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COVID-19 infection in chronic myeloid leukemia patients

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) caused by Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) may present with more severe symptoms in immunocompromised and elderly patients, including chronic myeloid leukemia (CML) patients.

Method: From Jan 2020 to June 2021 all adult CML cohort receiving treatment from Patan Hospital, identified with COVID-19 infection were included in the study to analyze the severity of symptoms of COVID-19 in different age groups, phases of the CML, types of Tyrosine Kinase Inhibitor (TKI) used, and overall outcome. Ethical approval was obtained. Data were analyzed for association between variables by Fisher exact test using SPSS software.

Result: Out of 882 CML cohort 23(2.60%) patients had COVID-19, more in the female population and in the younger age group, but the mortality was higher in the elderly age group which was statically significant. Regardless of symptoms, stages, different TKI used, about 92% recovered fully from COVID-19 infection.

Conclusion: The incidence rate of COVID-19 infection in CML cohort patients, was 2.6%, and 92% recovered. Advanced stage of CML and elderly were had a more severe infection and higher mortality rate.

Keywords: Chronic myeloid leukemia, reverse transcriptase-polymerase chain reaction, severe acute respiratory syndrome coronavirus 2, tyrosine kinase inhibitor.

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Introduction

Corona virus disease 2019 is an infectious disease caused by the newly discovered coronavirus Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). This virus was identified first in China. In Nepal first case was reported on 23 Jan 2020.[1] Patients suffering from malignancy are more prone to infections, which is the major cause of treatment-related mortality.[2,3]

Chronic myeloid leukemia (CML), a hematological malignancy arises from reciprocal translocation of ABL1 part of chromosome 9 and BCR part of chromosome 22 forming a Philadelphia chromosome.[4] Early identification of COVID-19 infection in these patients by PCR (polymerase chain reaction) may improve outcome by timely therapy.[5] Most of the COVID-19 infections have mild symptoms but symptoms may be more severe in immunocompromised and elderly patients.[6]

There are various types of effective Tyrosine Kinase Inhibitor (TKI) used for the treatment of CML i.e. Imatinib, Dasatinib, Nilotinib, Bosutinib, and Ponatinib.[7] this study aimed to find out the severity of the COVID-19 infection and outcome of COVID-19 in CML patients, especially in elderly age group, different phases of the CML and types of TKIs.

Method

This is a cross-sectional observational study conducted in a cohort of CML patients at Patan Academy of Health Sciences (PAHS) from Jan 2020 to June 2021. The diagnosis of CML, different phases, monitoring, and response to TKI-therapy was based on European Leukemia Net (ELN) recommendations.

Different phases of the CML were defined as:

1) Chronic phase: The peripheral blood and bone marrow contain less than 10% blasts;
2) Accelerated phase: 10% to 19% blasts in both the peripheral blood and bone marrow or more than 20% basophils in the peripheral blood;
3) Blast phase/blast crisis: 20% or more blasts in the peripheral blood or bone marrow.

All adult CML patients (≥18 y) treated at PAHS were included. Diagnosis of COVID-19 in these patients was based on RT-PCR.

The signs, symptoms, and the severity of the COVID-19 were based on WHO criteria: [8]

1) Asymptomatic*:* Individuals who test positive for SARS-CoV-2 but who have no symptoms that are consistent with COVID-19;
2) Mild: Individuals who have any of the various signs and symptoms of COVID-19 (e.g. fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea or abnormal chest imaging;
3) Moderate: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air;
4) Severe: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%;
5) Critical: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

The study was conducted after ethical approval from the Institutional Review Committee (IRC) of PAHS (reference number drs2107221559). Patients' charts were retrieved from the medical record section with the help of their hospital numbers. Their demographic profile, signs, and symptoms, the severity of symptoms, and CML-related information including diagnosis, staging, treatment response were retrieved for analysis. No personal data were retrieved to

maintain the confidentiality of the patients. The outcome was noted according to the PAHS discharge summary (i.e., Improved, Static, Left against Medical Advice, and Expired).

All the relevant data from the proforma were recorded in the Microsoft Excel sheet. The infection rate and severity in different age and sex groups, signs and symptoms, types of CML, and TKIs used were calculated using frequency and percentage. The severity of the COVID-19 symptoms with different age groups, in different phases of the CML and TKIs, the outcome of the COVID-19 infection was analyzed by fisher's exact test to find the association between variables. The SPSS software was used for analysis. The $p<0.05$ was considered as statically significant.

Result

There were 882 active CML patients under treatment at PAHS. Among this cohort 23(2.6%) were diagnosed with COVID-19. The mean age was 48.26 y (range 28-70), male to female ratio was 9:14 (1:1.56). The infection was seen in 17(73.9%) among the younger age group of <60 y. The most common symptom was fever in 17(73.9%), followed by cough in 14(53.8%) and shortness of breath in 10(43.5%). Asymptomatic or mild symptoms of COVID-19 were seen in 14(60%), moderate symptoms in 5(21%), and severe and critical symptoms in 2(8.7%) each, Table 1.

Patients in the chronic phase (CML-CP) were 19(82.6%), remaining in the accelerated phase (CML-AP). In TKI, 14(60%) had Imatinib, 5(21%) Dasatinib, and 2(8.7%) each Nilotinib and Ponatinib, Table 2. None of the patients from the treatment-free remission group was diagnosed with COVID-19. Among 23 COVID-19 CML patients 7(30.4%) required hospitalization for treatment and 2(8.7%) critical patients died due to overwhelming COVID pneumonia despite ICU (Intensive care unit) care, and 16(69.6%) recovered from home isolation, Table 3. Out of a total of 23 COVID-19 infections, 21 (91.3%) recovered regardless of the severity of the infection and stages of CML.

Table 1. Relation of age group to Severity of symptoms of the COVID-19 (n=23)

	Asymptomatic N(%)	Mild N(%)	Moderate N(%)	Severe N(%)	Critical N(%)	p-value
Age ≥ 60	0	2(8.7%)	1(4.3%)	1(4.3%)	2(8.7%)	0.163
Age <60	2(8.7%)	10(43.5%)	4(17.4%)	1(4.3%)	0	

Table 2. Relation of severity of COVID-19 infection in different phases of CML(n=23)

	Asymptomatic N(%)	Mild N(%)	Moderate N(%)	Severe N(%)	Critical N(%)	p-value
CML-CP	1(4.3%)	10(43.5%)	5(21.7%)	1(4.3%)	2(8.7%)	0.373
CML-AP	1(4.3%)	2(8.7%)	0	1(4.3%)	0	
CML-BC	0	0	0	0	0	

Table 3. Relation of COVID-19 infection severity to final outcome in CML patients(n=23)

	Improved N(%)	Expired N(%)	p-value
Mild	14(60.9%)	0	0.012
Moderate	5(21.7%)	0	
Severe	2 (17.4%)	0	
Critical	0	2(8.7%)	

Discussion

In our study, 2.6% (23 out of 882) CML patients got COVID-19 infection which is slightly more than earlier published literature.[9] As CML is a myeloproliferative disorder that occurs due to the reciprocal translocation of ABL1 part of chromosome 9 and BCR part of chromosome 22 forming a shortened chromosome no 22 which is known as Philadelphia chromosome (Ph positive chromosome). This fusion of BCR-ABL1 protein increases tyrosine kinase activity. This is manifested as high total leukocyte count, high platelet counts, splenomegaly and hepatomegaly. The diagnosis of the CML is the identification of fusion of BCR-ABL gene either by FISH (Fluorescence in situ hybridization) or RT-PCR method.[4] The diagnosis of CML, different phases, monitoring, and response to TKI-therapy were based on European Leukemia Net (ELN) recommendations. It is not known whether patients diagnosed with CML are immunocompromised. However, once these patients are on different TKI, they are considered as immunocompromised.[10]

Therefore, in this era of the COVID-19 pandemic, the infection rate is expected to be more in such patients in terms of infection rate, its severity, and case fatality compared to the general population since their immune system is impaired. This is probably due to the change in the behavior of immune cells by decreased apoptosis of lymphocytes or expression of myeloid suppressor cells which makes them impaired anti infectivity and anti-inflammatory host. Thus, infections in CML patients may quickly develop into acute circulatory failure or septic shock.[11]

Five different types of TKI are effective against CML. i.e. Imatinib, Nilotinib, Dasatinib, Bosutinib and Ponatinib. COVID-19 infection's incidence and severity may vary in different TKI groups. Patients on a newer generation of the TKI may be more prone to COVID-19 infection, as these drugs are initiated on disease progression.

Most of the literature shows COVID-19 infection rate is more in the male population in the CML cohort.[12] In contrast to that finding, we found more COVID-19 cases in the female 14(60.9%) population. Even though it's not statically significant, the infection rate was seen higher in the younger age group 17(74.9%) <60 y, Table 1. This is similar to the study done by the hematology scientific group in Turkey.[13] But we had more patients of CML under the age <60 y, so our findings may show infection rate more in the younger age group compared to the older population in the published literature.[6]

While the world was facing a great problem controlling the COVID-19 infection in the initial months of the pandemic, many drugs were explored as anti-COVID agents. Among these drugs, Imatinib which is a type of TKI for the treatment of CML was thought to be protective against COVID-19 infection because of its mode of action of internalization and endosomal trafficking and by inhibiting the fusion of the virions at the endosomal membrane. So, it was thought that those patients who are on Imatinib were protected against COVID-19 infection.[14] Just in contrast to what was thought, we had a majority of our CML patients who were on Imatinib 14(60.86%) got COVID-19 infection. Even though the mechanism of action of Imatinib was in favor of protecting from COVID-19 infection, our small cohort showed the other way around. Though most of our patients were asymptomatic or with only mild symptoms, the most common symptom was fever, followed by cough and dyspnea, diarrhea, sore throat, rhinorrhea, and myalgia which were more or less similar to earlier published articles.[9,15] Fever being one of the major symptoms in COVID-19 and also a majority of our patients did have fever as common symptoms, interestingly one Dutch study showed none of their patients had a fever in their cohort of the study.[16]

About 60% of our patients recovered from home isolation and 30% of patients who got admitted received treatment for COVID-19 infection. Out of these 30% hospital admitted

patients we had two mortalities, both from the advanced phase of CML, i.e., CML-AP and CML-BC. We had to interrupt the TKI for one of the ICU admitted due to severe cytopenia. None of the patients died from the CML-CP group. From this finding, we can say that the disease severity is less in the CML-CP group. These two deaths account for 8.7% (2 out of 23), almost two times more than the case fatality seen in a study conducted in China.[17] Higher mortalities in our series may be attributed to many factors, resource constraints, and COVID-19 being a novel disease, our understanding about the disease in terms of its infectivity, disease course and its management may be limited. Even though our sample size is small it suggests that COVID-19 infection severity is more in advanced cases of CML, which is proven by the studies done earlier.[18]

Before the era of Imatinib patients diagnosed with CML in the elderly age group were found to have a poor prognosis due to the poor performance status, and poor tolerance to the medication. After Imatinib therapy became the treatment of choice for CML patients, its outcome did not vary for different age groups of the patients which have been proven by several studies.[19,20] Majority of the COVID-19 infection was in the CML-CP group and almost everyone was asymptomatic or with mild symptoms. This is in contrast to the finding of the earlier study where they found a very low risk for opportunistic and viral infection in CML-CP on the Imatinib group.[21] All of the patients with COVID-19 infection in this group did recover well from the infection. But we found that chance of attracting more severe symptoms of COVID-19 is in more advanced phases of CML and the elderly age group, regardless of the TKI being used which is statically significant (p=0.012), Table 3. Once CML progresses to the advanced phase then its outcome is poorer compared to the CML-CP group. The disease progression itself without infection can be taken as a poor outcome, as suggested by the studies done earlier.[22] It proves that COVID-19 infection with comorbidities leads to a more severe outcome. This is probably because of the similarity in gene expression patterns, of the SARS-CoV 2 and the gene expression of leukemia patients. The genes encoding of various interferons, cytokines, chemokines, and mediators of the JAK-STAT pathway were positively regulated in leukemia as seen in COVID-19 infection. So, leukemia is one of the diseases which will increase the susceptibility of COVID-19 infection, this finding may be true for CML as well, after knowing the genetic analysis.[23]

Thus, these CML group of patients, who are elderly, advanced phases, and infected with COVID-19, should be monitored carefully with a low threshold for intervention to improve the outcome.

Some of the limitations of our study include retrospective observational design and a single center in a small sample size. We might have missed the asymptomatic and mild cases as presumptively these patients may not have undergone COVID-19 tests. The true incidence of COVID-19 infection may be higher, which may not have been reflected in our study.

Conclusion

Among adult chronic myeloid leukemia (CML) patients advanced age was associated with more severity and higher mortality due to COVID-19. The infection was higher in the chronic phase (CML-CP) and those taking Imatinib.

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Conflict of Interest

None

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Author Contribution

Concept, design, planning: ML, BP, KRS, RS, GKK; Literature review: ML; Data collection/analysis: ALL; Draft manuscript: ALL; Revision of draft: ALL; Final manuscript: ALL; Accountability of the work: ALL.

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