

CASE REPORT

Hematopoietic stem cell transplant in two pediatric patients testing positive for SARS-CoV-2: A case report

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Abstract

Background: The SARS-CoV-2 pandemic brought challenges to all areas of medicine. In pediatric bone marrow transplant (BMT), one of the biggest challenges was determining how and when to transplant patients infected with SARS-CoV-2 while mitigating the risks of COVID-related complications.

Methods: Our joint adult and pediatric BMT program developed protocols for performing BMT during the pandemic, including guidelines for screening and isolation. For patients who tested positive for SARS-CoV-2, the general recommendation was to delay BMT for at least 14 days from the start of infection and until symptoms improved and the patient twice tested negative by polymerase chain reaction (PCR). However, delaying BMT in patients with malignancy increases the risk of relapse.

Results: We opted to transplant two SARS-CoV-2 persistently PCR positive patients with leukemia at high risk of relapse. One patient passed away early post-BMT of a transplant-related complication. The other patient is currently in remission and doing well.

Conclusion: These cases demonstrate that when the risk associated with delaying BMT is high, it may be reasonable to proceed to transplant in pediatric leukemia patients infected with SARS-CoV-2.

KEYWORDS

allogeneic stem cell transplantation, bone marrow transplantation, hematopoietic stem cell transplantation, HSCT, infectious risk, pediatrics

1 | INTRODUCTION

The global SARS-CoV-2 pandemic forced a change in the way health-care specialties practice medicine, including in the field of bone marrow transplantation. The American Society for Transplantation and Cellular Therapy (ASTCT) and the European Society for Blood and Marrow Transplantation (EBMT) developed guidelines for BMT during the pandemic that include management of those who are

infected.^{1,2} The guidelines recommend delaying BMT in patients that test positive but also note the need to balance this against the urgency of BMT. This report details the courses for two pediatric high-risk leukemia patients who underwent BMT despite remaining polymerase chain reaction (PCR) positive for SARS-CoV-2. We housed these patients on a COVID-designated unit, and we followed all institution-wide isolation and safety procedures for SARS-CoV-2 positive patients.

Abbreviations: ALL, acute lymphoblastic leukemia; ASTCT, American Society for Transplantation and Cellular Therapy; AUC, area under the curve; BMT, bone marrow transplant; CIBMTR, Center for International Blood and Marrow Transplant Research; CNS, central nervous system; COG, Children's Oncology Group; CRS, cytokine release syndrome; EBMT, European Society for Blood and Marrow Transplantation; EFS, event-free survival; MIS-C, multisystem inflammatory syndrome in children; MRD, minimal residual disease; MUD, matched unrelated donor; NCI, National Cancer Institute; OS, overall survival; PICU, pediatric intensive care unit; SOS, sinusoidal obstructive syndrome; SOT, solid organ transplant.

2 | CASE SUMMARY

Patient 1 was a 16-year-old boy who was originally diagnosed at age 10.5 years with National Cancer Institute (NCI) high-risk B-cell acute lymphoblastic leukemia (ALL) with CNS3 disease. He was treated on a Children's Oncology Group (COG) study for high-risk ALL (AALL1131). End of induction minimal residual disease (MRD) level was 1.3% by multiparameter flow cytometry, though he achieved negative MRD by the end of consolidation. He, therefore, continued with chemotherapy alone, and also received 1800 cGy cranial radiation for treatment of CNS3 disease. Cytogenetics at the time of diagnosis showed that he had a CRLF2-rearrangement, consistent with Ph-like ALL. Subsequent course was complicated by an isolated central nervous system (CNS) relapse during the maintenance phase of chemotherapy. He enrolled onto COG AALL1331, a phase III study for first relapse of B-ALL, was considered low-risk and was randomized to receive conventional chemo without Blinatumomab, and also received an additional 1800 cGy cranial RT.

Two months after completion of treatment for his first CNS relapse, patient 1 had a second CNS relapse with positive MRD in the bone marrow. T-cells were collected in preparation for CAR-T infusion. He received triple intrathecal chemotherapy for bridging chemotherapy without any systemic chemotherapy since there was only minimal leukemia in the bone marrow. Evaluations prior to CAR-T infusion showed 82% blasts in his bone marrow as well as detectable CNS disease. His post-infusion course was complicated by development of grade 1 cytokine release syndrome (CRS), which did not require steroids or Tocilizumab, with MRD-negative remission documented at day 30 and day 100 post-CAR-T.

Sixteen months after CAR-T infusion, he presented with intermittent left shoulder pain for 6 weeks. CT of the chest showed a left lung apex soft tissue mass with mediastinal adenopathy. Core biopsy confirmed an extramedullary relapse of CD19⁺ pre-B-cell ALL. Genomic sequencing of the relapsed tissue again showed CRLF2-rearrangement, consistent with his original diagnosis of Ph-like ALL. Bone marrow revealed 0.081% CD19⁺ blasts and CSF was negative. The plan at that time was for chemotherapeutic bridge to BMT, but due to developing *Staphylococcus aureus* sepsis with microabscesses, a second CAR-T infusion was done instead, with complete remission prior to infusion.

Evaluation for matched unrelated donor (MUD) BMT was still in process in January 2021, when the patient developed low-grade fever and symptoms of a mild upper respiratory infection. On January 15, 2021, SARS-CoV-2 PCR was positive, and he was diagnosed with COVID-19. He was admitted and received a dose of convalescent plasma, but never developed an oxygen requirement or respiratory support so did not receive any additional treatment for COVID-19. His SARS-CoV-2 IgG antibody remained negative, and he tested SARS-CoV-2 PCR positive again on 1/29/21. The transplant team discussed with the patient and his family the benefits and risks of BMT while SARS-CoV-2 positive. However, given his very high-risk leukemia with multiple relapses, the decision was made to move forward to the matched unrelated BMT.

He began a myeloablative conditioning regimen 24 days after his initial positive SARS-CoV-2, consisting of rATG, busulfan (due to a high AUC estimated average exposure only three doses of busulfan were administered), fludarabine, and thiotepea, and he then received infusion of his MUD cryopreserved marrow. He remained positive for SARS-CoV-2 by PCR and negative on antibody testing throughout his hospitalization. Chest X-ray done as screening on day -2 was negative for pneumonia and other lung findings. He received a second dose of convalescent plasma as prophylaxis on day -1. Due to his high Busulfan AUC, prophylactic defibrotide was started on day +1. On day +10, the patient developed fluid overload, renal insufficiency, direct hyperbilirubinemia, as well as a persistent low-grade fever with tachycardia. On day +12, he was transferred to the Pediatric Intensive Care Unit (PICU) with respiratory distress, acute kidney injury, decreased neurologic function, and gastrointestinal bleeding with coagulopathy. Although these symptoms were consistent with sinusoidal obstructive syndrome (SOS), multisystem inflammatory syndrome in children (MIS-C) was considered, and inflammatory markers and an echocardiogram were done. Echocardiogram showed mildly reduced biventricular systolic function. In addition to pancytopenia, the patient's labs were notable for ferritin 5622 ng/ml, C-reactive protein (CRP) 24.3 mg/dl, Troponin 0.25 ng/ml, brain natriuretic peptide (BNP) 4437 pg/ml, total bilirubin 4 mg/dl, albumin 2.7 g/dl, and INR 2.09. Blood cultures and other infectious studies remained negative. High dose IVIG and methylprednisolone were ordered for the treatment of possible MIS-C on day +13, but due to deteriorating clinical status and multiorgan failure due to progressive SOS, the patient's family requested an Allow Natural Death order. He subsequently passed away later that day.

Patient #2 is a now 18-month-old girl who was diagnosed with mixed phenotype acute leukemia (B/myeloid MPAL) at 3 months of age and initiated treatment with five-drug induction chemotherapy as per COG AALL15P1. Following induction, consolidation, and blinatumomab treatments, she still had persistent MRD, so was referred for CAR-T as a bridge to BMT. Prior to planned CAR-T a small lump appeared on her scalp. MRI showed a midline mass with bilateral maxillary and soft tissue involvement, and biopsy confirmed extramedullary relapse. Initial T cell apheresis for CAR-T was aborted early due to rapidly progressive leukemia that required chemotherapy treatment. After completing bridging chemotherapy, the extramedullary disease resolved, though she still had persistent marrow involvement. The second T cell apheresis was successful, and she received her CAR-T infusion after lymphodepleting chemotherapy. Treatment was complicated by grade 2 CRS requiring PICU admission and tocilizumab. Day +30 post-infusion bone marrow showed 3.6% residual B-ALL. Despite re-induction chemotherapy, she developed a large right pleural effusion, confirmed to be malignant, and had persistent marrow disease. While inpatient for fever and neutropenia, the patient's mother, her bedside caregiver, developed new onset nasal congestion and rhinorrhea. Testing for SARS-CoV-2 by PCR was positive. The patient was also tested and was positive for SARS-CoV-2 infection by PCR. At the time of the positive SARS-CoV-2 test, she was asymptomatic, although she was

treated with convalescent plasma given her immunocompromised status. After multiple salvage chemotherapy regimens over a total period of 11 months, the patient finally achieved an MRD-negative remission. Her PCR test remained positive for SARS-CoV-2, so the transplant team discussed with her family the potential risks of undergoing BMT while still SARS-CoV-2 positive. Given her extremely refractory, very high-risk leukemia, the decision was made to proceed to BMT quickly since she had finally achieved an MRD-negative remission. Screening chest X-ray was done before conditioning was started, which showed a hazy opacification at the right lung base.

She began her cytoreduction of busulfan, fludarabine, and thiopeta 22 days after her initial positive SARS-CoV-2 PCR test, and she then received infusion of her matched sibling cryopreserved bone marrow. Her SARS-CoV-2 PCR remained positive on day +1 with a negative SARS-CoV-2 IgG, so she received a second dose of convalescent plasma. On day +5, she became febrile and received broad spectrum antibiotics. On day +8 she remained persistently febrile and tachycardic, and developed bilious emesis, gastrostomy tube drainage, and tender abdominal distention with diffuse anasarca. She had a prominent S3 gallop as well as tachypnea and bilateral rales. CT of her abdomen and pelvis showed active enterocolitis. Echocardiogram showed new mild left ventricular dysfunction. On day +11 in addition to pancytopenia, her labs were notable for BNP 1200 pg/ml, CRP 15 mg/dl, albumin 2.8 g/dL, ferritin 3126 ng/mL, INR 1.37, and PTT 52.8. Blood cultures and other infectious studies remained negative. MIS-C was considered as a cause of her symptoms, and she received methylprednisolone and IVIG. She promptly improved with vital sign normalization after the first dose of methylprednisolone. Her absolute neutrophil count recovery was noted on day +20, and she was discharged on day +28. One month post-BMT, she achieved full donor chimerism with no evidence of leukemia. She required steroids for mild acute skin graft versus host disease, but it has remained quiescent on tapering steroids. She has not had any further symptoms related to SARS-CoV-2 infection, and she had a negative SARS-CoV-2 PCR on day +40 and day +47, allowing for discontinuation of isolation precautions.

3 | DISCUSSION

The COVID-19 global pandemic has upended the practice of medicine across specialties. When considering whether to take these two high-risk patients to BMT while still PCR positive for SARS-CoV-2, we weighed the risk of COVID-19 complications, including MIS-C, against the risk of relapse. To date, there have been no other reports published on performing BMT on a patient who is PCR positive for SARS-CoV-2. A few studies have reported on outcomes of patients who developed SARS-CoV-2 infection after undergoing BMT. Sharma et al reported on 318 post-BMT patients diagnosed with COVID-19 as reported to the Center for International Blood and Marrow Transplant Research.³ The median time from BMT to COVID-19 diagnosis was 17 months for allogeneic BMT recipients. Eighteen percent of the allogeneic BMT recipients were receiving immunosuppression

within 6 months of the COVID-19 diagnosis. In July 2020, Belsky et al.⁴ published a systematic review of reports detailing SARS-CoV-2 infection in adult and pediatric cancer patients, BMT patients, and solid organ transplant (SOT) patients. Within the BMT cohort, 74.2% were allogeneic hematopoietic stem cell transplant with one CAR-T recipient. Median time from BMT to SARS-CoV-2 diagnosis ranged from 77 days to 3 years with 50% of studies reporting median time to infection ≥ 255 days. This review found that adult cancer and SOT patients with SARS-CoV-2 had higher comorbidities and higher rates of intensive care and hospital mortality than the general population with SARS-CoV-2. However, pediatric cancer patients and all BMT patients with COVID-19 tended to have clinical presentations and outcomes similar to the general population. Both of these reviews summarize the experience of contracting SARS-CoV-2 after cancer treatment or BMT, so it is unknown whether pediatric patients who acquire SARS-CoV-2 before BMT would fare similarly.

In pediatrics, the emergence of MIS-C added a new level of diagnostic complexity. The exact cause of MIS-C remains unclear, but it is thought to represent a post-infectious process that occurs about 4 weeks following SARS-CoV-2 infection.⁵ The approach to treatment continues to evolve, though MIS-C does appear to respond to anti-inflammatory medications, indicating a possible role for immune dysregulation in its pathogenesis.⁶⁻⁸ Diagnosis of a patient presenting with a hyperinflammatory severe illness is challenging, and now added to the differential diagnosis is a multisystem illness triggered through unknown mechanisms by a novel virus that remains poorly understood. That difficulty is compounded in patients who are already medically complex like BMT patients. In these immunocompromised patients, the etiologies of severe febrile illness are varied with protean potential infectious and non-infectious causes. These two patients infected with SARS-CoV-2 prior to BMT both developed fever without a clear etiology and had multisystem involvement and labs consistent with a hyperinflammatory syndrome. Patient 2 was treated presumptively for MIS-C, with good response, and unfortunately patient 1 died due to other post-BMT complications before he could receive MIS-C treatment. Even in retrospect it is not clear that the febrile presentation was related to MIS-C or to COVID-19, but both fulfilled diagnostic criteria and expected time course for MIS-C.

Ultimately, the overriding factor in the decision to proceed to BMT on our patients was the overwhelmingly high risk of relapse. Both patients had multiply relapsed and refractory B-ALL. Anticipated outcomes become worse following each salvage attempt.⁹ Patient 1 had a number of poor prognostic factors. He was originally diagnosed with Ph-like B-ALL, which has inferior outcomes, with a 5-year event-free survival (EFS) of 58.2% and 5-year overall survival (OS) of 72.8%, compared to 5-year EFS 83.9% and 5-year OS 92.1% in other high-risk B-ALL children.⁹ Patient 2 was a case of infant leukemia with an unfavorable finding of KMT2A-rearrangement. Relapse risk for infant ALL remains high at approximately 35%, with a shorter time to relapse compared to childhood ALL. Three-year OS following relapse in infant ALL is approximately 20.9%, with slight improvement to 24.9% in infants treated with curative intent.¹⁰ Those with early relapses and bone marrow

involvement (either isolated or combined) had worse outcomes.⁶ Outcome following relapses for infant B-ALL is still inferior to outcome following relapses for childhood B-ALL, even in the setting of more contemporary clinical trials.¹¹ The decision to proceed with or delay BMT in the setting of a positive SARS-CoV-2 PCR should be determined on an individual basis. Despite the positive SARS-CoV-2 infections by PCR, BMT was still planned for both patients because of the high risk of relapse with BMT offering the best chance of cure after having already received multiple lines of therapies. Although antigen directed therapies such as Blinatumomab, a CD 19 directed therapy, and Inotuzumab, a CD22 directed therapy, could be considered while awaiting a negative SARS-CoV-2 test to proceed to BMT, both patients had already received antigen directed therapy without achieving a durable remission. Targeted therapies with Ruxolitinib against CRLF2-rearrangement for Patient 1 or menin inhibitor against KMT2A-rearrangement for Patient 2 could also be considered. Although both targeted therapies against genomic abnormalities and antigen directed therapies are considered less intensive and better tolerated and may minimize complications of COVID-19 compared to conventional chemotherapy or BMT, neither were likely to induce a durable remission adequate enough to bridge to BMT. In addition, both patients had histories of extensive extramedullary disease that are generally not sufficiently treated by targeted treatments alone.

The two patients in this report are the first described in the literature treated with BMT while still positive for SARS-CoV-2 infection by PCR. Patient 1 passed away due to SOS, a known complication in BMT patients treated with Busulfan. His death did not seem to be related to SARS-CoV-2, but it is unclear if developing MIS-C contributed to his SOS. Treatment for possible MIS-C was planned but was held when the family opted to not escalate care further. Patient 2 developed a febrile hyperinflammatory syndrome consistent with MIS-C, and rapidly improved following IVIG and high dose steroid treatment currently recommended for MIS-C. She remains in remission more than 100 days post-BMT. Our experience demonstrates the importance of considering complications of SARS-CoV-2 infection in patients following BMT. Despite the potential for complications, the benefit of transplant in patients with high risk of relapse who are persistently positive for SARS-CoV-2 by PCR may outweigh the risks involved, but more patient experiences are necessary to determine this. Our limited experience demonstrates that it may be reasonable to proceed to BMT in patients with persistent positive SARS-CoV-2 PCR as long as MIS-C is kept in the differential for fever and other inflammatory complications during the post-BMT period.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Each author contributed equally and independently to the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study as this is a case report.

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How to cite this article: Krajewski J, Chen J, Motiani J, et al. Hematopoietic stem cell transplant in two pediatric patients testing positive for SARS-CoV-2: A case report. *Pediatr Transplant.* 2022;26:e14179. <https://doi.org/10.1111/ptr.14179>