had a mild clinical course of COVID-19 infection. This could depend on the normal hematological parameters of chronic myeloid leukemia patients or using tyrosine kinase inhibitors.

Keywords: Chronic myeloid leukemia, COVID-19 infection, tyrosine kinase inhibitors

ÖZ

Amaç: Malignitesi olan hastalarda koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu daha şiddetli ve mortalite daha sıktır. Biz bu çalışmada, kronik miyeloid lösemili hastalarımızda COVID-19 enfeksiyonunun klinik seyrini değerlendirdik.

Gereç ve Yöntem: Kronik miyeloid lösemili 327 hasta analiz edildi ve bu çalışmaya 21 COVID-19 enfeksiyonu olgusu dahil edildi. Bu hastaların başvuru anındaki şikayetleri, laboratuvar ve klinik bulguları, klinik seyirleri, COVID-19 enfeksiyonunun tedavisinde kullanılan ilaçlar incelendi.

Bulgular: Yirmi bir hastanın yaş ortalaması 45±15,85 yıl olup, olguların 8'i (%38,1) erkek, 13'ü (%61,9) kadındı. Bu olguların hepsinde kronik faz kronik miyeloid lösemi vardı. Hastaneye başvuru anında en sık şikayetler güçsüzlük (%66,7), kas ve/veya eklem ağrısı (%57,1), boğaz ağrısı (%42,9) idi. Dört (%19) olguda akciğer tutulumu vardı ve 4 (%19) olgu hastaneye yatırıldı. Hiçbir hastamızın yoğun bakım ünitesine yatış ve mekanik ventilasyon desteğine ihtiyacı olmadı. COVID-19 enfeksiyonu nedeniyle ölen olgu olmadı.

Sonuç: COVID-19 enfeksiyonu olan kronik miyeloid lösemi hastalarında COVID-19 enfeksiyonunun hafif klinik seyri vardı. Bu, kronik miyeloid lösemi hastalarının normal hematolojik parametrelerine veya tirozin kinaz inhibitörlerinin kullanımına bağlı olabilir.

Anahtar Kelimeler: Kronik miyeloid lösemi, COVID-19 enfeksiyonu, tirozin kinaz inhibitörleri

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a member of the family coronaviridae. It was first reported in Wuhan, Hubei province in December 2019, and the disease it caused was named coronavirus disease-2019 (COVID-19). It is with flu-like symptoms in about 80% of cases. However, severe (dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93% and/or 50% increase in lung involvement in 24-48 hours) illness develops in 14% of all cases and critical (respiratory failure, septic shock, multiple organ failure) illness in 5% of all cases (1). The mortality rate is approximately 2%; it causes a higher rate of death by causing severe pneumonia, especially in individuals with chronic diseases such as immunodeficiency, diabetes mellitus, hypertension, cancer, or chronic lung disease (2). The mortality rate associated with COVID-19 infection in cases with solid or hematological cancer is 16.7% (3). In cases with hematologic malignancy, COVID-19 infection causes serious/critical illness in 62% of the cases and the mortality rate is 33% (4). Chronic myeloid leukemia (CML) is a hematological cancer characterized by uncontrolled proliferation of clonal myeloid precursor cells (5). The expected life span of patients with chronic phase CML is longer than that of other hematological malignancies. Tyrosine kinase inhibitors (TKIs) used for treating CML are one of the most important causes of this condition. The expected 10-year survival rate in patients with CML using imatinib mesylate is 80% (6). In the guideline published by the European Leukemia Network group in 2013, the disease-free survival rate was 94% and the overall survival rate was 97% in chronic phase CML (7).

Although COVID-19 infection is more severe and has a high mortality rate in solid and hematological cancer cases, it rarely causes severe and critical disease in cases with CML. Some authors have reported that this is due to the antiviral effect of TKIs on coronavirus. Although the mechanism of action of TKIs in COVID-19 treatment has not been fully determined, Mulgaonkar et al. (8) reported that imatinib mesylate causes inhibition of virus fusion via the cellular kinase pathway, resulting in inhibition of virus replication. In this study, we examined our CML cases who had COVID-19 infection.

METHODS

Ethical approval was obtained from the Ataturk University Faculty of Medicine Clinical Research Ethics Committee for this study (decision no: 9, date: 25.03.2021). In addition written informed consent form was obtained from all participants. This study was designed in accordance with the 1964 Helsinki Declaration. This study was conducted before the start of the vaccination program for COVID-19 infection in our country. For this reason, only the cases who did not receive the COVID-19 vaccine before the COVID-19 infection were included in our study. In our study, the files in the hospital automation system of 327 patients with CML followed in the hematology departments were analyzed retrospectively. In 21 of these cases, SARS-CoV-2 virus was detected by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test in nasopharyngeal and/or oropharyngeal swabs. COVID-19 was diagnosed according to the World Health Organization diagnostic criteria. Age, gender, complaints at the time of admission to hospital, comorbid diseases, laboratory findings, QT interval on electrocardiogram, lung involvement status, drugs used for treating COVID-19 infection, need for oxygen support, hospitalization and intubation was recorded. The name of the TKI used by patients with CML and the continuation of TKI treatment during the COVID-19 infection period was also recorded.

Low-molecular-weight heparin (LMWH) (enoxoparin 0.1 mg/kg/day) was given to all of our cases because the risk of thrombotic complications was high in CML cases. Patients with O_2 saturation <90% in room air were hospitalized. The corrected QT interval >440 ms in men and >460 ms in women was considered a prolonged QT interval. TKI treatment was discontinued in cases with prolonged QT interval. Control RT-PCR test was not performed in our cases after COVID-19 infection treatment.

Statistical Analysis

The IBM SPSS-20 program was used to evaluate the data. Descriptive statistics were used to evaluate the data. Categorical data were presented as numbers and ratios and numerical data as mean ± standard deviation (SD).

RESULTS

COVID-19 was detected in 21 (6.4%) of 327 cases followed up a diagnosis of CML. The mean (SD) age of 21 patients was 45.0 years (14) (range 25 to 74 years); 8 (38.1%) of the cases were male and 13 (61.9%) were female. All the cases had chronic stage CML; 14 (66.7%) patients were treated with imatinib mesylate, 5 (23.8%) patients with dasatinib and 2 (9.5%) patients with nilotinib. Diabetes mellitus, chronic renal failure and Behçet's disease each were in one (4.8%) patient. The body temperature was 37.3±0.6 °C in patients at the time of admission to the hospital. The complaints and laboratory tests of our cases at the time of admission are shown in Table 1. Additionally, the laboratory tests are indicated in Table 2.

O_2 saturation at the time of admission was 93.5±3.7% in patients. Thorax computerized tomography (CT) was performed in 5 (23.8%) cases due to pulmonary symptoms (cough and/or dyspnea), physical examination findings and/or posteroanterior chest radiography findings. Four (19%) cases had pulmonary involvement and 4 (19%) cases were hospitalized. None of our patients needed intensive care unit admission and mechanical ventilation support.

Favipravir treatment was administered to 15 (71.4%) patients [2x1,600 mg (peroral) loading dose on day-1 followed by 1,200 mg maintenance dose (2x600 mg, 2 times daily) on day 2-5]. Favipravir treatment was discontinued at the end of the 5th day in patients. LMWH (enoxoparin 0.1 mg/kg/day) was administered to all cases. Other treatments applied to these cases are shown in Table 3. Imatinib mesylate treatment was discontinued for 14 days because of QT distance (QT interval was: 440 ms) in the electrocardiogram of one patient. None of our cases died from COVID-19 infection.

DISCUSSION

Since December 2019, when the first case of COVID-19 infection was reported, 256,104,097 confirmed COVID-19 infected cases have been reported worldwide, and this number is 3.2% of the world population. The first case with COVID-19 infection in our country was reported on March 11, 2020 and 5,440,368 persons were diagnosed with COVID-19 infection until July 3, 2021. This rate is approximately 6.5% of the country's population. In our study, the rate of COVID-19 infection in CML cases was 6.4%. This rate was higher than the frequency of COVID-19 infection worldwide and it was similar to the rate in our country. 4,336 patients with CML were examined in Brazil and COVID-19 infection was detected in 28 (0.64%) cases (9). 6,883 cases followed up with a diagnosis of CML in Italy were examined and confirmed COVID-19 infection was reported in 12 people (0.17%), two of whom were healthcare workers (10). In our study, the frequency of COVID-19 infection in CML cases was higher than that in Italy and Brazil. This may be due to differences in the number of patients included in the studies and countries have different strategies for testing COVID-19 infection.

5,143,940 (2%) cases died from COVID-19 infection worldwide. In our country, 49,874 (0.9%) cases died from COVID-19 infection since March 11, 2020. Ozturk et al. (11) compared COVID-19 infected cases with and without a history of hemodialysis, chronic renal failure, and renal transplant. They found the mortality rate as 4% in the control group. In our study, In our study, none of our patients with CML needed intensive care and none of them died. The mortality rate in our CML cases was found to be lower than that of the normal population in our country and worldwide. In a study conducted in China, it was reported that COVID-19 infection led to the need for more intensive care and intubation in patients with cancer,

Table 1. Complaints of CML and COVID-19 infection cases at the time of admission

Complaint	n (%)
Sore throat	9 (42.9%)
Weakness	14 (66.7%)
Muscle and/or joint pain	12 (57.1%)
Cough	5 (23.8%)
Dyspnea	3 (14.3%)
Diarrhea	1 (4.8%)
Loss of taste	4 (19%)
Loss of smell	5 (23.8%)

CML: Chronic myeloid leukemia, COVID-19: Coronavirus disease-2019

Table 2. Laboratory tests of CML and COVID-19 infection cases

Laboratory test	Mean ± standard deviation
Hemoglobin (g/dL)	13.92±2.04
Hematocrite (%)	42.03±6.72
Leukocyte (µL)	17385±29899
Neutrophil (µL)	14.51±28.58
Lymphocyte (µL)	2440±1503
Monocyte (µL)	1154±1486
Platelet (µL)	214800±88737
Creatinine (mg/dL)	0.9±0.2
Sodium (mEq/L)	137.22±4.29
Potassium (mEq/L)	4.18±0.31
Calcium (mg/dL)	9.13±0.48
Phosphorus (mEq/L)	4.13±0.32
AST (U/L)	36.1±23.4
ALT (U/L)	29±23
LDH (U/L)	336.11±188.14
CRP (mg/L)	44.8±78.5
Ferritin (ng/mL)	227.56±277.15
D-dimer (ng/mL)	588.29±452.83
Fibrinogen (mg/dL)	336.7±184.1

CML: Chronic myeloid leukemia, COVID-19: Coronavirus disease-2019, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Table 3. Drugs given to CML and COVID-19 infection patients in addition to favipravir treatment

Drug	n (%)
Oseltamivir (2x75 mg/day, perorally for 5 days)	5 (23.8%)
Hydroxychlorachine (2x200 mg/day, perorally for 5 days)	6 (28.6%)
Prednisolone (1 mg/kg or pulse steroid)	2 (9.5%)

CML: Chronic myeloid leukemia, COVID-19: Coronavirus disease-2019

and the morbidity and mortality rate was significantly higher than in non-cancer cases (39% and 8%, respectively) (12). In a study conducted in Italy, 355 cases who died from COVID-19 infection were examined and active cancer was detected in 20% of the cases (13). Especially in patients who received chemotherapy and immunotherapy in the 2 weeks before COVID-19 infection, death was observed more (14). In a study in Brazil, 3 of 28 CML cases with COVID-19 infection died (9). A patient who died had advanced age and comorbidity, another case had a newly diagnosed CML disease accompanied by leukocytosis and bacterial infection, and the other case had hematological remission. One case had accelerated phase CML and died 2 months after discharge from the hospital due to pulmonary infection and CML progression. In our study, none of our patients with CML died. This result was less than the mortality rate in COVID-19 infected CML cases in Brazil. The reason for this may be the easy access to the drugs used for treating COVID-19 infection and the free treatment in our country. Additionally, all patients with COVID-19 infection who require hospitalization can be hospitalized because there are enough beds and medical staff in our hospitals. This may have contributed to the absence of COVID-19 related death events in our CML cases.

Yigenoglu et al. (15) reported that 11.5% of cases with COVID-19 infection in our country required follow-up in the intensive care unit. Başcı et al. (16) detected 28 patients with CML with positive SARS-CoV-2 RT-PCR test but they evaluated 16 patients with complete data in Turkey. They compared the clinical and laboratory findings of these cases with the findings of 48 COVID-19 infected cases without cancer. In CML cases compared to the control group, the length of hospitalization stays, mortality rate, the rates of required follow-up in the intensive care unit and mechanical ventilation support was lower than the control group, but no statistical significant difference. In our study, none of our patients with CML required intensive care unit admission and mechanical ventilation support.

Yılmaz et al. (17) examined 243 patients with chronic phase CML and detected COVID-19 infection in 5 patients (2%). Three patients were using imatinib mesylate, one patient was using nilotinib due to imatinib mesylate resistance, and the other patient was using nilotinib due to imatinib mesylate intolerance. None of the patients needed oxygen support in this study. In our study, 2 patients required O_2 support. However, in our study, a patient who required O_2 supplementation had diabetes mellitus and the other case had chronic renal failure. Yılmaz et al. (17) found lung involvement in torax CT in 60% of the cases. In our cases, this rate was 19%. The reason for this may be that our patients with only pulmonary symptoms should undergo torax CT. Asymptomatic lung involvement can also be observed in patients with COVID-19 infection. Yılmaz et al. (17) discontinued nilotinib of 2 patients due to concerns about QT prolongation. In our study, imatinib mesylate was interrupted because the QT distance was in the upper limit of normal in a patient. QT prolongation was not detected in the electrocardiography of our patients whose TKI treatment was continued during the follow-up.

COVID-19 infection causes impaired immune response. Decreased immune response to COVID-19 infection leads to increased viral replication. Increased immune response causes a cytokine storm, increased use of T-cells and lymphopenia. TKIs increase monocyte chemotaxis (18). Baruzzi and Berton (19) reported that abelson (abl) expression is essential for macrophage migration. There are protrusions named podosomes that have abl in their structure on myeloid leukocytes and they are important for the transport of myeloid cells to tissues and cell migration in the interstitium. TKIs prevent cell migration by affecting podosomes. Sisk et al. (20) reported that Imatinib mesylate prevented the entry of coronavirus into the cell (virus-cell and cell-cell) and the viral load of SARS-CoV and Middle East respiratory syndrome coronavirus decreased significantly. Dasatinib contributes to the reactivation of NK cells (18). It has been reported that T-cell activation *in vivo* in leukemia patients with dasatinib (21). It was reported that the very low rate of COVID-19 infection in CML cases was associated with TKI treatment (10). As a result, TKIs have regulatory effects on the immune system. This may contribute to the mild clinical course in patients with COVID-19 who receive TKI treatment. In our study, COVID-19 infection had a mild clinical course, supporting this view.

CONCLUSION

In our study, the mortality rate was lower in our patients who had COVID-19 infection while receiving TKI treatment for

CML compared to the general population in accordance with the literature. The reason for this may be that cases of chronic phase CML have normal hemogram parameters and/or TKIs may reduce the development of SARS by preventing the entry of coronavirus into the cell. Prospective studies with more cases are needed on this subject.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Ataturk University Faculty of Medicine Clinical Research Ethics Committee for this study (decision no: 9, date: 25.03.2021).

Informed Consent: All patients were informed and written informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: G.S., Y.K., E.K., F.E., E.A.K., M.E., A.T., Concept: G.S., E.K., F.E., Design: G.S., Y.K., M.E., A.T., Data Collection or Processing: G.S., Y.K., E.A.K., M.E., Analysis or Interpretation: G.S., E.A.K., Literature Search: G.S., E.A.K., A.T., Writing: G.S., E.K., E.A.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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