# COVID-19 Infection in Chronic Myeloid Leukemia Patients Receiving Tyrosine Kinase Inhibitor in Makassar, Indonesia: A Six-Case Report and Literature Review

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## ABSTRACT

*Management of chronic myeloid leukemia (CML) in patients who are infected with COVID-19 is a challenging task due to disease-related or treatment-related factors that place such patients at a higher risk of complications. However, a low-infectivity-rate mechanism has been proposed by some researchers. In CML patients with COVID-19 infection, the most important treatment-related factor involves tyrosine kinase inhibitors (TKIs). In this case report, six patients with chronic-phase CML who experienced COVID-19 of mild–moderate severity all continued to receive TKI treatment for CML concurrently with COVID-19 treatment. All patients fully recovered. In the present study, we also review four other cases of COVID-19 infection in CML patients. Outcomes for TKI-treated CML patients who contract COVID-19 are influenced by many factors. Tyrosine kinase inhibitor therapy may benefit CML patients due to its antiviral effect, but the interaction between TKIs and drugs used for COVID-19 treatment requires careful monitoring. An individual approach is needed in every case.*

***Keywords*** *: Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitor, COVID-19, Case Report*

## INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have become a first-line treatment modality used in almost all cases of chronic-phase CML (CML-CP) identified by breakpoint cluster region-Abelson (*BCR-ABL*).[1] Several TKIs have been approved for CML treatment, namely, imatinib, nilotinib, dasatinib, bosutinib, and ponatinib.[2] In Indonesia, leukemia is the seventh-most-common type of cancer, with a proportion of 4.44%**.** Chronic myeloid leukemia accounts for 15% of all new leukemia cases and has an incidence of 1–2 cases per 100,000 people. In Makassar, South Sulawesi, Indonesia individuals diagnosed with CML cases have a mean age of 37.6±10.76 years, which is younger than the range age of 56–57 years reported in western populations.[3,4]

The chronic side effects of TKIs which can be tolerated in an otherwise healthy individual may become intolerable when a CML patient is also infected with SARS-CoV-2. However, and interestingly, low COVID-19 infectivity rates have been reported among CML patients.[5,6] Tyrosine kinase inhibitors (TKI) acting through Abl kinase inhibitors are known to block the entry of viruses into host cells, upregulate "antiviral" genes, and decrease gene expression with "proviral" actions [7]. However, any disease factors specific to CML that may influence the course of COVID-19 have not yet been identified. In the present study, we report six

cases of individuals with chronic-phase CML who were infected with COVID-19.

## CASE ILLUSTRATION

We identified six cases of patients with chronic-phase chronic myeloid leukemia (CML-CP) who were infected with COVID-19 between January and July of 2021. Chronic-phase CML was diagnosed by the results of bone marrow examination which revealed myeloid maturation differentiation with blast <10%, and by molecular examination in which BCR-Abl was detected, either qualitatively or quantitatively with real time polymerase chain reaction in GeneXpert® BCR-ABl monitor system. All patients received tyrosine kinase inhibitor (TKI) therapy for their CML, and all continued this treatment with good compliance during their COVID-19 infection periods.

COVID-19 diagnosis was confirmed by positive polymerase chain reaction (PCR) nasopharyngeal swabs in all patients. The severity of COVID-19 was assessed according consensus made by five professional medical organizations (Indonesian Society of Internal Medicine, Indonesian Society of Pulmonology, Indonesian Society of Cardiovascular, Indonesian Society of Anesthesiology and Intensive care, and Indonesian Society of Pediatric) which adopted the 2020 World Health Organization (WHO) criteria.

Our patients consist of four (67%) women and two (33%) men. The mean age were 37.8 years. Of the six patients, two received the tyrosine kinase inhibitor (TKI) nilotinib and the remaining four received the TKI imatinib. All of the patients continued their TKI therapy while infected by COVID-19. Patient characteristics and outcomes are set out in Table 1 and can be briefly summarized, as follows:

Patient no. 1 had Bcr-Abl levels of 0.14%. During COVID-19 infection, she experienced fever, shortness of breath, chest pain, loss of smell, nausea, vomiting, and skin rash (moderate symptoms). She was hospitalized for 25 days and treated with oxygen therapy, favipiravir, azithromycin, paracetamol, cough medicine, and vitamin D. On day 26, she was discharged after a negative PCR result.

Patient no. 2 had Bcr-Abl levels of 0.003%. During COVID-19 infection, she experienced fever, cough, painful swallowing, loss of smell, and diarrhea (mild symptoms). She was treated in an outpatient department with favipiravir, azithromycin, paracetamol, cough medicine, and vitamin D. On day 7, her condition was evaluated, and a PCR swab test showed a negative result.

Patient no. 3 had Bcr-Abl levels of 83%. During COVID-19 infection, she experienced fever, cough, loss of smell, nausea, and vomiting (mild symptoms). She did not require hospitalization but did self-quarantine. She was treated with favipiravir, azithromycin, paracetamol, cough medicine, and vitamin D. By day 10, she had recovered, and a PCR test showed a negative result.

Patient no. 4 had Bcr-Abl levels of 17%. During COVID-19 infection, she experienced fever, shortness of breath, fatigue, and headache (moderate symptoms). She was hospitalized, and received oxygen therapy for 7 days, along with a regimen of favipiravir, azithromycin, paracetamol, cough medicine, and vitamin D. On day 7, she was discharged after a negative PCR swab, having recovered from COVID-19.

Patient no. 5 had Bcr-Abl levels of 1.4%. During COVID-19 infection, he experienced fever, cough, and loss of smell (mild symptoms). He was treated in an outpatient department with favipiravir, azithromycin, paracetamol, cough medicine, and vitamin D. On day 14, his condition was evaluated, and a PCR swab test showed a negative result.

Patient no. 6 had Bcr-Abl detected qualitatively. During COVID-19 infection, he experienced fever, cough, shortness of breath, and loss of smell (moderate symptoms). He was hospitalized for 8 days and received oxygen therapy, favipiravir, azithromycin, paracetamol, and cough medicine. On day 8, he was discharged after a negative PCR swab test, having recovered from COVID-19.

## DISCUSSION

During the COVID-19 pandemic, individuals who were in receipt of TKI treatment for chronic

**Table 1.** CML patient characteristics

| Patient ID | Gender | Age (years) | Vaccination | TKI therapy | Bcr-Abl | Treatment response | COVID-19 symptoms and severity | Therapy | Duration of COVID-19 infection | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1.C | Female | 22 | Sinovac 2 times | Imatinib for 9 years | 0,14% (IS) | Molecular response | Fever, shortness of breath, chest pain, loss of smell, nausea, vomiting, skin rash **(moderate symptoms)** | Hospitalized, oxygen therapy, favipiravir, azithromycin, paracetamol, cough medicine, vitamin D | 25 days | Recovered |
| 2.H | Female | 49 | Sinovac 2 times | Imatinib for 11 years | 0,003% (IS) | Molecular response | Fever, cough, painful swallowing, loss of smell, and diarrhea **(mild symptoms)** | Favipiravir, azithromycin, paracetamol, cough medicine, vitamin D | 7 days | Recovered |
| 3.K | Female | 38 | Sinovac 2 times | Nilotinib for 6 years | 83% (IS) | Hematological response | Fever, cough, loss of smell, nausea and vomiting **(mild symptoms)** | Favipiravir, azithromycin, paracetamol, cough medicine, vitamin D | 10 days | Recovered |
| 4.M | Female | 29 | Sinovac 2 times | Imatinib for 7 years | 17% (IS) | Hematological response | Fever, shortness of breath, fatigue, and headache **(moderate symptoms)** | Hospitalized, oxygen therapy, favipiravir, azithromycin, paracetamol, cough medicine, vitamin D | 7 days | Recovered |
| 5.S | Male | 49 | Sinovac 2 times | Imatinib for 8 years | 1,4% (IS) | Hematological response | Fever, cough, loss of smell **(mild symptoms)** | Favipiravir, azithromycin, paracetamol, cough medicine, vitamin D | 14 days | Recovered |
| 6.I | Male | 39 | Sinovac 2 times | Nilotinib for 1 years | Detected | Hematological response | fever, cough, shortness of breath, loss of smell **(moderate symptoms)** | Hospitalized, oxygen therapy, favipiravir, azithromycin, paracetamol, cough medicine, vitamin D | 8 days | Recovered |

**Table 2.** Reports on TKI treatment of CML patients with COVID-19 infection.

| **Author** | **Type of Report** | **Origin** | **Duration of CML** | **Number of patients** | **Patient Age** | **Bcr-Abl** | **Response** | **COVID-19 severity** | **TKI** | **Outcome** |
|---|---|---|---|---|---|---|---|---|---|---|
| Ibrahm et al. (2020) [8] | Case report | Egypt | CML-CP 10 years | 1 | 57 years old | 0.0001% | MMR | Severe | Imatinib withheld | Patient survived |
| Nesr et al. (2021) [7] | Letter to editor | United Kingdom | CML-CP 3.9 years | 9 | 56 years old (21–72) | N/A | 78% MMR | 6 mild, 1 moderate, 2 severe | 7 imatinib, 2 bosutinib | 8 survived<br>1 died |
| Yilmaz et al. [9] | Letter to editor | Turkey | CML-CP 9.4 years | 5 | 52 years old (32–86) | N/A | 1 MMR<br>4 DMR | 4 mild, 1 moderate | 3 withheld, 2 continued | All 5 Patients survived |
| Li et al. [10] | Cohort | China | 3 CML-CP, 2 Ap-CML | 5 | 57 years old (41–89) | N/A | 2 MMR<br>2 No CHR<br>1 CCyR | 4 mild, 1 severe | 1 withheld, 4 continued | 4 survived<br>1 died |

myeloid leukemia and who were then infected with COVID-19 exhibited unique characteristics relating to COVID-19 and their TKI therapy. In this case report, we describe six CML patients who fully recovered from COVID-19 infection with mild–moderate disease severity. To date, the CANDID study represents the largest global cohort study of COVID-19 infection in CML patients, and this reported a COVID-19 mortality rate of 13.7% among such patients.[11] There were many risk stratification of COVID-19 in general population but author found limited study reported in CML population. Radich et al evaluated risk model for CML patients with COVID-19 that the mortality rate for MMR, no MMR, and AP/BC was 4%, 11% and 26%.[12]

There are no data indicating that cancer patients with COVID-19 have poor clinical outcomes, but immunocompromised patients are known to be susceptible to infection. Patients undergoing active chemotherapy or radiotherapy face an increased risk of infection.[13] However, the severity of COVID-19 in such cases depends on the type and stage of cancer involved, and the type of therapy received. Blood malignancies have been reported as a cancer type associated with high levels of COVID-19 morbidity and mortality.[14]

At present, there is no evidence to suggest that those with chronic-phase CML in receipt of TKI therapy are at a higher risk of contracting SARS-CoV-2, or of experiencing a more severe form of the viral infection, compared to the general population.[14] Interestingly, two large cohort studies in Italy and Turkey reported low (0.17 and 4.1%) incidence rates for COVID-19 infection among CML patients.[5,6]

Various studies have sought to explain the mechanism behind such low infectivity rates. The most important factor appears to be the role played by TKIs. An antiviral effect of tyrosine kinase inhibitors (TKIs) has been reported, involving an off-target Abl kinase inhibitor which blocks viral entry into host cells, upregulates "antiviral" genes, and decreases the expression of genes with "proviral" action.[7]

Abelson kinase inhibitors are a potent inhibitor of SARS-CoV.[15] Researchers have demonstrated that the c-Abl1 kinase signaling mechanism plays an important role in coronavirus (CoV) replication.[15] Imatinib prevents fusion of the virion with the endosome and its subsequent release into the cytoplasm, thereby blocking viral entry and viral replication by Abl-mediated cytoskeletal rearrangement. At a later stage of infection, the expression of the Abl2 protein, which is inhibited by imatinib and dasatinib, facilitates the replication of SARS-CoV and MERS-CoV.[16] Galimberti et al. highlighted the role played by genes during treatment with imatinib. They found that several "antiviral" genes, such as CD28 and IFN gamma, were upregulated, while genes with "proviral" actions, such as ARG-1, CEACAM1, and FUT4, were less expressed during imatinib treatment.[17]

However, researchers have also investigated CML patients who did not achieve a complete hematological response, as well as patients in advanced phases of the disease who did not achieve either a complete cytogenetic or a major molecular response, and found that both groups faced an increased risk of developing COVID-19.[10] An optimal response to TKI treatment may be associated with immune recovery. CML patients exhibit selective depletion of effector T-reg cells, while TKIs increase the number of natural killer cells (NKs), i.e., NK-LGL, and T-LGL cells, which play a role in regulating immunity.[8,18]

Management of CML in patients who are infected with COVID-19 is a challenging task. Chronic side effects of TKIs include myelosuppression, fluid retention, pulmonary toxicity (dasatinib),[19] as well as increased risk of thrombosis (nilotinib, ponatinib),[20] all of which can be tolerated in otherwise healthy individuals, but which may become intolerable during SARS-CoV-2 infection.[21] TKIs are metabolized by cytochrome-P450 (CYP), and all TKIs used in CML therapy can cause prolonged QTc intervals which can lead to torsades de pointes and sudden death. Azitromycin was recommended as a COVID-19 treatment early in the pandemic. However, the use of TKIs in combination with Azitromycin may increase the risk of prolonged QTc intervals.[22] The interaction between TKIs and drugs used for COVID-19 treatment requires careful monitoring and necessitates a single-

patient treatment approach. Remdesivir can cause liver problems and, in combination with nilotinib, imatinib, or bosutinib, may increase the risk of such problems.[23,24] Favipiravir may also interact unfavorably with imatinib, bosutinib, and dasatinib. A combination of favipiravir and imatinib decreases the metabolism of the latter. When CYP2C8 substrates are administered concurrently with a CYP2C8 inhibitor, their CYP2C8-mediated metabolism is reduced. As a result, serum concentrations increase, and the incidence and/or severity of adverse effects associated with exposure to the given substrate also increase.[25] Favipiravir increases the serum concentrations of dasatinib and serum bosutinib. The simultaneous administration of p-glycoprotein inhibitors and p-glycoprotein substrates may block their efflux out of cells, hence increasing drug exposure and deleterious effects.[26] However, no interaction between favipiravir and nilotinib has been reported.

We continued TKI treatment in all our CML patients. A small number of reports have been published concerning such treatment in CML patients with COVID-19 infection.[9] Such studies identified variations in decision-making concerning the continuation or withholding of TKI treatment in such cases (**Table 2**). Li et al. reported continuation of TKI treatment in one patient severely affected by COVID-19.[10] Contrarily, Ibrahm et al.[8] withheld TKIs in one severe COVID-19 case, and resumed TKI treatment when the patient was stable. Yilmaz [9] withheld TKI treatment in three of five patients. In two of these cases, nilotinib was withheld due to concerns of drug–drug interaction and QTc prolongation. In the other case, imatinib was withheld, but no reason was mentioned.

Currently, there are no guidelines for the management of COVID-19 in the CML population, yet. The American Society of Hematology has recommended that patients with CML who are in treatment-free remission (i.e., stable and deep molecular response while off TKIs) and who become infected should be managed in the same way as the general population. In the presence of non-severe confirmed SARS-CoV-2, or of symptoms compatible with non-severe SARS-CoV-2, the interruption of TKI treatment is considered unnecessary. In cases of severe COVID-19, TKI interruption should be considered on a case-by-case basis. However, TKI treatment should be withheld from patients with cardiopulmonary toxicity due to TKI who develop SARS-CoV-2 until both the infection and any adverse events are resolved.[27]

Outcomes for CML patients in receipt of TKI therapy who contract COVID-19 are influenced by many factors, including patient age, comorbid diseases, and drug interactions, both synergistic and antagonistic. Rasyid, Harjianti et al. showed that patient age had a significant impact on outcomes for COVID-19 patients.[28] The average age of patients in our case series was 37.8 years. This is younger than the average reported in other studies, which is 52–57 years. Age was clearly a contributing factor in the good clinical outcomes of the patients in our series. One meta-analysis study showed that an age of >65 years, male sex, and comorbidities were all associated with severe events in cancer patients with COVID-19.[29] Overall, younger people develop severe COVID-19 symptoms less frequently than adults, and they are at lower risk of hospitalization and of life-threatening complications. However. Sandoval et al. revealed a significant risk of severe disease and readmission among some young adult populations, especially marginalized communities and people with comorbidities.[30]

Larger-cohort studies are needed to evaluate the effect of TKIs on COVID-19 outcomes. Factors specific to CML which may influence the course of COVID-19 also need to be further investigated in future research**.**

## CONCLUSION

Chronic myeloid leukemia patients may have disease-related or treatment-related factors that place them at a higher risk of complications during SARS-CoV-2 infection. Tyrosine kinase inhibitor therapy may benefit CML patients due to its antiviral effect, but the interaction between TKIs and drugs used for COVID-19 treatment requires careful monitoring. An individual approach is needed in every case.

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## CONFLICTS OF INTEREST

None to declare.

## AUTHOR CONTRIBUTIONS

**Harjianti T :** conceptualization, writing—review and editing; **Benyamin F :** visualization, writing—review and editing; **Minhajad R:** conceptualization, writing—review and editing; **Saleh S :** conceptualization, writing—original draft; **Bayu D :** visualization, writing—review and editing; **Pababari W :** writing—original draft.

**Data availability :** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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