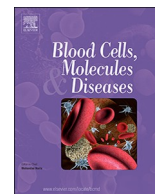




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Letter to the Editor

Facing COVID-19 in the hematopoietic cell transplant setting: A new challenge for transplantation physicians



Coronavirus disease (COVID-19) Pandemic has put enormous pressure on the health care system worldwide. As of 8th April 2020, more than 220 countries are already affected with a total of 1,462,698 confirmed COVID-19 cases and 84,792 deaths across the globe [1]. Absence of a specific antiviral agent and vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has strangled the treating health care providers. The special population that is at high risk of acquiring SARS-CoV 2 infection are immunocompromised, and HIV infected persons, pregnant woman, and cancer patients [2]. We hereby discuss the challenges being faced by cancer patients, specifically the transplant recipients and their respective donors during COVID-19 pandemic. Transplantation societies are working closely to provide optimal support and recommendations to the transplant specialists to guide them to conduct hematopoietic cell transplantation (HCT) in the safest manner.

1. COVID-19 in cancer patients. What do we know so far?

Studies on COVID-19 confirmed cases are pouring in from all corners of the world [2,3]. Most of these retrospective studies have mentioned cardiovascular disorders, hypertension, and diabetes as the most common associated comorbidities [4]. Cancer has also been mentioned as a comorbidity in many of these studies, however, except for the Liang et al. paper, none of the other studies have discussed cancer-related aspects in-depth like the type of cancer, stage of cancer, and treatment (chemoradiotherapy, surgery, etc.) received [3]. The study by Liang et al. (*National Clinical Research Center for Respiratory Disease group*) was conducted across 575 Chinese hospitals involving 1590 COVID-19 cases. It showed that patients with cancer had a higher chance of acquiring SARS-CoV-2 infection than the normal Chinese population [3]. What is more concerning is the higher chance of requiring the intensive level of care, mechanical ventilation and potential deaths amongst the cancer patients, as compared to non-cancer patients (39% vs 8%, $p = 0.0003$) [3].

2. COVID-19 in post-HCT patients. What is the current literature?

Transplant recipients constitute a special population of cancer patients, that need more specialized and tailored attention and care. Unfortunately, we do not have any database as of now regarding such patients during present pandemic or previous outbreaks of coronaviruses (MERS and SARS).

A recent report (dated 20th March 2020) from the European Society for Blood and Marrow Transplantation (EBMT) society mentioned about 15 cases of post-transplant COVID-19 confirmed cases in Europe (Spain-5, Italy-3, Sweden-2, Belgium-2, France-2, Greece-1). The median age of patients was 59 years with 12 allogeneic HCT, the remaining 3 had autologous HCT. The majority of patients (10 cases) had symptoms related to the upper respiratory tract. Till the time of the

report briefing, one patient already died due to COVID-19 [6]. Another report by Huang et al. from China discussed the grave prognosis of two post-transplant patients (transplant done for acute myeloid leukemia, and end-stage renal failure) on immunosuppressants. Both patients went to acute respiratory distress syndrome (ARDS), developed multi-organ failure and eventually died [7]. An interesting finding of low T cell count was noted in both patients which could serve as a surrogate marker for poor prognosis, but this needs confirmation by further studies.

While there is a rising trend in the number of COVID-19 related reports in HCT patient, as of now there is no single universal portal to assimilate the data to consolidate the findings and analyze the outcome. Center for International Blood and Marrow Transplant Research (CIBMTR) has taken its first step and recently updated Transplant Essential Data (TED) and Comprehensive Report Forms (CRF) to capture any new case of COVID-19 in the HCT setting [8].

3. The daunting task of differentiating COVID-19 from other opportunistic infection in HCT patients

As clear from the above discussion, we can anticipate that worldwide more cases of COVID-19 in the post-transplant setting are going to pick up and tracking these patients are of utmost importance so that we can learn from others' experiences. "*Prospective survey on the impact of COVID-19 on stem cell transplant recipients*" is a recently initiated program by Infectious Diseases Working Party (IDWP), EBMT that could be extremely beneficial in order to gather live data from clinical practice [9,11].

From the post-transplant perspective, a transplant specialist still needs to think about common differentials like fungal infections and viral syndromes (cytomegalovirus [CMV], herpes simplex virus, etc.) in addition to COVID-19. Regarding the gastrointestinal symptoms, we now have enough data mentioning gastrointestinal (GI) symptoms like diarrhea, nausea, and vomiting as presenting symptoms for COVID-19 disease [5]. This GI symptomatology of COVID-19 can easily be confused with other differentials like acute graft-versus-host disease, CMV colitis, mucositis, etc. With regards to the treatment, an important consideration should always be given to drug-drug interactions due to the multiple prophylactic medications (antivirals, antifungals, immunosuppressants) which transplant patients are usually on. For example, anti-COVID-19 medications can either alter the therapeutic level of many life-saving drugs-digoxin, coumadin, steroids, and immunosuppressants (e.g. lopinavir/ritonavir) or may increase the risk of rejection (e.g. beta-interferon).

4. Predicting the worst outcome in COVID-19 transplant patients

In case, a post-transplant patient gets a COVID-19 disease, it would

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be best if we could have a surrogate marker to predict which transplant recipients are more likely to have a complicated course than others. Studies on COVID-19 patients, in general, have shown lymphopenia as a poor prognostic factor [10]. In HCT, interpretation of lymphopenia is not straight forward and multiple other non-COVID-19 causes like non-SARS-CoV-2 viral infections, conditioning chemotherapy, pending bone marrow recovery, transfusion-associated graft-versus-host disease, etc. need to be considered and ruled out. Similarly, Huang et al. suggested a low T cell count as a possible marker of poor prognosis in post-transplant recipients with COVID-19 [7]. However, their patients were already on steroids, cyclosporin-A and mycophenolate mofetil which can also lead to T cell depletion. Hence, at present, we do not have an ideal marker in cancer/HCT patients that can be used confidently to predict the clinical course or outcome of COVID-19.

5. Severe blood shortage: Matter of concern for cancer and transplant patients

Blood donation is another sector that has been affected due to the unprecedented cancellations of blood donation drives. A recent report by Pagano et al. mentioned how the number of blood donations went down significantly when the US administration promoted social distancing, and school and university closures to contain community transmission of SARS-CoV-2 [12]. By implementing measures like judicious use of blood products, cancellations of elective surgeries and public awareness, Pagano et al. were able to overcome the scarcity of blood products. This is something very crucial for transplant patients because they need blood and blood components in amounts which are exceedingly higher than in routine patients. One can always ask if SARS-CoV-2 can be transmitted via blood transfusions? At least, to date, there is no documentation of transfusion-related coronavirus reaction in the current COVID-19 pandemic as well as during the past outbreaks of MERS and SARS.

6. Emotional breakdown during COVID-19 pandemic in HCT

Undergoing treatment for cancer and HCT are a great psychological stressors by themselves. There are ample evidences which suggest that such patients often need dedicated psychological and pharmacological interventions during cancer treatment [13]. The anxiety, fear, and panic revolving around current COVID-19 pandemic could make cancer patients, transplant recipients, and donors more nervous, that endorses the importance of constant and continuous psychological stress monitoring. Similarly, ensuring the well-being and mental stability of the transplant staff is equally important. Measures include maintaining an adequate backup pool, relocating susceptible staff to non-clinical tasks, regular psychological checkups, etc. could help the working team from getting overwhelmed and burnout [14].

In Conclusion, we emphasize the urgent need for all the national and international bone marrow transplantation societies to come together, share and disseminate their experience of transplant patients during current COVID-19 pandemic. This will help to assimilate the data and formulate a guideline to approach COVID-19 in the scenario of HCT.

Ethical statement

The article doesn't contain the participation of any human being and animal.

Verification

All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

Declaration of competing interest

Authors have no conflicts of interest to declare.

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Kamal Kant Sahu, AD Siddiqui, Jan Cerny: performed the research. Kamal Kant Sahu, Jan Cerny AD Siddiqui, Vishal Jindal: designed the research study.

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References

- [1] K.K. Sahu, A. Lal, A.K. Mishra, Latest updates on COVID-2019: a changing paradigm shift, *J. Med. Virol.* (2020), <https://doi.org/10.1002/jmv.25760> (Mar 20).
- [2] B. Dholaria, B.N. Savani, How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat? *Br. J. Haematol.* (2020), <https://doi.org/10.1111/bjh.16597> (Mar 16).
- [3] W. Liang, W. Guan, R. Chen, et al., Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China, *Lancet Oncol.* 21 (2020) 335–337.
- [4] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet* 395 (10223) (2020) 497–506.
- [5] X. Jin, J.S. Lian, J.H. Hu, J. Gao, L. Zheng, Y.M. Zhang, et al., Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms, *Gut* (2020) (Mar 24). pii: gutjnl-2020-320926.
- [6] <https://www.ebmt.org/covid-19-and-bmt>.
- [7] J. Huang, H. Lin, Y. Wu, Y. Fang, R. Kumar, G. Chen, et al., COVID-19 in post-transplantation patients- report of two cases, *Am. J. Transplant.* (2020) (Apr 3).
- [8] <https://www.cibmtr.org/ReferenceCenter/Covid19/Pages/default.aspx#comm>.
- [9] <https://www.mdedge.com/hematology-oncology/article/219068/transplant/covid-19-astct-issues-interim-guidelines?channel=63993>.
- [10] L. Tan, Q. Wang, D. Zhang, J. Ding, Q. Huang, Y.Q. Tang, et al., Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study, *Signal. Transduct. Target. Ther.* 5 (2020) 33 Mar 27.
- [11] <https://www.ebmt.org/ebmt/news/prospective-survey-impact-covid-19-stem-cell-transplant-recipients-and-patients-treated>.
- [12] M.B. Pagano, J.R. Hess, H.C. Tsang, E. Staley, T. Gernsheimer, N. Sen, et al., Prepare to adapt: Blood supply and transfusion support during the first 2 weeks of the 2019 novel coronavirus (COVID-19) pandemic affecting Washington State, *Transfusion* (2020) (Mar 21).
- [13] A. Warchala, I. Krupka-Matuszczyk, K. Krysta, Anxiety and depression in patients with acute leukaemia treated with hematopoietic stem cell transplantation, *Psychiatr. Danub.* 31 (Suppl. 3) (2019) 231–236 Sep.
- [14] K.K. Sahu, V. Jindal, A.D. Siddiqui, K.K. Sahu, V. Jindal, A.D. Siddiqui, Managing COVID-19 in patients with cancer: a double blow for oncologists, *JCO Oncol. Pract.* (2020) OP2000167.

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