ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has emerged as a global pandemic as it has affected millions of individuals and caused hundreds of fatalities. This pandemic has posed serious challenges to health care professionals related to the treatment and management of cancer especially chronic myeloid leukemia patients. Objectives: This review has summarized some latest studies and case reports conducted to evaluate the prevalence and effects of COVID-19 infection in chronic myeloid leukemia patients and how anti-neoplastic drugs act as antiviral agents.

Methodology: All the literature were searched by using different electronic databases.

Results: The rate of COVID-19 infection in cancer patients is higher as compared to the normal population. The reason may be immunosuppression due to cancer progression or a therapeutic approach applied to control the progression of cancer. Studies have indicated a low risk of infection in chronic myeloid leukemia patients who received tyrosine kinase inhibitor therapy.

Conclusion: It has been found that tyrosine kinase inhibitors may act as an antiviral agent. That gave the idea that anti-neoplastic agents could be repurposed as antiviral agents to fight the battle against the current pandemic. This will provide new insights into the management of COVID-19 infection in chronic myeloid leukemia patients.

Keywords: COVID-19, CML, SARS-CoV-2
COVID-19 AND CANCER

The coronavirus disease caused by severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) has rapidly shaken out globally and this rapid escalation has imposed serious complications for other disease treatments such as cancer (1). According to recent data, the pandemic had posed a significant impact on cancer patients. The rate of infection of COVID-19 could be substantially higher in cancer patients as compared to the common healthy individuals, as described by two observational reports (2, 3). Moreover, such research analysis has suggested that cancer patients could be at a higher risk of serious COVID-19-related risks, such as hospital admission, respiratory failure, and mortality (2, 4). It has been observed that several factors have been involved that play an important role in increasing the incidence and complications of COVID-19 infection in cancer patients. Figure 1 has demonstrated some risk factors. The immune system of cancer patients is usually suppressed due to cancer progression or treatment regimens that are applied to control the growth of cancerous cells. Such immuno-compromised condition of patients increasingly elevates the risk of acquiring COVID-19 infection and its severity as compared to normal persons. Coronavirus infection could also increase the risk of other complications due to suppressed immune response and thus can cause prolonged treatment and hospital stays resulting in a poor prognosis of the disease. According to Liang et al. cancer patients have a greater potential for serious complications, with a 3.5-fold spike in the risk of incurring mechanical ventilation, ICU admission, or death relative to patients who do not suffer from cancer (2). Patients who had already received chemotherapy or undergone surgery within the one month prior to infection with COVID-19 had a greater susceptibility to developing serious complications.
Figure 1. Factors that increase the risk of COVID-19 in cancer patient

Most cancer patients are old, mostly smokers, while some have cancer-related medical issues as compared to normal individuals, all of these parameters are considered as risk factors for serious COVID-19 infection (5). In addition to these factors, cancer treatment regimens often require a longer exposure in medical centers as well, which presents a risk of viral transmission regardless of the treatment (6). Anti-neoplastic treatments are significantly important for patients but at the same time, these formulations are a matter of concern for professional oncologists as well because they are also associated with a number of side effects that may be dangerous for COVID-19 infected individuals. Such as cancer-related myelosuppression. Apart from these, anti-tumor therapies also increase the possibility of pulmonary viral infection (7). Because some antitumor substances may be toxic for the respiratory tract, that might be deleterious if a patient is already infected with the coronavirus. Certain monoclonal antibodies such as anti-CD38 antibodies like daratumumab and isatuximab cause deficiency of NK-cells, which ultimately increase the risk of viral infection in the respiratory tract (8). It has been indicated that in severe conditions of COVID-19 infection the proinflammatory T-cells become hyperactive (9). As a
result of this, some health experts believed that inhibitors that are being applied to target immune checkpoints could result in more serious symptoms of coronavirus infection and thus doctors feel the reluctance to use such inhibitors for the treatment of cancer patients infected with COVID-19 (10). Additionally, corticosteroids have been mostly used by a large number of cancer patients during prophylactic treatment, which could cause acute respiratory failure (11).

The above-mentioned information is not enough related to the serious impact of Covid-19 on cancer patients as compared to normal individuals. The prevalence and severity of COVID-19 infection may be dependent on the type of cancer that’s why more comprehensive research is required in order to adopt better treatment regimes in the case of cancer patients suffering from Covid-19 infection.

**COVID-19 AND CHRONIC MYELOID LEUKEMIA**

Cancer, as well as its therapeutic approaches, sometimes may impose a negative impact on the immune system, which is a matter of concern during this pandemic. A study conducted in the United Kingdom (UK) on cancer patients having COVID-19 infection, revealed that all types of cancers do not impose the same types of risk factors during COVID-19 infection (12). Patients who suffered from different types of leukemia such as multiple myelomas, and lymphomas, may be more prone to severe COVID-19 infections, especially these patients who are at higher risk of death from the viral infection according to the analysis held by the Coronavirus Cancer Monitoring Project (UKCCMP) of the UK (12, 13). The UKCCMP was founded in March after global exposure to COVID-19. The organization has performed a comparative analysis on 1,044 cancer patients who had SARS-CoV-2 infection with 145,000 cancer sufferers who were not subjected to COVID-19 infection. After analyzing different variables like age, gender, and type of cancer in patients, investigators discovered that infection of COVID-19 was 57% higher in
patients with leukemia than in other types of cancers. Moreover, the mortality rate due to COVID-19 is higher in leukemia patients who had recently received chemotherapy. As well as individuals who are over the age of 80 are more prone to serious risks of contracting the infection. The rate of COVID-19 infections and deaths is less common in patients with prostate, lung, breast, and female reproductive system cancers (12).

A study reported that out of 125 hospitalized patients, COVID-19 was found in 10% of individuals suffering from hematological cancers, and none of the patients reported chronic myeloid leukemia (CML) (14). Chronic myeloid or myelogenous leukemia is a myeloproliferative type of cancer in which the matured immune cells, primarily granulocytes production become uncontrolled. It is basically caused by an abnormal chromosomal translocation between the t-arm of chromosome no. 9 (9; 22), which is known as the Philadelphia chromosome. This altered chromosome has the BCR-ABL1 fused gene that translates into BCR-ABL1 fusion protein causing dysregulated action of tyrosine kinase (15). There are three phases of CML including the chronic phase, accelerated phase, and blast phase. For CML treatment tyrosine kinase inhibitors (TKIs) that are primarily used by physicians include dasatinib, nilotinib, and bosutinib, etc (16). Literature has revealed contradictory information regarding the effect of TKIs treatment on CML management. According to studies conducted by (17, 18, 19) dasatinib causes immunosuppression and recurrent respiratory infection increased, leading to prolonged medical care duration. However, another study (20) did not found any engrossing pieces of evidence that dasatinib increases the risk of respiratory infection (COVID-19) during chronic phase CML.

The first case of SARS-CoV-2 infection in a CML patient was reported by Abruzzese et al. when a young female CML patient who was on dasatinib (in deep molecular response) showed
symptoms of SARS-CoV-2 like fever. She was hospitalized and treated with medicines including amoxicillin, clavulin, and Panadol for seven days. During her stay in the hospital, this patient was on dasatinib treatment as well till her discharge (21). In other cross-sectional research work, Sorà et al. identified a 55-years-old man with CML (in MMR) along with COVID-19 infection. Researchers found that the old man had serious hemolysis and haemophagocytic, lymphohistiocytosis even he was continuously receiving the dose of imatinib (400 mg). After that antiviral intervention, steroids and intravenous immunoglobulins were given to the patient, and following the administration of intravenous immunoglobulins, hemolysis stopped, ferritin level’s dropped significantly and patient was recovered in the end after complete eviction of viral infection (22). Additionally, another report described that a 58-year-old female CML patient with extreme obesity, high blood pressure, gout and renal failure was hospitalized with fever and breathing difficulties, which was subsequently exacerbated by a circulated erythematous and papular eczema; biopsy was aligned with bullous interface dermatitis (23).

Research has been conducted to evaluate the prevalence and clinical manifestation of COVID-19 infection in CML patients. In this regard, Li et al. conducted a cross-sectional study on non-hospitalized individuals with CML undergoing TKI treatment in Hubei Province (24). According to this survey, the prevalence of COVID-19 in CML patients was about 0.9%, which was remarkably higher than non-cancer patients but less than hospitalized patients who suffer from other types of hematological cancers. It means that the prevalence of COVID-19 in CML is nine times higher than that of the published 0.1% prevalence in the normal population (non-CML population) by April 10, 2020. The pathological characteristics of patients with confirmed COVID-19 infections were the same as in non-cancer COVID-19 infected individuals. Although one participant expired during their survey study, their representative sample was insignificant to
equate to the reported case-mortality rate of around 4% (24, 25, 26). It has been evaluated during the diagnosis of patients in the chronic phase of CML that they were at higher risk of infection even after receiving the complete cytogenetic response (CCyR) and major molecular response (MMR). The results of their cross-sectional study showed that out of 21 patients who received third-generation TKIs, only 1 patient developed COVID-19 infection, and then these results were compared with those 346 individuals who were given imatinib and out of them three patients developed COVID-19 infection while none of 162 patients who received second-generation TKIs developed COVID-19 infection (24). In addition, one of the two flumatinib-treated individuals acquired COVID-19 (27) conducted a cross-sectional survey study in 29 centers of CML patients in China. This data indicates that CML patients who respond well to CML treatment have a low infection risk as compared to those who have poor responses towards CML treatment. Ector et al. conducted a questionnaire-based survey termed as “Dutch observational cohort survey”, in order to evaluate the seriousness of disease in CML patients and susceptibility of SARS-CoV-2 as compared to their spouses or housemates that were taken as control. On 6th April 2020, volunteers and their housemates were invited for this survey through a web-based portal system on Duct CML Patients. This study involved 123 housemates as the control group or general population representation and 148 CML patients, receiving regular TKI intervention as well as those who were experiencing discontinuous TKIs treatment and all of participants gave their consent to become part of this study. After two weeks of follow-ups and close check on symptoms, preventive measures, TKI intake and hospital admissions, the researcher concluded that about half of volunteers having CML exhibited multiple medical issues or comorbidities. Thus, at the end of the survey researchers concluded that COVID-19 was found in 0.7 percent of CML patients, particularly due to suppressed immune system (28).
al. reported in his research that a campus CML was created in Italy where a network of physicians shared their relevant experiences, treatment regimes, diagnostic approaches, disease prognosis as well as improved measures to inhibit the toxic effects of pharmaceutical formulations taken during the management of disease and to different CML patient conditions. Therefore, they conducted survey in different regions of Italy including Veneto, Lombardia, Emilia-Romagna and Piemonte. For this purpose, the researcher sent a questionnaire to 51 medical centers treating CML patients in these regions. From this survey, a data was collected from large number (6883) of patients and till middle of April from this large data only 12 patients (0.17%) found to be COVID-19 positive. So, they concluded their research by reporting that the onset of coronavirus infection in TKI treated CML patients is significantly low. Hence TKI plays an important role in prevention of COVID-19 infection (29). In another retrospective study carried out by Baçi et al. in Turkey studied the effect of TKIs on the COVID-19 (30). As from the previous literature, it had found to play an active antipodean role for different types of Coronaviruses (CoVs). The anti-viral action of dasatinib and imatinib mesylate and nilotinib was investigated against Middle East Respiratory Syndrome coronavirus (MERS-CoV) and SARS-CoV respectively (31). The TKIs prevent the incidence of infection by interacting with S-protein that are present on the outer surface of Coronavirus because these proteins basically form linkages with the angiotensin-converting enzyme (ACE)-2 which are mostly present in the gastrointestinal tract, lungs, heart, kidney as well as in lower respiratory tract of host cells. The binding of S protein with ACE-2 receptor of host cell results its proteolysis and then virus entered into the body of host cell and spread infection. In this research work, they reported that 16 CML patients who were on TKI therapy developed COVID-19 infection (5). The authors compared the COVID-19 prevalence and fatality rate of CML, and non-CML COVID-19
affected persons on the basis of age, gender, and associated diseases. They found a 3:1 ratio in CML-COVID-19 patients and non-CML-COVID-19 patients, respectively from March 2020 to May 2020. This study revealed that a lower fatality rate was observed in CML patients having TKIs treatment i.e., 6.3% because imatinib, dasatinib, sorafenib, nilotinib and nintedanib are major anti-inflammatory agents and they possess strong potential to treat different types of pulmonary disorders. Furthermore, comparative analysis was done by taking different age groups, males and females’ gender and comorbidities-matched control group. They found that the outcomes of COVID-19 infection in CML patients undergoing TKI therapy are minor and patients do not need intensive care and mechanical ventilation assistance along with reduced hospitalizations. Also, immune suppression was not detected by TKIs in chronic phase CML (30).

Thus, all of these comparative research findings suggest that the prevalence of COVID-19 infection in CML depends on the treatment already carried out to manage CML and different other risk factor including gender, age and associated comorbidities. Further investigation should be carried out to evaluate why different treatments have different effects on the risk of COVID-19 in CML patients.

**EFFECT OF COVID-19 ON CML INTERVENTIONS**

The continuous use of BCR-ABL1 TKIs is implied as CML therapy. Due to their underlying malignancy or TKI treatment, CML patients seem to be at lower risk of developing COVID-19 infection as mentioned earlier. Thus, there is no need to stop TKIs therapy in severe cases of CML patients. The adverse effects of every TKIs must be contemplated in the light of COVID-19-related risks in the case of newly diagnosed patients. Due to adverse side effects, the complications can be respiratory failure, thrombosis, indigestion, cardiovascular failure including
congestive heart failure and heart attack that may happen in around one-third of patients (32, 33). Side effects of TKIs can exacerbate the complications. COVID-19 can also interfere with the TKIs treatment. Such as COVID-19 positive patients may have a lower respiratory reserve if they are taking dasatinib. Also, they may experience severe cardiac issues or thrombus formation, if they are taking nilotinib or ponatinib, and they can encounter diarrhea if receiving bosutinib therapy (34).

**POSSIBLE MANAGEMENT OF COVID-19 IN CML PATIENTS**

Although there is no 100% effective vaccine developed till date which can inhibit the spread of the COVID-19 virus and effectively minimize the severity of disease, several drugs are thought to be effective against COVI-19 infection. Interestingly, several anti-cancers drugs have shown antiviral potential. Imatinib is a TKI that had been used previously as a potent CML therapeutic drug because it is a key factor that acts as a potent immunoregulatory agent in coronavirus-positive patients through several pathways. In chronic myeloid leukemia, it blocks the BCR-ABL protein to exert its action in the oncogenesis of CML. Imatinib blocks the constitutive action of tyrosine kinase that ultimately modifies the role of several genes involved in cell cycle regulation, cell adhesion, the structure of cytoskeleton as well as eventually causes apoptosis in Ph(+) cells (35,36).

The concept of the potential efficacy of imatinib as an anti-COVID-19 therapeutic agent emerged from existing literature in which imatinib was used against SARS-CoV-1. According to the research work of Sisk et al, Abelson (AbI) kinase inhibitors for example imatinib played an important role in reducing the total count of infected cells by minimizing the COVID-19 titer rate and blocking the entry of SARS-CoV-2 in the host cell because it actually inhibits the binding of viral S protein to form syncytia. The researchers speculated that since Ab11 kinase
regulates reorganization of cytoskeleton, imatinib, which inhibits Abl1, might interfere with the remodeling of actin that is necessary for viral entry and then fusion with host receptor cell (37, 38). Two recent surveys conducted in Italy may be the real proof that these *in vitro* findings are also valid *in vivo*. One study involved Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) affected patients while the second study involved CML patients. Results of the study indicated that out of 267 selected Ph+ ALL patients, only 1 patient was found to be infected with COVID-19 with the onset of pneumonitis and cellulitis. Of those patients, 128 participants belonged from most COVID-19 infected in 4 regions of Italy (39). According to another pilot-scale study, just 12 out of 6,883 CML patients reported at 51 hospitals in Italy tested positive for COVID-19 (Bersanelli, 2020). TKIs have already proven to be immensely effective for the management of coronavirus such as MERS-CoV (40). This potential efficacy of tyrosine kinase inhibitors can be used implied to fight against the current SARS-CoV-2 pandemic.

A Dutch research team recently used imatinib for COVID-19 pneumonitis treatment. Previous experimental findings in SARS CoV and MERS-CoV models, where imatinib prevented virus entry by blocking the attachment to human host cells (38), were used to support the idea of imatinib potential against COVID-19. As mentioned earlier, in survey studies of Ph+ ALL and CML patients, only a few SARS-CoV-2 positive cases have been identified (39). Two types of research studies were performed by Galimberti et al. 41) in order to figure out why the rate of COVID-19 infection in Ph+ ALL and CML patients having TKIs treatment is lower from healthy persons. Coronavirus is also associated with the incidence of two other severe disorders including frenzied immune response and uncontrolled production of cytokines which are ultimately linked with organ transplant failure. Macrophage activation syndrome (MAS) and acute graft versus host disease are the most prominent disorders related to
organ damage. Therefore, in this study scientists investigated the effect of certain drugs in order to control these disorders associated with COVID-19. Researchers suggested the beneficial role of TKIs and Ruxolitinib a JAK1/2 inhibitor with effective and brisk anti-inflammatory and anti-cytokines effect respectively in this regard (41). To begin with, they used the torqueteno virus (TTV), a DNA virus belonging to the Anelloviridae family, which was found in almost 60% of asymptomatic normal persons. In the context of COVID-19 positive patients, if the rate of infection and replication of SARS-CoV-2 would sustain by TKIs, then it could be expected that TTV load might be increased during nilotinib therapy. Later, they observed the immune responses of the 5 CML patients who were receiving the imatinib therapy, to see whether and how this TKI activated the expression of genes linked to immunity. If their potency can be used in case of COVID-19, it could be a great step to inhibit its progression. Through the TTV model, researchers (41) investigated whether nilotinib TKI promotes or inhibits replication of the virus. After analysis scientists reported that in 50% of patients, no replication of TTV occurred at any stage. Moreover, the replication rate of the virus was low in those patients that possess higher TTV load. Evidently, according to the results of this study, in COVID-19 positive patients, the mean value of TTV load was 2.8 log copies/ml, which was less than that of immunocompromised individuals with a mean TTV load of 4.1 log copies/ml (41, 42, 43, 44). All of these results were consistent with healthy individuals with a mean TTV load of 2.3 log copies/ml (45). Therefore, the above findings are strong evidence that nilotinib is not involved in the replication of the virus. Furthermore, only 20% patients in this study had a detectable TTV load threshold. These findings reflected a significantly low fatality rate in patients with Ph+ ALL and CML as well as infected with the novel coronavirus. However, the processes by which TTV enters into host cells are still unclear and require further research, because scientists suggested
that it might be possible that fewer number of TTV receptors present on CML cells.\textsuperscript{41}\ But this could not be true in the case of coronavirus because it has been a widely accepted phenomenon that expression of CD26 is high in CML leukemic cells, which is one of the SARS-CoV-2 receptors. Thus, there should be a role of certain antiviral genes that are overexpressed due to nilotinib therapy. The findings of the 2nd part of Galimberti et al. research added that TKIs might impair the normal immunological control of the individual. Also, this research work had indicated the enhanced expression of certain “pro-immune” genes including $CCL5$, $CD28$, and $IFN_\gamma$, as well as “anti-immune” genes like $ARG-1$ and $FUT4$, showed down-regulated expression throughout the experiment. They also supported that TKIs did not impede immune control during COVID-19 infection (41, 46-49). However, large clinical trials are required before conclusively proving a possible effective role of TKIs in the coronavirus pandemic.

All of the above studies have suggested that anticancer drugs could be repurposed as anti-viral drugs due to their beneficial anti-inflammatory, anti-cytokine, and proteolytic effect. However, still more research work is required to validate the potency and efficacy of such drugs and interventions in patients suffering from CML as well as COVID-19.

**FUTURE DIRECTION**

Researchers tried to find out whether CML patients are as vulnerable to COVID-19 infection as other cancer patients as well as properly examined the prognosis of the disease. Hematologists are now facing new challenges regarding standardized and critical care systems for a wide number of CML patients. Complete understanding of dynamics of SARS-CoV-2 infections in CML and then management of disease and its proper treatment strategies are thus critical with the progression of the disease. Moreover, till now no current data describes the effect of COVID-19 on the molecular mechanism of CML and reason for the severity of infection is different in
patients receiving different types of anticancer therapies. Scientists have observed that patients who received TKIs to manage CML, have a low rate of COVID-19 infection. Due to the following reasons, the rate of COVID-19 infection in CML patients having TKIs therapy is low.

(i) The recovery of the immune system can be started from the positive response of TKI therapy. Effectors T-cells are depleted selectively in CML patients. While on the other hand, tyrosine kinase inhibitors ultimately increase the number of natural killer (NK) cells, NK-LGL, and T-LGL cells and all of these immune cells significantly regulate the immune response. (ii) Secondly, previous reports have demonstrated that imatinib and other TKI drugs exhibit potential antiviral action in vitro against MERS and SARS coronavirus. It will be interesting to observe the activity of TKIs against SARS-CoV-2. In conclusion, according to the findings of research studies and case reports it is concluded that incidence of COVID-19 infection is significantly low in patients having CML as compared to other hematological cancers. In addition, TKIs such as dasatinib, nilotinib, etc. are potential candidate pharmaceutical formulations that profoundly inhibit the viral entry inside the host cell by restricting the binding of viral spike protein with the receptors of host cells. Researchers are aiming to evaluate the potential role of TKIs as an antiviral agent against COVID-19. Still, more research work is required in order to cope with other comorbidities so that new curative strategies could plan to get better results.

CONCLUSION

COVID-19 is a respiratory infection caused by a virus and usually shows flu symptoms in the mild stage. However, those individuals who have other comorbidities such as metabolic diseases, hypertension, diabetes mellitus, pulmonary diseases, and cardiovascular problems may experience severe conditions like acute respiratory failure. Furthermore, it is difficult to identify patients that are at risk of infection, and data on the risk in patients with hematological
malignancies is insufficient that is why further research is required during the ongoing SARS-CoV-2 outbreak.

Authors’ contributions

HSB identified the research area, prepared the project, and performed all the research analytically. SA interpreted the findings and assisted in the project's design and set up a research facility and assisted with the writing. MFS assisted in writing the article and final proofreading and approval. All the authors have contributed equally and approved the final manuscript.

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REFERENCES


