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TRANSFUSION

Planned hematopoietic stem cell transplantation in a 17-month-old patient with high-risk acute myeloid leukemia and persistent SARS-CoV-2 infection

To the Editor:

The coronavirus disease 2019 (COVID-19) pandemic outbreak raised many issues concerning global health policies. The necessity for strategies to guarantee the best standard-of-care dramatically emerged in specific settings.[1] Managing the oncologic patient means maintaining access to cancer therapy while minimizing the risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its potential severe complications.[2] Despite hematopoietic stem-cell transplantation (HSCT) in high-risk hematologic cancer being crucial, its indication in patients with SARS-CoV-2 infection poses several challenges.[3]

We already reported the case of this patient at 13-months-old with high-risk acute myeloid leukemia (AML) and SARS-CoV-2 infection with interstitial lung involvement during the induction phase of treatment following the Italian Association of Pediatric Hematology and Oncology AML 2013 protocol (EudraCT 2014–000652-28). At that time, the patient received antiviral and immunomodulant therapy but the reverse-transcriptase polymerase-chain-reaction (RT-PCR) testing for SARS-CoV-2 on nasal swab remained positive after discharge at outpatient evaluations, despite clinical recovery.[4] Sustained complete remission (CR) was achieved after the second chemotherapy course. Thus, considering high-risk AML and clinical recovery, 1 month later the patient received an additional chemotherapy course, despite her persistently positive SARS-CoV-2 swab. Because of patient's age (<1 year) and cytogenetic features at diagnosis [MLL-AF10-t(10;11)], allogeneic HSCT was indicated at first CR. A first attempt of passive immunization with hyperimmune plasma,[5] aimed to eradicate the virus before HSCT, was unsuccessful. Thus, a second infusion was administered 2 months later. However, the immune response to the virus was still lacking, but proceeding to HSCT was considered anyway. As a matter of fact, the course of her SARS-CoV-2 infection had been favorable even when the patient was highly immunocompromised. Absence of comorbidities, young age, good clinical condition with a Lansky index of 100%, and persistent CR tipped the balance against further postponing HSCT. A protocol was designed ad hoc in collaboration with the Infectious Disease Department of our Center. Scheduled infusions of hyperimmune plasma every 3 weeks and strict monitoring of SARS-CoV-2 viral load from nasal swab, plasma, and rectal swab specimens were performed throughout the whole hospitalization period. The hyperimmune plasma was collected through apheresis of convalescent patients. Neutralizing antibodies were titered 1:320 using a plaque reduction neutralization test. Since neither HLA-identical sibling nor matched unrelated donor were available, T-cell repleted haploidentical HSCT was performed using parental (father) G-CSF mobilized peripheral blood as graft source. The conditioning regimen included treosulfan and fludarabine. Post-transplant cyclophosphamide, cyclosporine-A, and mycophenolate mofetil were administered as graft-versus-host disease (GvHD) prophylaxis, and rituximab as post-transplantation lymphoproliferative disease prophylaxis (Figure 1). During the aplasia phase, the patient developed oral and esophageal grade-3 mucositis, and febrile neutropenia, but no respiratory symptoms were observed. Platelet recovery, defined as a platelet count reaching or exceeding 20,000/μl without transfusion, and neutrophil recovery, defined as the first of three consecutive days with absolute neutrophil count exceeding 500/μl, were reached on days +15 and + 16, respectively. Donor engraftment, defined as chimerism >95%, was assessed on day +19. No evidence of acute GvHD or infectious complications was observed during hospitalization. Repeated RT-PCR SARS-CoV-2 assessments on plasma and rectal swab remained persistently negative, while nasal swabs resulted temporarily negative (Figure 1). SARS-CoV-2-specific IgG were detected, with persistently negative IgA and IgM, but such finding was likely due to hyperimmune plasma administration. Chest computed tomography before discharge was comparable to that performed at admission, showing only a limited ground-glass pattern in the left inferior lobe. At discharge, the patient was in good clinical condition, had

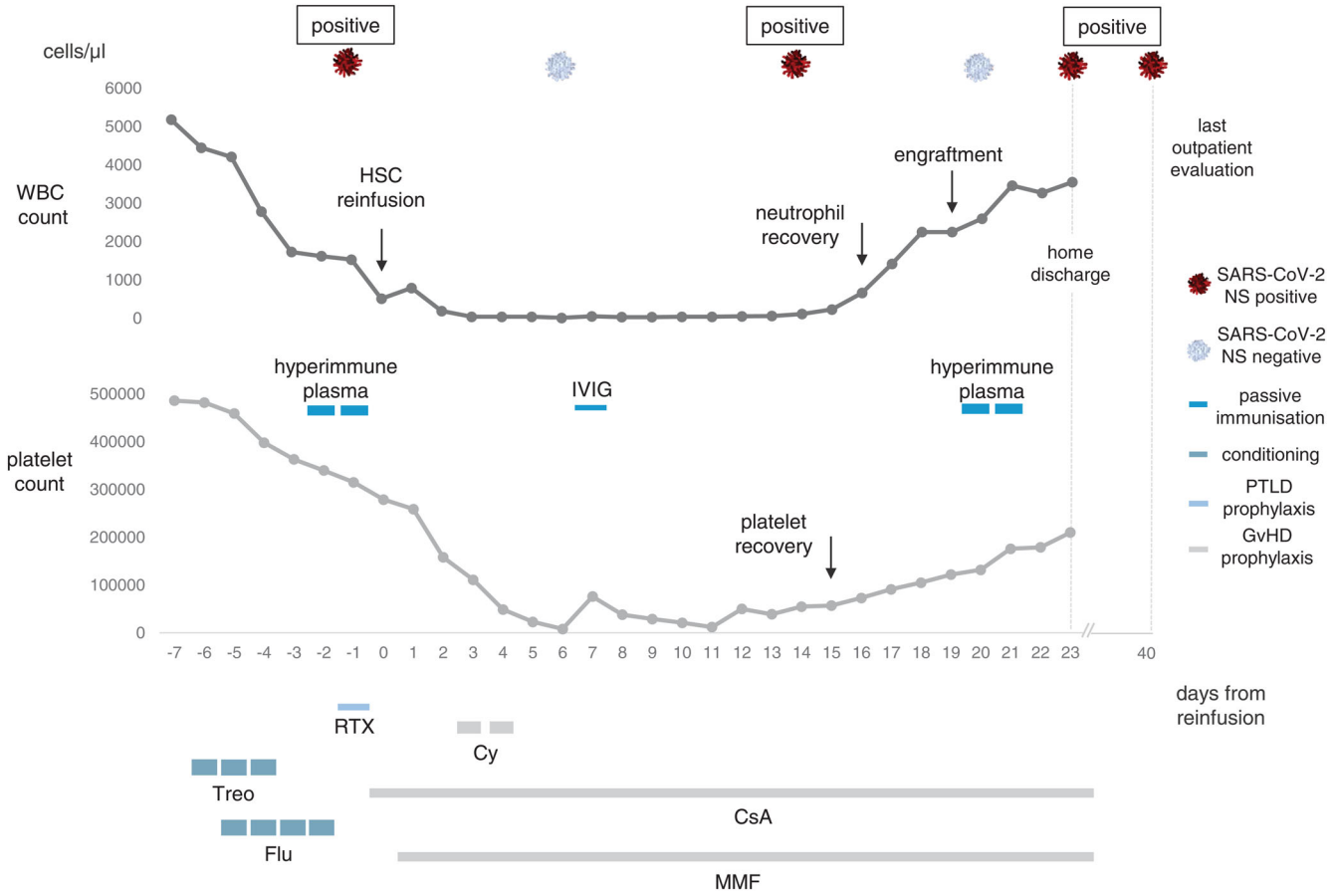

FIGURE 1 Visual summary including laboratory findings and treatments. Conditioning: Treo 14 g/m^2 iv daily, days −6 to −4, and flu 40 mg/m^2 iv daily, days −5 to −2. GvHD prophylaxis: Post-transplant cy 50 mg/kg iv daily, days +3 and + 4, CsA, and MMF. PTLD prophylaxis: RTX 200 mg/m^2 day −1. Passive immunization: Hyperimmune plasma 100 mL iv daily, days −1 to −2 and + 20 to +21, and IVIG 5 g iv, day +7. *Abbreviations used in the figure*. WBC, white blood cells; HSC, hematopoietic stem cell; Treo, treosulfan; Flu, fludarabine; Cy, cyclophosphamide; CsA, Cyclosporine-A; MMF, mycophenolate mofetil; RTX, rituximab; IVIG, intravenous immunoglobulins; NS, nasal swab; PTLD, post-transplantation lymphoproliferative disorder; GvHD, graft-versus-host disease [Color figure can be viewed at wileyonlinelibrary.com]

a complete hematopoietic recovery and no signs of acute GvHD, despite positive SARS-CoV-2 nasal swab, as observed at the last outpatient evaluation on day +40 (Figure 1).

To our knowledge, this is the first report of planned HSCT in a patient with SARS-CoV-2 infection. The adapted protocol included strict viral-load monitoring and periodic hyperimmune plasma infusions, while antiviral treatment (e.g. remdesivir) was deemed unnecessary. No signs of clinical reactivation or SARS-CoV-2-related complications were observed within the early post-transplant phase. Such unprecedented condition required a multidisciplinary approach and dedicated medical staff and setting, to face unexpected complications during the critical phase of therapy-induced immunosuppression. In the management of cancer - and specifically leukemia - a delay in crucial interventions could impair the prognosis. Performing HSCT in a patient with persistent SARS-CoV-2 infection might be perceived as hazardous. However, such a therapeutic dilemma is likely to be increasingly frequent as the infection spreads and the need for adapting clinical care in the pandemic landscape grows alongside it. Evidence from larger cohorts is required to select and refine the best strategies for treating oncologic patients while facing the COVID-19 pandemic.

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AUTHORS' CONTRIBUTIONS

D.C. and F.P. wrote the manuscript, C.F. and F.B. revised it. D.C., S.F., T.C., L.G., E.G., V.T. and C.F. followed the patient.

CONFLICT OF INTEREST

None of the authors has any kind of conflict of interest with the publication of this paper.

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Improving education on transfusion medicine in medical school: A perspective from students

We read with great interest the article by Al-Riyami et al. which highlighted an inadequacy in transfusion medicine (TM) education in the global medical curricula.[1] With approximately one in 20 patients falling victim to preventable harm,[2] often from the medications that healthcare professionals themselves provide, we agree that it is paramount that education on transfusions and their associated risks is improved.

Al-Riyami et al. comment on lectures and seminars being the most widely used education modalities within their sample, while simulations occur far less frequently.[1] These findings resonate with us as current medical students in the United Kingdom where transfusion teaching has similarly been approached largely with academic lectures. The focus is primarily on the indications for various transfusion products and what they constitute, rather than gaining confidence and experience safely transfusing a patient. Despite its importance, this runs the risk of underemphasizing the very real and severe clinical implications of incorrectly transfused medications and blood products.

We think that in light of Al-Riyami et al.'s findings, there is an opportunity to further explore the perceptions of transfusion-associated harm in medical students relative to the mediums with which they were taught. When simulated scenarios have been cited to increase emotional engagement and enhance learning experiences,[3] we find it