bjh commentary

How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat?

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At the time of this writing, the World Health Organization has upgraded the global risk of the Coronavirus Disease 2019 (COVID-19) outbreak to 'very high'. Since the first reports less than 3 months ago, over 80,000 cases have been confirmed worldwide, with over 2,800 deaths attributed to COVID-19.[1] Many factors related to this pathogen remain unknown at this point, such as incubation period, rate of asymptomatic infection, quality of host immune response, etc., which makes it extremely difficult to model the potential spread of the infection or effective mitigation strategies. As with similar zoonotic-origin viral epidemics in the recent past, such as Middle Eastern Respiratory Syndrome (MERS)-CoV and Severe Acute Respiratory Syndrome (SARS)-CoV, the current novel coronavirus strain appears to cause most severe infection with potentially-fatal outcomes in the older patients and patients with underlying co-morbidities.[2,3] With over 50,000 hematopoietic cell transplantations (HCT) carried out annually, individuals who are actively undergoing HCT or who are HCT survivors with compromised immune systems make up a large population of susceptible patients in which COVID-19 infection may lead to devastating consequences. It is still too early to forecast the risk of infection and disease severity of COVID-19 in HCT patients, but it likely to follow the deleterious course previously reported by other community-acquired respiratory viruses.[4,5] Here we outline the potential challenges and solutions to mitigate the impact of COVID-19 in HCT patients (Table I).[6]

This infection is spread via respiratory droplets, so universal protective measures are key to safeguard patients as well as healthcare workers. Many centres are performing outpatient HCT, where a patient stays in proximity to the transplant centre. In areas with confirmed community spread of COVID-19, HCT patients actively getting conditioning or in the pre-engraftment period can be admitted pre-emptively to the hospital. This planning needs to happen well in advance given the extra resources required to manage confirmed COVID-19 cases during an epidemic. The Worldwide Network for Blood and Marrow Transplantation (WBMT) has recommended deferring non-urgent HCT in areas with endemic or high-frequency COVID-19 infection.[7] Hospital-wide enhanced screening measures for patients and family members will be needed for rapid triage and testing of all potential cases. In the absence of a vaccine or effective anti-viral drug at the current stage, maximum emphasis should be placed on personal protection by avoiding unnecessary travel to high-risk areas and exercising good hygiene for patients who are at home but still on immunosuppressive therapy. The other aspect of this equation is donor health and the potential impact on supply-chain operation for delivering the cell therapy product. Taking into consideration the fact that this virus has not been shown to be transmitted by cell therapy or blood products, the National Marrow Donor Program (NMDP)/Be The Match® has implemented a donor screening questionnaire and a similar advisory is in effect from WBMT.[7] It is also important to coordinate with local and international authorities to minimize disruption of couriers traveling with cell therapy product, considering travel restrictions to the endemic areas. At this stage, it is still too early to recommend an alternate donor option for patients in urgent need of an allogeneic HCT.

In confirmed COVID-19 cases, standard principles of communicable respiratory viral infection should be followed. In an early report, case fatality rates in non-severe and severe COVID-19 infections were 0.1% and 8.1%, respectively.[3] Ongoing immunosuppression, mucositis, malnutrition and/or graft-versus-host disease may increase the risk of complications in HCT patients with COVID-19. Patients should be closely monitored for superimposed bacterial infection and other common viral reactivation, such as cytomegalovirus or Epstein-Barr virus. A multidisciplinary, team approach is essential in order to orchestrate the management of this patients and make adjustments based on new information as it is disseminated from early epidemic areas. Teams should make an effort to systemically documenting the outcomes and rapidly reporting it, in order to allow other centres to benefit from their findings. We urgently need a safe and effective treatment for COVID-19. An adaptive, randomised, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents has been initiated by

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British Journal of Haematology, 2020, **189,** 239–240

First published online 16 March 2020
doi: 10.1111/bjh.16597

Table I. Recommendations for COVID-19 and HCT (based on EBMT).[6]

Recipients			
Scenario	Low-risk disease	High-risk disease	Notes
Confirmed diagnosis	Deferred for 3 months	Deferred, until asymptomatic and 3 negative PCR at least a week apart	
Symptoms of URTI	Testing with multiplex respiratory viral PCR, consider deferral	Testing with multiplex respiratory viral PCR, consider deferral	COVID-19 testing on case-by-case basis per local guidelines
Close contact with COVID-19 case	PCR test for COVID-19, deferred for 14–21 days	PCR test for COVID-19, deferral based on clinical judgment	Follow local guidelines for isolation and testing for COVID-19
Travel to high-risk areas* or close contact with person travelling from high-risk areas*	Deferred for 14–21 days	Deferral based on clinical judgment	Follow local guidelines for isolation and testing for COVID-19
Donors			
Confirmed diagnosis	Excluded from donation	Unclear when can be cleared for future donation	
Close contact with COVID-19 case	Exclude from donation for at least 28 days, monitor closely for symptoms	Follow local guidelines for isolation and testing for COVID-19	
Travel to high-risk areas* or close contact with person travelling from high-risk areas*	Exclude from donation for at least 28 days, monitor closely for symptoms	Follow local guidelines for isolation and testing for COVID-19	
Consider cryopreservation of unrelated donor graft for at least 21 days, monitor donor for symptoms			
If possible, ensure that an alternative stem cell source will be available.			
Donors should practice good hygiene at least 21 days before donation.			

Abbreviations: PCR: polymerase chain reaction.
*As defined by healthcare authorities.

the National Institute of Allergy and Infectious Diseases (NIAID) (NCT04280705). Remdesivir is the first antiviral agent being evaluated under this protocol which has previously shown antiviral activity against other single-stranded RNA viruses.[8,9] Ahmed *et al.* recently reported a set of B cell and T cell epitopes which may help guide the escalated vaccine development.[10]

Only the future will tell what will be the long-term impact of COVID-19 on human health and the socioeconomic fabric of our society. This outbreak has once again exposed the shortcomings of our ability to respond and curtail novel pathogen outbreaks. We encourage the development of a robust, dynamic and widely-applicable strategy at institutional, national and international level, in coordination with the Center for Disease Control (CDC), NMDP and WBMT, so we are better prepared to protect our most vulnerable patients from future viral epidemics.

Conflict of Interest

The authors report no relevant conflict of interests in relation to this work.

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