

## **Management of hematologic disease under the COVID-19 pandemic: experience from China**

Suning Chen<sup>1,2</sup>, Yu Hu<sup>3</sup>, Jianfeng Zhou<sup>1,4</sup>, He Huang<sup>5</sup> and Depei Wu<sup>1,2</sup> on behalf of Chinese Society of Hematology and National Clinical Research Center for Hematologic Diseases.

1. National Clinical Research Center for Hematologic Diseases, Suzhou, Jiangsu Province, China
2. Jiangsu Institute of Hematology, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China
3. Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China
4. Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China
5. Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China.

Correspondence: Depei wu

Email: [wudepei@suda.edu.cn](mailto:wudepei@suda.edu.cn)

Tel: +86 512 6778 1856

Fax: +86 512 6778 1850

Address: 188, Shizi Street, Suzhou, 215006, Jiangsu Province, China

Since its first outbreak in December 2019, coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) has quickly become a global health emergency and was declared on March 11th as a pandemic by the World Health Organization. It is particularly deadly in those vulnerable populations with underlying conditions. Currently, exactly how susceptible patients with hematologic diseases are to infection with SARS-CoV-2 remains unknown. But patients with compromised immune systems caused by disease itself or undergoing active therapy with chemotherapy, radiotherapy, immunosuppressive therapy, or hematopoietic stem cell transplantation (HSCT) are deemed to be at increased risk of severe illness from COVID-19. Once infected with COVID-19, clinical manifestations of patients with hematological diseases are easily confused with other concurrent infections and may cause high mortality and rapid spread in hospital. Therefore, it is crucial to prevent and control the spread of COVID-19 infection in Hematology facility.

### **Education**

Patients and health care workers should be educated up-to-date information about COVID-19 via phone, text messages, brochure, and Wechat etc. Patients should be informed about the actions taken by the facility in detail. Some important issues regarding hand hygiene, cough etiquette, and wearing a mask should be emphasized regularly. Because the infection of medical staff in the early stage of the epidemic is often caused by insufficient protection, health care workers should be educated about selection and use of personal protective equipment. Health care workers with cough, shortness of breath or fever should be screened for SARS-CoV-2 and not come to work.

### **Outpatient service**

Patients are encouraged to make appointment and postponed non-urgent appointments to outpatient facility. On-site registration is suspended. Checkpoints are set at hospital entrances to screen for anyone with fever or cough in recent 14 days. Patients with fever or suspicious respiratory symptoms are sent to fever clinics to screen COVID-19 infection. All patients and accompanying persons must wear a protective mask in hospital. All medical staff should wear the cap, latex gloves, and mask. Make sure to keep at least 1 meter of distance between patients and clinic staff.

### **Inpatient service**

The number of patients in inpatient facility should be reduced to mitigate the risk of transmission of COVID 19. Patients with hematologic malignancies in stable remission are encouraged to postpone their treatment plan. They were asked to stay at home and minimize social contact. It is necessary to verify the history and clinical symptoms of all newly-admitted patients. And it would be better to screen for COVID-19 (complete blood count, CRP, IgM or IgG, nucleic acid detection, and chest

CT) for newly-admitted patients. All newly-admitted patients need to stay in a single ward for 72 hours and transfer to ward with two or more patients until rule out of COVID 19 infections. Visitors are strictly limited and usually not allowed to enter the ward. If the companion of family member is necessary, only one person is allowed and required to fill out an epidemic survey form to determine whether the family member was confirmed or suspected COVID-19 patient, whether there was fever or suspected symptoms, and whether contacted any confirmed or suspected COVID-19 patient. The family member allowed to stay in ward must undergo lung CT screening, serum IgM or IgG for SARS-CoV-2, and obtain once throat swab or a sputum virus nucleic acid test negative. All patients stay in ward should be monitored daily for respiration frequency and finger blood oxygen saturation. For symptomatic patients, blood panel tests, C-reactive protein (CRP), throat swab or sputum virus nucleic acid test and serum-specific new coronavirus antibodies should be regularly tested. Given the risk of infection and shortage of blood products, intensive chemotherapy hematopoietic stem cell transplantation, or cellular immunotherapy should be avoid or selected with caution to reduce the effect on the immune system and the requirement for infusion of blood products. Oral biologics or small molecule targeted drugs are preferred to intensive chemotherapy or chemoimmunotherapy.

### **E-medicine**

With the increasing concern for patients with hematologic diseases, it is helpful to provide online resources or guidelines about COVID-19 for health-care workers and patients. It is helpful to organize volunteer hematologists to offer online consultancy to patients with hematologic diseases. Consult or prescribe medicine over the internet (e.g., telephone, video chat, internet hospital, or other channel) will provides convenient and cost-effective care for patients with hematologic diseases. All above measures of E-medicine could potentially reduce the risk of SARS-CoV-2 infection of patients with hematologic diseases by avoiding close contact with infected patients in public areas.

### **Early quarantine and referral of patients with COVID-19**

Patients stay in ward should closely monitor fever or suspected symptoms and perform relevant COVID-19 examinations once symptoms occur (pulmonary CT, throat swab or sputum virus nucleic acid test, serum-specific SARS-CoV-2 antibodies and tests for influenza virus, adenovirus, respiratory syncytial virus, etc.). Patients cannot retain in the ward of Hematologic disease once they are considered as suspected or confirmed infection cases of COVID-19, and consultation from the relevant specialist is urgently required. They should be transferred to the quarantine negative pressure room for COVID-19. If they can't be transferred in time, they should be temporarily quarantined in single rooms. For hematologic malignancies patients infected by SARS-CoV-2, chemotherapy, or immunochemotherapy should be postponed or replaced by oral targeted drugs or low intensity chemotherapy with mild influence on hematopoietic and immune systems.

### **Treatment recommendations for patients with hematologic disease**

### **I. For patients with benign/indolent disease**

For newly diagnosed patients who had indications for treatment and required immediate therapy, physicians were still trying to provide the best treatment options. In addition, if there is more than one option for front-line treatment, the regimens which can be taken at home will be preferred. For patients with relative indolent diseases such as indolent lymphomas, chronic myeloid leukemia (CML), and some kinds of hemorrhagic diseases, etc, physicians could choose oral regimens that were available in China as front-line treatment. For example, BTKi (e.g. ibrutinib) could be recommended as front-line treatment for patients with chronic lymphocytic leukemia and Waldenstrom macroglobulinemia; TKIs (e.g. imatinib, dasatinib, etc) and hydroxyurea could be recommended for patients with CML as initial treatment; and oral glucocorticoid and TPO-RAs (e.g. eltrombopag) treatment could be considered for patients with primary immune thrombocytopenia.

For patients who were already on oral therapy, physicians should take into consideration the potential benefits and risks and then determined whether to continue or interrupt therapy. For patients who have already had intravenous chemotherapy/CIT, treatment could be postponed, and if possible, patients could be switched to oral regimens so as not to affect the efficacy due to delayed intravenous treatment. Please noted, when oral treatment was continued the safety and efficacy of drugs in patients should be closely monitored by regularly online follow up.

### **II. For patients with aggressive disease**

In general, the standard of care of patients with aggressive diseases (such as aggressive lymphoma, acute leukemia, severe aplastic anemia (SAA), high-risk myeloma, high-risk MDS, etc.) should not be changed. But for patients with relapsed/refractory(R/R) disease or on the maintenance period, oral agents could be considered. For example, BTKi (e.g. ibrutinib) and IMiDs (e.g. lenalidomide) could be used for patients with R/R B-cell lymphomas or maintenance; proteasome inhibitors(e.g. ixazomib) and IMiDs (e.g. lenalidomide) could be used for patients with myeloma; TPO-RAs (e.g. eltrombopag) could be considered for patients with refractory AA; and IMiDs (e.g. lenalidomide, Thalidomide) could be considered for some patients with MDS, etc.

Similarly, when patients received oral treatment at home the safety and efficacy of drugs in patients should be closely monitored by regular online follow-up. If possible, patients should obtain laboratory assessments at a hospital closer to home or in an area with a lower risk of infection to evaluate efficacy and disease status in time.

### **III. For allogenic hematopoietic stem cell transplant candidates and their donors**

Under the pandemic of COVID-19, hematologists might prefer to delay the transplantation procedure to avoid the ongoing immunologic deficiency. However, the risk of underlying disease progression led by delay of transplantation should also be taken into account. Sometimes it is difficult to balance the risk and benefit of delay of

transplantation. The outbreak of COVID 19 makes obstacles to obtain donations. Donors may understandably worry about travelling and spending several days in hospital. And If donors are infected with SARS-CoV-2, they will not be able to make a donation until they have fully recovered. Thus it is crucial to prepare back-up donors, in case the intended donor is ruled out. Actually, for the patients in urgent need of transplantation, transplantation from family haploidentical family donor is possible preferred to unrelated donor considering the potential risk of travel.

Before admission, the patient and the donor will be asked to complete the screening (detailed travel information or contact history, testing of SARS-CoV-2 nucleic acid, IgM and IgG for SARS-CoV-2, chest CT scan) mandatorily. After that, an expert panel consisted of respiratory and infectious disease department will evaluate the patient and the donor again. After exclude the COVID-19, patients were admitted for transplantation. Allogenic hematopoietic stem cell transplantation might involve a risk of transmission of viral infection from donor to recipient, as shown in the previous SARS outbreak, and therefore donor screening and testing is crucial. BM or PB grafts from potential COVID-19 donor should be prohibited. If patients experience fever (temperature  $>37.2^{\circ}\text{C}$ ) and any other respiratory symptoms during transplantation, the patient should be isolated as soon as possible and screened for SARS-CoV-2. And other respiratory viral pathogens including cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza A/B virus, human herpes virus 6 (HHV6) and herpes simplex virus (HSV) also need particular attention.

### **Management of prevention and control of COVID 19 in ward**

All patients and visitors are required to wear surgical masks. Although inpatient facility for hematologic diseases unlikely to reach the strict standard of two-routes between three partition areas same as that in division of respiratory infectious disease, it is mandatory to make a basic separation of the areas. Doctors and nurses' lounges should be placed on one side of the ward which is relatively clean areas. Others are relatively polluted areas. Buffer areas are set between the relatively clean areas and the relatively polluted areas. Disinfectants and air disinfection equipment are installed in the buffer areas. Environmental sterilization is strictly performed throughout the ward. Medical staff should wear PPEs in the relatively clean area.

The ward keeps at least one room as a temporary quarantine ward. In the situation of suspected patients cannot be transferred in time, the patients are quarantined in a single room under the existing conditions. The temporary quarantine ward is closed to normal personnel and managed by special medical staff. The room should do strict thoroughly disinfection after patients are transferred. Set up medical waste barrels and hand disinfectants on the inner side of the door of the temporary quarantine ward, where medical staff takes off the external gloves, isolation gowns and shoe covers, the medical waste bags should be taken away daily and the exterior of the medical waste bags should be sprayed and disinfected. Set up medical waste buckets and hand disinfectants on the outer side of the door of the temporary quarantine ward, where medical staff take off protective clothing, gloves, goggles, protective face screens, outer masks. Medical waste buckets should be immediately

disinfected and medical waste bags are packaged and disinfected. Medical personnel should not walk across the normal ward wearing protective clothing.

### **Management of laminar flow ward**

The sterile laminar flow ward mainly removes more than 99.9% of dust particles and bacteria with a diameter greater than 0.3  $\mu\text{m}$  through a high efficiency filter. The size of SARS-CoV-2 is about 0.1  $\mu\text{m}$ , which is usually spread by particles such as droplets or dust. The size of these droplets is mostly 0.3  $\mu\text{m}$  and above. Therefore, laminar flow ward can generally block coronavirus particles spreading. However, the laminar flow ward cannot block virus particles with smaller size, so that the laminar flow ward is not absolute safe and should also be disinfected. Furthermore, unlike the high safety of “negative pressure ward”, the laminar flow ward and the laminar flow bed are both in a positive pressure state, which increase the risk of virus transmission. Thus it is necessary to strengthen environmental disinfection and protective procedures for medical personnel. Stop the usage of laminar flow bed when it is necessary.

### **Grade of personal protection equipment of medical staff**

Medical staff should perform first-level protection for contact of ordinary patient: surgical masks, N95/KN95 medical protective masks if necessary, latex gloves, and work caps should be worn. When performing aerosol-generating operations, wear N95/KN95 medical protective masks, goggles or face shields, isolation gowns, disposable latex gloves, and work caps. If medical staff need to contact suspected or confirmed COVID-19 patients, perform second-level protection: N95/KN95 medical protective masks (preferably wearing on another surgical mask), protective clothing, goggles, disposable latex gloves (two layers), shoe covers, work caps. If there is a risk of contacting the patient's blood, body fluids and secretions, it is necessary to add an isolation gown and a protective face shield. When collecting samples from suspected or confirmed COVID-19 patients with throat swabs or performing operations that may produce aerosols, etc., perform third-level protection: add a comprehensive protective screen with the basis of second-level protection.

### **Summary**

In view of the huge threat of COVID-19 to patients with hematologic diseases and medical staff, it is crucial to rapidly employ appropriate preventive strategies in outpatient and inpatient hematology facilities. This summary is aimed at highlighting the strategies to minimize its spread in hematology facilities. We hope our experience could help to protect the susceptible population with hematologic diseases, ensure medical quality and safety of patients and health care workers.