



A Review on Hematologic Malignant Patients Infected with 2019 Novel Coronavirus

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Abstract

Since late 2019, when novel coronavirus pneumonia emerged in China and spread worldwide, there has been a need for data concerning the clinical characteristics of infected immunocompromised patients. It has been reported that a significant mortality rate occurs in individuals with underlying comorbidities such as hematologic malignancies. Therefore, it is vital to illustrate the clinical manifestations and outcomes of COVID-19 in these vulnerable patients and identify safe therapeutic strategies. This study reviewed the clinical course, laboratory findings, and risk factors associated with hematologic malignant patients with COVID-19 along with the management and therapeutic regimens.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2, Hematological Malignant Patients

1. Context

The novel coronavirus disease 2019 (COVID-19) has emerged as a global threat and healthcare issue. It is a respiratory tract infection developed by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to high mortality and morbidity worldwide (1-4). The disease spread rapidly worldwide, thereby rapidly evolving into a pandemic (5). Since its outbreak in China and as of June 16, 2020, the pandemic has affected approximately eight million people and has caused 434,796 deaths worldwide (6). Respiratory droplets and direct interaction with infected people or indirect interaction with fomites in their settings entail the human-to-human transmission of the virus (7). The reproduction number of this novel virus has been assessed between 1.4 and 3.9. This means that each infection produces one to four novel infections when nobody in the community is immune, and no preventive measures are taken (7). COVID-19 is defined by flu-like symptoms with mild to severe respiratory symptoms. Advanced age and comorbidities, such as diabetes, heart, lung, and kidney disease, and cancer, are correlated with a higher mortality rate and ICU admission (4, 7).

COVID-19 has become a new challenge for physicians, particularly those who treat immunocompromised patients (8). It has been reported that cancer patients, especially those with hematological malignancies, are at a higher risk of infection with SARS-CoV-2 than is the general population (2, 9, 10). Early reports suggest an increased mortality rate in patients with hematological malignancies (11). Cancer patients are commonly immunosuppressed by their disease and treatment. In addition, they are more likely to develop severe events (ICU admission, invasive ventilation, or death) than individuals without cancer (4, 5). Furthermore, many hematologic malignant patients will have additional risk factors for severe disease manifestations, such as advanced age and comorbidities (5). Cancer patients have a shorter average time to severe events (12).

This article reviewed the clinical manifestations, laboratory findings, risk factors, and therapeutic methods related to patients with hematologic malignancy and COVID-19 (4).

2. Risk Factors

Evidence from several studies implies that malignant patients run an increased risk of infection by SARS-CoV-2. Also, they are more bound to exhibit higher mortality than are other patients (13). Advanced age and medical comorbidities are two reported risk factors associated with severe COVID-19 in adults (14). In a Chinese report of patients with COVID-19, chemotherapy or cancer surgery was a risk factor for severe complications (15). It has also been documented that severe complications of COVID-19 have a higher rate among patients with cancer (15). Among adult hematology patients, there exist certain risk factors for seasonal coronavirus infections (not SARS-CoV-2), including 50 years of age or higher, using corticosteroids, Graft Versus Host Disease (GVHD), neutropenia, lymphopenia, and hypogammaglobulinemia (5, 16-18).

3. Pathogenesis

Infected patients are currently the main source of COVID-19 transmission. Noteworthy, asymptomatic infections can also result in infection (19). SARS-CoV-2 is spread through respiratory droplets when patients talk loudly, cough, or sneeze. Another source of transmission is the contact of the contaminated hand with the nose, mouth, or eye conjunctiva (20).

To enter the cells, SARS-CoV-2 employs angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptors. These receptors are largely produced in the monocytes, monocyte-derived macrophages, and cardiopulmonary systems (21). Macrophages and monocytes are commonly associated with cells that express ACE2 in different tissues. Furthermore, the cells of the bone marrow niche express ACE2, where it interacts with the granulocyte-colony stimulating factor receptor to down-regulate the recruitment of hematopoietic progenitor cells (3).

Hematologic malignancies and related treatments could lead to humoral and cellular immune deficiency. The nature of the disease or the adverse effects of treatments and the subsequent discharge of CD4+ T cells reduce cytokine production in lung tissues. Accordingly, interstitial pneumonitis and delayed viral clearance may occur (22). Damaged B-cell responses to SARS-CoV-2 and hypogammaglobulinemia possibly cause more secondary infections following malignancies, such as multiple myeloma (23).

3.1. Cytokine Storm

Cytokine release syndrome (CRS), induced by some drugs and infections, is a general inflammatory process

that has significantly increased the level of many pro-inflammatory cytokines (24-26). Based on the recent clinical data, mild or severe CRS has been reported in patients with severe conditions, playing a major role in the death of COVID-19 patients (27). SARS-CoV-2 binds to the epithelium and stimulates the innate and adaptive immune systems, resulting in the generation of many cytokines, including IL-6. These cytokines increase vascular permeability. Therefore, by releasing a great amount of fluid and many blood cells, they ensue dyspnea and even respiratory failure (28, 29). IL-6 has a determinative role in acute inflammation (30), indicating the importance of its management to control patients with severe conditions. Tocilizumab is an antagonist of the IL-6 receptor that can prevent the IL-6 signal transduction pathway (27).

4. Clinical Manifestation of COVID-19 in Hematologic Malignant Patients

Since the outbreak of novel coronavirus in China, many studies have attempted to define the clinical findings and symptoms of infection by this virus. COVID-19 shares some symptoms with the early stages of common cold, including fever, dry cough, fatigue, and myalgia, initiating 3 - 6 days after exposure (31). Chinese studies have reported fever and cough as the most prevalent symptoms. Other symptoms presented in some cases are myalgia, headache, and mental disorders (19, 32). In some patients, gastrointestinal disorders like diarrhea were reported (33). A study in New York City on 393 patients revealed that the most common symptoms were cough, fever, dyspnea, myalgia, diarrhea, nausea, and vomiting; the reported clinical manifestations were mainly alike those in China, although gastrointestinal manifestations presented in more cases (34).

Some studies have focused on the main characteristics of COVID-19 patients with comorbidities. A study on 13 malignant hematological patients who developed COVID-19 reported that this group of patients was more likely to manifest severe conditions, such as ARDS, proposing that cancer patients had a statistically worse prognosis (35). Some other studies reported that hospitalized patients with hematological neoplasms had the same infection rate, but they had an increased mortality rate. Additionally, they were more likely to exhibit severe manifestations of infection. It has been reported that in these patients, the most frequent symptoms were fever, dry cough, and dyspnea (23, 36).

O'Kelly et al. (37) reported a 22-year-old woman with Hodgkin lymphoma who had been infected with SARS-CoV-2. She had a cough, sore throat, pyrexia, chills, and rig-

ors for three days. Jin et al. (38) presented a 39-year-old male with confirmed COVID-19. He had non-Hodgkin lymphoma and chronic lymphocytic leukemia. He presented in a clinic on February 16, 2020, with fever, sore throat, productive cough, and dyspnea. In a study by Dhakal et al. (23), the clinical findings of seven multiple myeloma patients with COVID-19 were reported, among which the most common symptoms were fever, dry cough, and progressive dyspnea. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) were further detected in one of the patients.

5. Diagnosis

Diagnostic procedures for COVID-19 patients include physical examination, laboratory tests, and imaging scans. One of the most common diagnostic laboratory procedures for SARS-CoV-2 is the PCR assay performed on nasopharyngeal swab specimens (34, 39). A common physical examination result is basal crackles on the auscultation of both lungs.

5.1. Imaging Findings

The main imaging findings in patients with COVID-19 pneumonia included infiltrates in the lower areas, bilaterally, on chest X-rays (37, 40). The most characteristic features in CT scans of these patients were white patches called “ground-glass opacity”, locating fluids in the lungs with reticular or interlobular septal thickening (41), and bilateral consolidation (a multilobar and subsegmental form) (33, 42).

The important CT findings of patients with underlying hematologic cancers were described as interstitial or alveolar infiltrations, presenting with reticulations or ground-glass opacities. Non-infectious disorders like hemorrhage and adult ARDS might be characterized by similar features in leukemic patients (43). In addition, the lesions in the CT scan of AML patients may be atypical or subtle; in this regard, just minimal small ground-glass lesions were sometimes detected in these patients, incompatible with symptoms. Therefore, even with atypical radiologic findings, COVID-19 should not be overlooked as a differential diagnosis in patients with hematologic malignancies.

According to some reports, cancer patients with COVID-19 had more severe CT scan findings than had other patients, while chest X-ray findings were not different (4, 15). Li et al. (44) reported that among 1,449 subjects with confirmed SARS-CoV-2 infection, CT scans showed bilateral pneumonia in 1,215 (87%), ground-glass opacities in 1,041, patchy shadows in 579 (42%), and consolidation in 242 (18%). In a study conducted by Jin et al., the lung CT scan

of a chronic lymphocytic leukemia (CLL) patient revealed two-sided ground-glass opacities and a low amount of fluid in the pleural space; they suspected COVID-19, which was confirmed by positive real-time RT-PCR test (38).

5.2. Laboratory Findings

Among the laboratory tests of COVID-19 patients, the most common tests are WBC and platelet count, Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST), creatine kinase, Lactate Dehydrogenase (LDH), procalcitonin, and C-reactive protein (CRP) (32, 34). He et al. (36) reported differences in laboratory items between patients with both COVID-19 and hematological cancer and those who had only COVID-19. They reported that with the initiation of the COVID-19 pandemic, patients with hematological malignancy and COVID-19 had significantly more levels of CRP and procalcitonin. The hemoglobin level, lymphocyte, and platelet counts were lower than in the other group. However, there was no difference between cancer patients and others regarding the levels of LDH, AST, ALT, bilirubin, creatinine, and blood urea nitrogen. Some or all of these changes might be attributed to hematological cancer treatment rather than COVID-19. Therefore, the effect of SARS-CoV-2 on blood tests may be complicated with other factors in hematological malignancy patients (39).

As COVID-19 progresses, patients with cancer show reduced levels of hemoglobin, lymphocyte, lymphocyte subset, and platelet and elevated levels of D-dimer, AST, LDH, CRP, procalcitonin, and ferritin in comparison with other groups. However, it should be noted that no difference was observed regarding the concentrations of cytokines (interleukine-2, interleukine-6, interleukine-10, interferon- γ , and tumor necrosis factor- α) (36). In a study by Jin et al. (38), the reduced levels of immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) were reported in the plasma (3.18 g/L for IgG, 0.45 g/L for IgM, and < 0.17 g/L for IgA), and the plasma concentrations of brain natriuretic peptide (BNP), glomerular filtration rate (GFR), and hepatic enzymes, as well as echocardiography tests, were not significant.

6. Treatment

Until now, there has been no certain vaccine or pharmacological treatment for COVID-19, supported by randomized clinical trials (45). Lopinavir and ritonavir are used to manage the Human Immunodeficiency Virus (HIV). It is reported that these protease inhibitors could reduce death, intubation, and use of methylprednisolone when announced as a treatment for the early stages of SARS

(46). Ribavirin is a broad-spectrum antiviral widely used in SARS. Early SARS cases cured by both corticosteroids and ribavirin showed improvements (47). Ribavirin has certain adverse effects, including anemia and increased ALT (48). Combination therapy with lopinavir/ritonavir and ribavirin exhibited greater suppression of the viral load and decreased use of steroids (49). Also, among agents considered for the current outbreak are interferons, which were could stop the viral duplication of SARS in vitro (50). Recently, the findings of several early-stage interferon therapy studies have been promising (51, 52). One study found that the addition of interferon beta-1b to lopinavir-ritonavir and ribavirin could decrease the duration of viral shedding and hospital stay of mild to moderate COVID-19 patients (51). These regimens were suggested by the Chinese guidelines to manage COVID-19 pneumonia (31). Corticosteroids were used in SARS to prevent cytokine storm (an acute severe systemic inflammatory reaction) (53). They were further applied to H1N1 viral pneumonia (54) and severe community-acquired pneumonia (55). Corticosteroids are being widely administered for the current outbreak (33). They have some adverse effects, such as late viral clearance, vascular necrosis, diabetes mellitus, osteoporosis, and psychosis (56). Remdesivir is yet another antiviral showing to be effective against COVID-19 (57). Convalescent plasma or immunoglobulin was further utilized in the treatment of Ebola and SARS with a probable therapeutic effect, but the related evidence was inadequate (31, 58). One of the most important cytokines during cytokine storm is IL-6 (10). Zhou et al. speculated that a monoclonal antibody targeting the IL-6 receptor might be effective in treating novel coronavirus pneumonia (59). Tocilizumab is one of the antagonists of the IL-6 receptor that has been speculated to be effective against COVID-19 (10).

In a retrospective study, COVID-19 patients with hematological malignancies used the weight-based dosing of tocilizumab. Only were patients with ARDS development and increased levels of IL-6 considered for treatment with tocilizumab. They reported that the level of IL-6 increased after treatment with tocilizumab, resulting in the release of a fraction of IL-6 attached to its specific receptor (35). In another study, a 22-year-old patient with a history of Hodgkin lymphoma presented with cough, pyrexia, sore throat, chills, and rigors. On admission, broad-spectrum antibacterial agents, such as piperacillin-tazobactam and doxycycline, were prescribed against community-acquired pneumonia in a SARS-CoV-2 swab test. When COVID-19 was confirmed, lopinavir, ritonavir, hydroxychloroquine, azithromycin, and corticosteroids were used to treat the patient (37). Zhang et al. (10) reported a 60-year-old man with a history of symp-

tomatic multiple myeloma infected with SARS-CoV-2 who received intravenous moxifloxacin and tocilizumab. The patient's clinical condition improved following the use of tocilizumab, indicating that tocilizumab is effective against the novel coronavirus infection. Furthermore, in Wuhan, China, He et al. (36) analyzed the data of 13 hospitalized patients with hematological cancer who had developed COVID-19. To treat these patients, they used umifenovir, interferon, antibiotics, and corticosteroids. In another study conducted in China, a 39-year-old patient with non-Hodgkin lymphoma and chronic lymphocytic leukemia was treated with nebulized α -interferon, intravenous human immunoglobulin, and intravenous methylprednisolone (38).

7. Prevention and Control

The confirmed cases of COVID-19 are increasing globally, and people are changing their habits due to the measures applied to slow the transmission of SARS-CoV-2 (60). With the WHO declaration of the COVID-19 outbreak as a pandemic, health providers have focused on the impact of this fast-spreading viral infection on malignant patients. Individuals with cancer have also made important changes in their lives. Most hematology malignant individuals either undergo anticancer therapy with bone marrow suppression or have disorders of the immune system. Therefore, they run a higher risk of infection with this virus (2, 13, 36).

Patients with hematologic malignancies must be protected against COVID-19, stay at home, and be given a chance to work from home whenever possible (61). Education on handwashing, the symptoms of COVID-19, infection control measures, high-risk contact, and reporting new related symptoms to doctors should be reinforced (13). Consultation appointments with physicians should be reduced in order to avoid healthcare contact. Patients should have updated their vaccination, notably against *Streptococcus pneumoniae*. Secondary bacterial infections may complicate viral infections, a condition recognized in influenza, and possibly COVID-19 (61).

The special condition of hematologic malignant patients highlights the risk of infection in health centers during a pandemic. An oncologist in a clinical center in Canada was infected with SARS-CoV-2 after examining 14 patients in a clinic (13). The suggested actions to decrease the risk of transmission include a call to the patient before a scheduled appointment to detect the symptoms of COVID-19 and ask for recent travels and contact history (62, 63). Entry and exit points should be reduced (64). Triage staff must equip patients with masks and record

their symptoms and body temperature. Patients with a suspected history of contact and symptoms, such as cough, fever, and dyspnea, should be directed to special clinics and examined based on the diagnostic criteria.

To avoid cancer treatment delays, the units of chemotherapy infusion should act through the usual capacity (65). Only must patients with severe conditions requiring immediate intervention and those whose chemotherapy may not be delayed enter the hematology and oncology wards (2). If possible, some patients on active outpatient anticancer therapy can switch intravenous chemotherapy to suitable alternative oral anticancer therapy on a case-by-case basis (65, 66). In outpatient settings, the follow-up sessions for treatment with oral anticancer drugs may be reduced to the lowest number (13). Unlike medical or surgical treatments, interruption in radiotherapy is clinically unacceptable. Radiotherapy patients should daily attend the hematology and oncology wards. Patients with a history of high-risk contact should be treated in a separate room (67).

After admission, inpatients should not leave the ward during hospitalization. Furthermore, their body temperature must be monitored daily. Each malignant patient has to be taken care of by the same nurse. All individuals with recent respiratory infections must be isolated as soon as possible, and the COVID-19 screening process should be conducted once again (2). Regarding the confirmed COVID-19 cases, grouped zones with the minimization of health providers overlap with other patients can be a good approach to reduce human-to-human transmission (13).

8. Recommendations and Management

At present, there is no effective antiviral treatment against SARS-CoV-2. Interim guidance for the management of SARS-CoV-2 infection in malignant individuals is available elsewhere. Weinkove et al. (5) proposed no difference between patients with and without cancer as far as the management of COVID-19 is concerned. Malignant cases with suspected or confirmed SARS-CoV-2 infection should be examined by an infectious disease specialist. Among these patients, the differential diagnosis based on respiratory symptoms and fever is highly common. Clinicians should also be aware of secondary infections. Early detection and treatment of bacterial infection remain important, particularly in neutropenic patients. Pneumonitis may result in certain cytotoxic chemotherapies, immune checkpoint blockade, or radiotherapy. In these cases, pneumonitis shows some of the clinical and radiological features of COVID-19. To reduce the risk of drug interaction or

avoid treatment-related immunosuppression, the temporary discontinuation of cancer therapies will be warranted for patients with malignancy who develop the symptoms of COVID-19. This should be considered after consultation with a hematologist familiar with the management of malignancy (5).

9. Impact of the Pandemic on Cancer Research

Due to their global reach and worldwide concern, the pandemics attract the most attention during a specific period. With the initiation of the COVID-19 pandemic, the number of new cancer clinical trials was reduced (13), and some of the former trials stopped surveying new patients. The governments used these strategies to devote more finance to managing this global issue (68).

The American Cancer Society reported that more than half of their grantees their research and trials at the time (May 2020) stopped until the recovery of conditions (69). In response to this situation, some international committees made decisions to facilitate the investigation of cancer/COVID research. The National Cancer Institute (NCI) took measures to establish the NCI COVID-19 in Cancer Patients Study (NCCAPS) to facilitate the procedures of cancer/COVID-19 research. There are some challenges concerning data collection in both COVID-19 and cancer patients, including the lack of a proper control group, a high proportion of patients in remission, and problems associated with proper volunteer subjects (4, 70).

Some studies have focused on clinical features, outcomes, and concerns related to patients suffering from both COVID-19 and cancer (4). According to these studies, patients with COVID-19 and cancer are more vulnerable to dangerous pulmonary manifestations typically shown in the severe types of COVID-19. This fact has affected the trials directed at investigating the management of the pathological procedures in this high-risk population.

Footnotes

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