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Case Report

Outcomes of hematopoietic stem cell transplantation in patients with SARS-CoV-2 infection during the Omicron era

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ABSTRACT

Here, we present the outcomes of four patients with COVID-19 who underwent hematopoietic stem cell transplantation (HSCT) at the National Cancer Center in South Korea. Despite concerns about the unfavorable course of COVID-19 in HSCT recipients, none of our patients experienced severe COVID-19. Moreover, extended viral shedding in case 1, lasting over 100 days, was resolved after successful engraftment. Contracting the virus when the host could not mount enough of an immune reaction might result in a paradoxically favorable course. Vaccination, monoclonal antibodies, and antiviral agent usage against COVID-19 might also be effective. We suggest, if necessary, HSCT should not be deferred in COVID-19 patients.

Introduction

During the COVID-19 pandemic, patients with hematologic malignancy have been disproportionately impacted compared to those with a healthy immune system [1–3]. Given the potential asymptomatic infection with SARS-CoV-2, hematopoietic stem cell transplantation (HSCT) in patients with COVID-19 could happen inevitably although usually not intended [4]. This report presents the outcomes of four patients with COVID-19 who underwent HSCT at the National Cancer Center in South Korea during the Omicron era. Patients' characteristics are provided in Table 1.

Case reports

Case 1: A 32-year-old woman diagnosed with acute myeloid leukemia (AML) achieved complete molecular remission after induction and consolidation chemotherapy in 2021. However, in August 2022, the AML relapsed, prompting the re-induction and consolidation chemotherapy in September and November 2022.

From day 9 of consolidation chemotherapy, her absolute neutrophil count (ANC) gradually decreased. On day 17, she developed respiratory symptoms and fever. The reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 was positive, with a cyclic threshold (Ct) value of 19.31 (Supplementary Figure 1). The patient received a 10-day course of remdesivir, and Piperacillin/tazobactam and Caspofungin were also administered for febrile neutropenia.

Despite receiving empirical antibiotics, a chest computed tomography (CT) on day 22 revealed consolidation in the left upper lobe (LUL) and right lower lobe (RLL). Furthermore, the serum galactomannan test yielded a positive result. It raised suspicion of invasive pulmonary aspergillosis, leading to the switch from Caspofungin to Voriconazole. On day 36, with hemoptysis, the chest CT scan showed a worsened condition with a reversed halo sign in the LUL (Supplementary Figure 2). As co-infection with mucormycosis could not be ruled out, the antifungal agent was changed to

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Table 1
Patient clinical characteristics and outcomes.

	Age/Sex	Diagnosis	Comorbidity	Prior Chemotherapies	Conditioning	HSCT type and date	COVID-19 diagnosis date	COVID-19 status during HSCT	COVID-19 treatment	COVID-19 vaccination	Tixagevimab/ cilgavimab usage	Outcome (1-year post transplantation)
Case 1	32/F	R/R AML	Hypothyroidism	DA, HD-Ara-C, FLAG-I + Venetoclax	Myeloablative	AlloSCT (matched unrelated), Feb 16, 2023	Dec 7, 2022	Positive viral activity at D0	Remdesivir for 10 days	None	Oct 17, 2022/Feb 3, 2023	Alive without disease relapse
Case 2	72/F	ND MM	HTN	VRD	High-dose intravenous Melphalan (200 mg/m^2)	AutoSCT, Dec 2, 2022	Dec 2, 2022	Diagnosed at D0	Remdesivir for 5 days	ChAdOx1 1st (April 7, 2021), 2nd(July 2, 2021), BNT162b2 3rd (Nov 26, 2021)	Aug 11, 2022	Alive without disease relapse
Case 3	40/M	R/R/ Ph+ ALL	HTN	Imatinib+VPDL, Dasatinib + MEC, Blinatumomab, Ponatinib + Hyper-CVAD	Myeloablative	AlloSCT (matched sibling), Nov 29, 2022	Dec 4, 2022	Diagnosed at D5	Remdesivir for 3 days	Ad26.COV2.S (June 16, 2021)	Aug 9, 2022	Died on Dec 5, 2023 due to TA-TMA
Case 4	44/M	R/R Ph− ALL	None	VPDL, Blinatumomab, Blinatumomab + hyperCVAD	Myeloablative	AlloSCT (matched sibling), Dec 26, 2022	Jan 2, 2023	Diagnosed at D7	Remdesivir for 3 days	BNT162b2 1st (Sep 14, 2021), 2nd(Oct 19, 2021), 3rd (Feb 17, 2022)	None	Ph− ALL relapse after HSCT and hospice care on April 14, 2023

AML, acute myeloid leukemia; AlloSCT, allogeneic hematopoietic stem cell transplantation; AutoSCT, autologous hematopoietic stem cell transplantation; DA, Daunorubicin/Cytarabine; FLAG-I, Fludarabine, Cytarabine, Granulocyte-colony stimulating factor, and Idarubicin; HD-Ara-C, high-dose Cytarabine; HTN, hypertension; HSCT, hematopoietic stem cell transplantation; HyperCVAD, Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone; MEC, Mitoxantrone, Etoposide, Cytarabine; MM, multiple myeloma; ND, newly diagnosed; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; Ph− ALL, Philadelphia chromosome-negative acute lymphoblastic leukemia; R/R, relapsed and refractory; TA-TMA, transplantation-associated thrombotic microangiopathy; VRD, Bortezomib, Lenalidomide, and Dexamethasone; VPDL, Vincristine, Prednisolone, Daunorubicin, L-asparaginase.

high-dose liposomal amphotericin B (5 mg/kg/day). Notably, even at this stage, the SARS-CoV-2 RT-PCR yielded a positive result (Ct = 14.92). After 7 days of liposomal amphotericin B administration, the extent of pneumonia decreased for the first time, and the patient clinically improved. On day 47 of consolidation, ANC reached 1,116 cells/μl.

Considering the relapse of leukemia, HSCT was deemed necessary in a timely manner. However, the presence of extensive pneumonia and prolonged shedding of SARS-CoV-2 posed challenges to the transplantation process. A multidisciplinary team including a cardiothoracic surgeon, infectious disease specialist, and hematologist concluded that the potential benefits of surgical resection of the affected pulmonary lesions outweighed the risks. Consequently, on day 57 of consolidation, the patient underwent LUL segmentectomy and RLL wedge resection without postoperative complications. The analysis of the left lung section revealed vascular invasion with fungal hyphae in LUL, consistent with pulmonary mucormycosis, while the right lung section revealed aspergillosis in RLL (Supplementary Figure 2). Subsequently, liposomal amphotericin B was replaced with posaconazole.

In February 2023, the conditioning for HSCT commenced. However, because the patient remained positive for SARS-CoV-2 molecular testing, and the viral culture demonstrated viable viruses, she could not be placed in the positive-pressure transplantation unit. Instead, she was accommodated in a negative-pressure isolation room with an anteroom. The infusion of donor stem cells took place on February 16, 2023, and the transplantation was successfully completed without any COVID-19-related events. As the patient's cytopenia gradually improved, the Ct values of SARS-CoV-2 RT-PCR began to rise and eventually reached an undetected level in March 2023. As of February 16, 2024, which marked 1 year post-transplantation, the patient remained alive without complications.

Case 2: A 72-year-old woman diagnosed with multiple myeloma in 2022 achieved a stringent complete response after induction chemotherapy. She was admitted to the transplantation unit in November 2022, after a negative SARS-CoV-2 RT-PCR result. After conditioning chemotherapy, autologous stem cells were infused. Following infusion, she developed a cough and rhinorrhea, with a positive SARS-CoV-2 RT-PCR result (Ct = 16.71).

She was isolated in a negative-pressure room with an anteroom. Despite temporary desaturation necessitating 2 l/min of oxygen, chest radiography showed no pneumonia. She received remdesivir for 5 days, after which supplemental oxygen was no longer needed. The nadir period of ANC was lasted for 5 days. Despite cytopenia, she did not present worsened respiratory symptoms and was discharged soon. The patient was still alive 1 year post-transplantation.

Case 3: A 40-year-old man was diagnosed with Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia (ALL) in 2021. He failed to achieve remission after three induction chemotherapy phases but reached complete morphologic remission after fourth-line treatment.

Given his young age and recurrent relapses, an immediate allogeneic HSCT from a matched sibling donor was planned. Before the transplantation, SARS-CoV-2 RT-PCR tested negative. Following the conditioning, stem cells were infused on November 29, 2022. Five days post-infusion, he presented fever, cough, and sputum with an ANC below 100 cells/μl, but chest radiography showed no abnormalities. A positive SARS-CoV-2 RT-PCR test (Ct = 21.02) led him to negative-pressure isolation. Treatment for febrile neutropenia with Piperacillin/tazobactam and a 3-day course of remdesivir was initiated. His cytopenia resolved by the 14th day post-infusion, without developing pneumonia. The patient remained COVID-19 issue-free until ALL relapsed in May 2023.

Case 4: A 44-year-old man was diagnosed with Philadelphia chromosome-negative ALL in 2022. He did not achieve remission after the induction chemotherapies. Then the salvage chemotherapy was planned with Blinatumomab and hyper cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) and successfully resulted in complete molecular remission.

Considering disease relapse, an immediate allogeneic HSCT with a matched sibling donor was planned. Before the transplantation, SARS-CoV-2 RT-PCR results were negative. During the conditioning, the patient presented with febrile neutropenia and was treated with Piperacillin/tazobactam empirically, and the fever subsided. Stem cells were infused on December 26, 2022.

Seven days later, he developed a fever, cough, and rhinorrhea. SARS-CoV-2 RT-PCR tested positive (Ct = 16.50), and the patient was transferred to the negative-pressure isolation room. Although he was in a state of neutropenia, the chest radiograph did not show abnormalities. Remdesivir was administered for 3 days, and ANC recovered by day 14 of infusion. He did not suffer from COVID-19-related issues but later experienced seizures due to leptomeningeal seeding.

Discussion

This report describes four COVID-19 cases among HSCT recipients at our institution between January 2022 and January 2023, a period dominated by the Omicron variant [5]. By January 2024, two patients had favorable outcomes, while the others suffered a relapse. Notably, none developed severe COVID-19 during transplantation. In case 1, extended viral shedding lasting over 100 days, which was known as one of the risk factors of invasive fungal infections [6], finally resolved post-engraftment.

Several studies indicate higher mortality rates in HSCT recipients with SARS-CoV-2 infection compared to the general population, both in the pre-Omicron and Omicron periods [2,7–9]. Those patients received HSCT several months before SARS-CoV-2 infection, after immune reconstitution. Conversely, our patients were infected during cytopenia, and experienced a milder COVID-19 progression, possibly due to the inability to mount a severe immune reaction [10–13].

Our hospital implemented strict infection control measures, such as requiring negative SARS-CoV-2 RT-PCR results before admitting patients to the transplantation unit. Despite these precautions, three patients developed COVID-19 post-admission, possibly due to being in the incubation period or nosocomial transmission. Prompt isolation in negative-pressure rooms prevented secondary transmission [14].

Although the number of patients is small, it might enlighten that HSCT could be considered as one of the critical treatment options even in patients with active COVID-19 under meticulous infection control and multidisciplinary collaboration. The British Society of Blood and Marrow Transplantation and Cellular Therapy recommends careful risk-benefit assessment for HSCT in COVID-19 patients. If deemed necessary, the procedure should not be deferred [15].

Declarations of competing interest

The authors have no competing interest to declare.

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Ethical approval

This study was granted a waiver of review by the Institutional Review Board (IRB) at the National Cancer Center (IRB number NCC2024-0040).

Author contributions

WJC, JYC, and EL wrote the manuscript. JJ, HL, YJC, HSE, JYC, JHC, and EL treated the patients. JL, KC, and KDM contributed to the infection control. JHC performed the pulmonary resection surgery. NH conducted pathological examinations on specimens from the pulmonary resection surgery. JY Choi performed the viable cell culture with the patient's nasopharyngeal swab sample. All authors read and agreed to the final version of the manuscript.

Availability of data and materials

Individual patient data will be shared upon reasonable request to the corresponding author. For original data, contact eunyounglee@ncc.re.kr.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107207.

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