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## Brief Article

## Hematopoietic Cell Transplantation is Feasible in Patients with Prior COVID-19 Infection



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## A B S T R A C T

There are limited data on outcomes of patients with prior Coronavirus disease 2019 (COVID-19) who proceeded to autologous or allogeneic hematopoietic cell transplantation (HCT). Whether these patients are more susceptible to poor outcomes and recurrence of COVID-19 is unknown. We report a retrospective analysis of outcomes of 15 consecutive patients with hematologic malignancies who experienced COVID-19 and subsequently underwent autologous (n = 8) or allogeneic (n = 7) HCT between June 17, 2020, and February 17, 2021. The cohort included patients with asymptomatic past infections or symptomatic COVID-19 disease. Data were obtained from chart review.

Descriptive statistics were used to summarize patient characteristics. Among eight patients who underwent autologous HCT, four had a diagnosis of multiple myeloma and four had a diagnosis of non-Hodgkin's lymphoma. Four of these eight patients did not test positive for anti-SARS-CoV-2 IgG antibody at any point during the course of treatment. The other four patients had detectable anti-SARS-CoV-2 IgG antibodies before undergoing autologous HCT, but only two of these patients remained anti-SARS-CoV-2 IgG antibody-positive at their last follow-up. One patient died from progression of disease. Seven patients with prior COVID-19 underwent allogeneic HCT for acute lymphoblastic leukemia (n = 3), acute myelogenous leukemia (n = 1), chronic myelogenous leukemia in lymphoid blast crisis (n = 1), myelodysplastic syndrome (n = 1), or myelofibrosis (n = 1). Three of the seven patients tested positive for anti-SARS-CoV-2 IgG antibodies following the initial COVID-19 diagnosis; however, only one of these patients retained anti-SARS-CoV-2 IgG antibody following allogeneic HCT. One patient died of infection (fungal and *Pneumocystis jirovecii* pneumonia) occurring in the context of ongoing treatment for graft-versus-host disease. None of the 15 patients had recurrent COVID-19 infection. Based on our experience, autologous and allogeneic HCT can be safely performed in selected patients with previous COVID-19 infection.

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## INTRODUCTION

Patients with hematologic malignancies are at high risk for severe Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), due to an immunocompromised state from their disease or treatment [1]. There are limited data on outcomes of patients

with prior COVID-19 who proceed to autologous or allogeneic hematopoietic cell transplantation (HCT) and specifically whether such patients are more susceptible to poor outcomes and recurrence of COVID-19 [2,3]. Here we report a retrospective analysis of outcomes of 15 consecutive patients with hematologic malignancies who experienced COVID-19 and subsequently underwent autologous (n = 8) or allogeneic (n = 7) HCT during the COVID-19 pandemic.

## METHODS

Data on patients with hematologic malignancies who experienced COVID-19 and subsequently underwent HCT were obtained through

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**Table 1**  
Patient and Transplantation Characteristics

Patient	Gender	Age	Diagnosis	Days between COVID-19 diagnosis and HCT	Pre-HCT DLCO (Hgb-adjusted, % predicted)	Pre-HCT FEV1 (% predicted)	HCT-CI	Donor	Conditioning Regimen	GVHD prophylaxis	Cause of Death
1	M	55	ALL	328	57	81	3	HLA-MMUD	FLU/MEL	PT CY/TAC/MMF	
2	F	63.2	MM	258	77		1	Auto	MEL		
3	M	67.5	MF	305	99	117	1	HLA-haploidentical related	FLU/BU	PT CY/TAC/MMF	
4	F	52.8	AML	215	84	111	2	HLA-MUD	BU/FLU/MEL/rATG	CD34+ Cell Selection	
5	M	45.1	ALL	225	80	93	2	HLA-MRD	CY/FLU/THIO/TBI	TAC/MTX	
6	M	37.1	CML in blast crisis	210	79	117	2	HLA-MUD	CLO/MEL/THIO/rATG	CD34+ Cell Selection	
7	F	49	MM	203	85	98	0	Auto	MEL		
8	M	57.4	DLBCL	193	66	92	3	Auto	BEAM		
9	M	54.8	POEMS	186	67	89	2	Auto	MEL		
10	M	38.9	AITL	162	108	112	2	Auto	BU/CY/THIO		
11	F	71.6	MM	130	37	86	4	Auto	MEL		Disease progression
12	M	61.6	TCR-BCL	105	102	117	0	Auto	BEAM		
13	M	67.7	PTCL	44	74	95	2	Auto	BEAM		
14	F	37.8	ALL	42	86	95	1	HLA-MRD	CLO/MEL/THIO/rATG	CD34+ Cell Selection	
15	F	70.6	MDS	55	83	129	1	HLA-haploidentical related	CY/FLU/TBI	PT-CY/TAC/MMF	PJP/fungal pneumonia

DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in the first second; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; M, male; F, female; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; MF, myelofibrosis; CML, chronic myelogenous leukemia; DLBCL, diffuse large B cell lymphoma; POEM, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; AITL, angioimmunoblastic T cell lymphoma; TCR-B CL, T cell-rich B cell lymphoma; PTCL, peripheral T cell lymphoma; MDS, myelodysplastic syndrome; MMUD, HLA-mismatched unrelated donor; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; FLU, fludarabine; MEL, melphalan; BU, busulfan; rATG, rabbit antithymocyte globulin (2.5 mg/kg/day for 2 days); CY, cyclophosphamide; THIO, thiotepa; CLO, clofarabine; BEAM, carmustine, etoposide, cytarabine, and melphalan; TBI, total body irradiation; MMF, mycophenolate mofetil; PJP, *Pneumocystis jirovecii* pneumonia

retrospective chart review. Any patient with prior hematologic malignancy who was treated at Memorial Sloan Kettering Cancer Center for their autologous or allogeneic HCT and had a prior COVID-19 infection was included in our study. The cohort included patients with past asymptomatic infections and symptomatic COVID-19 disease.

Standard eligibility criteria based on organ function and pretransplantation performance status were applied. These criteria have not changed substantially during the study period. Data on demographic and disease characteristics, organ function, previous treatment of COVID-19, peritransplantation clinical course, and specific transplantation-related information were collected.

Relapse was defined as clinical, radiologic-, or biopsy-proven evidence of disease after a period of remission from the disease. The International Bone Marrow Transplant Registry classification was followed when grading acute graft-versus-host disease (GVHD), except grades A to D were labeled grades I to IV. Graft-versus-host disease with purely acute features was graded accordingly, even if it occurred after day +100 [4]. Grading was reviewed by a transplantation clinician panel to reach consensus on the maximum grade of GVHD.

Routine surveillance testing for SARS-CoV-2 was not performed after admission for HCT. Symptom-based testing was performed with guidance from infectious disease experts. For anti-SARS-CoV-2 IgG antibody testing, the Abbott Architect SARS-CoV-2 IgG assay (Abbott, Abbott Park, IL) was used to detect serum IgG antibodies directed against the nucleocapsid protein of SARS-CoV-2 in routine clinical practice.

Descriptive statistics were used to summarize patient characteristics. The time from diagnosis of COVID-19 to HCT and time from HCT to last follow-up were calculated for each patient and graphically charted.

Patients received care in private rooms, in accordance with standard practice at our institution. All patients received supportive care and prophylaxis against opportunistic infections according to standard guidelines [5,6]. Patients conditioned with busulfan received seizure prophylaxis with levetiracetam. All patients received cryopreserved peripheral blood stem cell grafts. Granulocyte colony-stimulating factor was given beginning on day +7 post-transplantation and continued until an absolute neutrophil count of  $2 \times 10^9/L$  was measured for 3 consecutive days.

## RESULTS

Fifteen patients with hematologic malignancies and prior COVID-19 infection underwent HCT. Of these, eight patients

underwent autologous HCT and seven patients underwent allogeneic HCT. Patient demographic data and transplantation characteristics are summarized in Table 1. Baseline blood cell counts on admission and ferritin levels (when assessed within 30 days before HCT) are outlined in Supplementary Table S1. At the time of admission, all patients tested negative for SARS-CoV-2 by PCR. Patients meeting the study definition underwent HCT between June 17, 2020, and February 17, 2021, at the Adult Bone Marrow Transplant Service of Memorial Sloan Kettering Cancer Center. During this period, COVID-19 vaccination was not widely available or recommended, therefore none of the 15 patients included in this analysis received COVID-19 vaccination before undergoing HCT.

Among eight patients who underwent autologous HCT, the median age was 60 years (range, 39 to 72 years), and the median time between diagnosis of COVID-19 and autologous HCT was 174 days (range, 44 to 258 days). Four patients had multiple myeloma (MM) and received conditioning with single-dose melphalan (3 with 200 mg/m<sup>2</sup> and 1 with 140 mg/m<sup>2</sup>). The other four patients had non-Hodgkin lymphoma (NHL) and received conditioning with BEAM (carmustine, etoposide, cytarabine, and melphalan; n = 3) or TBC (thiotepa, busulfan, and cyclophosphamide; n = 1). Before undergoing autologous HCT, four of the eight patients were incidentally diagnosed on routine SARS-CoV-2 PCR screening. The other four patients presented with symptoms of COVID-19, prompting SARS-CoV-2 PCR testing and hospital admission; symptoms included fever, dry cough, and shortness of breath. Two patients required supplemental O<sub>2</sub> by nasal cannula. One patient required intensive care unit (ICU) admission and mechanical ventilation. All four hospitalized patients received treatment with azithromycin and hydroxychloroquine. The

patient requiring ICU admission and mechanical ventilation also received methylprednisolone and 1 dose of tocilizumab.

Pre-HCT pulmonary function testing (PFT) showed a diffusion capacity of the lung for CO (DLCO; hemoglobin-adjusted) of <65% in 1 patient, between 66% and 80% in 4 patients, and >80% in 3 patients. Pretransplantation lung imaging for five patients showed abnormalities, including ground glass opacities (n = 2), scattered pulmonary nodules (n = 2), and atelectasis (n = 3). None of the patients required supplemental O<sub>2</sub> at the time of HCT admission. One patient with MM had history of deep venous thrombosis (DVT) that preceded the diagnosis of COVID-19. This patient developed recurrent DVT at a different site in the early post-transplantation period. There were no other thromboembolic events in this cohort.

All eight patients engrafted. The median time to neutrophil engraftment was 10 days (range, 9 to 12 days), and the median time to platelet engraftment was 12 days (range, 10 to 15 days). In the early post-transplantation period, two patients (one with MM and one with NHL) developed engraftment syndrome and were treated with dexamethasone in accordance with standard clinical practice.

Four of the eight patients (2 with MM and 2 with NHL) did not test positive for anti-SARS-CoV-2 IgG antibody at any point during their course. The other four patients had detectable anti-SARS-CoV-2 IgG antibodies prior to undergoing autologous HCT; two of these patients remained anti-SARS-CoV-2 IgG antibody-positive on post-transplantation days +141 and +171 (Figure 1).

During their post-transplantation course, none of the eight patients developed COVID-19 reinfection or any complications attributable to prior COVID-19. One patient with MM died of disease progression on post-transplantation day +150.

Seven patients with prior COVID-19 underwent allogeneic HCT for acute lymphoblastic leukemia (ALL; n = 3), acute myelogenous leukemia (AML; n = 1), chronic myelogenous leukemia (CML) in lymphoid blast crisis (n = 1), myelodysplastic syndrome (MDS; n = 1), or myelofibrosis (n = 1). The median time between diagnosis of COVID-19 and allogeneic HCT was 215 days (range, 42 to 328 days). The median patient age was 53 years (range, 37 to 71 years). Conditioning regimens were myeloablative (n = 3), reduced intensity (n = 3), and nonmyeloablative (n = 1). Donors were HLA-identical related (n = 2), HLA-matched unrelated (n = 2), HLA-haploidentical related (n = 2), and HLA-mismatched unrelated (n = 1). The graft source was granulocyte colony-stimulating factor-mobilized peripheral blood stem cells in all seven patients. GVHD prophylaxis was CD34<sup>+</sup> cell selection in three patients; post-transplantation cyclophosphamide, tacrolimus, and mycophenolate mofetil in three patients; and tacrolimus/mini-dose methotrexate in one patient.

There are limited data on the pre-HCT COVID-19 course for two patients who were diagnosed and treated for COVID-19 at outside institutions. Six patients presented with symptoms prompting evaluation for COVID-19, with no data on one patient's presentation. Symptoms included fever, cough, sore throat, and shortness of breath. Five patients required

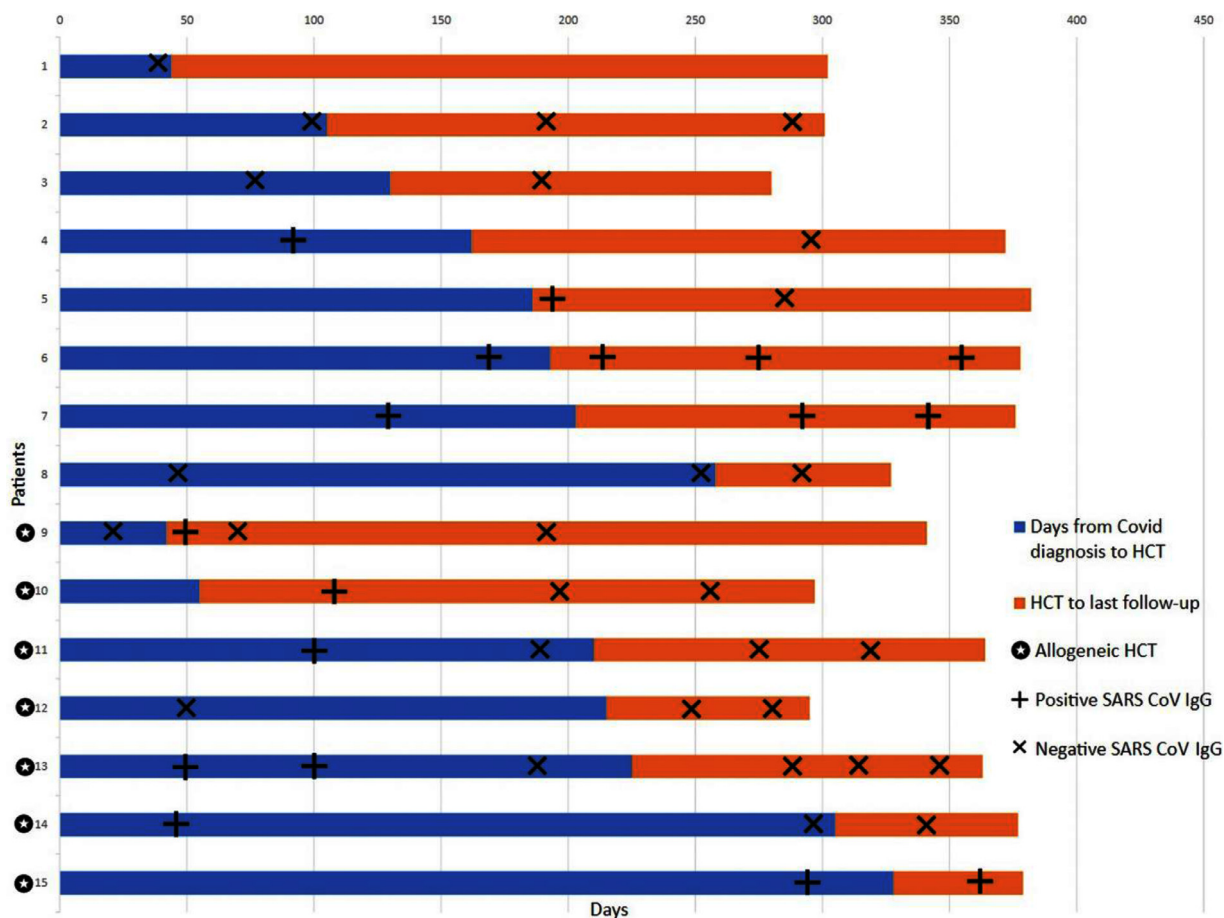


Figure 1. SARS-CoV-2 IgG antibody seroconversion among HCT recipients. The order of patients is the same as in Table 1.

hospitalization for COVID-19, with one patient requiring supplemental O<sub>2</sub> by nasal cannula and one patient requiring ICU admission and mechanical ventilation. Hospitalized patients were treated with azithromycin (n = 2), hydroxychloroquine (n = 1), remdesivir (n = 1), methylprednisolone (n = 1), anakinra on a clinical trial (n = 1), and convalescent plasma (n = 1).

Pre-HCT PFT showed a hemoglobin-adjusted DLCO of < 65% in one patient, between 66% and 80% in two patients, and >80% in four patients. Pretransplantation lung imaging showed nearly resolved previously seen patchy ground glass opacities (n = 2), stable interstitial thickening and bronchiectasis when compared to previous studies (n = 1) or unremarkable findings (n = 4). None of the patients required O<sub>2</sub> supplementation at the time of allogeneic HCT. None of the allotransplant recipients had prior history of thromboembolic events, developed DVT or pulmonary embolism in the first 100 days post-transplantation.

All seven patients engrafted. The median time to neutrophil engraftment was 12 days (range, 10 to 26 days), and the median time to platelet engraftment was 12 days (range, 11 to 34 days). None of the allogeneic HCT recipients developed engraftment syndrome.

Three of the seven patients tested positive for anti-SARS-CoV-2 IgG antibodies following the initial COVID-19 diagnosis; however, only one of these patients retained anti-SARS-CoV-2 IgG antibody on day +37 after allogeneic HCT (Figure 1).

Like patients who underwent autologous HCT, none of the allogeneic HCT recipients developed reinfection with COVID-19. Four patients required transient supplemental O<sub>2</sub> early post-transplantation for another reason, such as fluid overload. Two patients developed grade II acute GVHD, and one patient developed grade III acute GVHD. One patient died of infections (fungal and *Pneumocystis jirovecii* pneumonia) occurring in the context of ongoing treatment for GVHD, and the other 6 allogeneic HCT recipients were alive with no evidence of disease relapse at the time of this analysis.

## DISCUSSION

Our study adds to growing body of knowledge regarding COVID-19 and its impact on clinical outcomes of a distinctly vulnerable clinical population of HCT recipients. We previously showed that the COVID-19 pandemic caused substantial delays in HCT, that these delays resulted in inferior outcomes in a selected group of patients, and that patients who developed COVID-19 after HCT had varied clinical outcomes [7–9]. In our present cohort of patients with previous COVID-19 infections autologous and allogeneic HCTs were feasible and safe; no recurrent COVID-19 infection was observed.

We also found persistent COVID-19 infection in immunocompromised patients, highlighting the potential risk of proceeding to HCT [10]. Our analysis supports proceeding with planned autologous or allogeneic HCT in patients who have recovered from COVID-19. Cohorting of patients beyond standard HCT algorithms or surveillance testing is not supported by our findings, as patients did not have reactivation or recurrence of COVID-19. The patients in this series developed COVID-19 infection early in the pandemic, and their treatment reflects the therapies available at that time. Given the low prevalence of SARS-CoV-2 in the community at the time of this study, routine surveillance testing for SARS-CoV-2 was not performed after admission for transplantation. Symptom-based testing was performed with guidance from infectious disease experts.

Limitations of the present study are its retrospective nature, small sample size, a relatively short follow-up period,

and potentially a selection bias, given that patients with more severe complications after COVID-19 infection were not considered appropriate candidates for HCT. There also may have been a referral bias in which patients who had significant complications from COVID-19 were not referred to the transplantation program. Although patients in this cohort did well after HCT, the median interval from diagnosis of COVID-19 to HCT was long, and patients with recent SARS-CoV-2 infection in need of urgent HCT should be evaluated on a case-by-case basis to optimize outcomes.

Furthermore, all the patients in this cohort had COVID-19 infections between June 17, 2020, and February 17, 2021, before the emergence of SARS-CoV-2 variants that are currently present in most areas in the United States. Based on clinical reports, the currently prevalent variant is more contagious and appears to carry higher rates of morbidity and mortality. This may have an impact on the applicability of some of our findings to patients who develop COVID-19 infection with a variant before undergoing HCT.

Our observation that the majority of patients with prior COVID-19 infection undergoing autologous or allogeneic HCT did not maintain durable antibody response is an important consideration in the post-transplantation care and vaccination strategies in this vulnerable patient population.

Based on our data, autologous and allogeneic HCT can be safely performed in patients with previous COVID-19 infection. All patients in our cohort had a negative SARS-CoV-2 PCR result immediately before undergoing HCT. In addition, all patients had stable or near-complete resolution of radiographic changes associated with COVID-19 and preserved or recovered lung function, as determined by PFT. The dynamics of improvement in symptoms, negative nasopharyngeal swab for SARS-CoV-2 by PCR testing, imaging, and PFT provide objective measures for determining optimal timing of HCT in patients with prior COVID-19 infection.

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Kite Pharma, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros, Takeda, VectivBio, and Vor Bio-pharma; has served on DSMBs for Cidara Therapeutics, Medigene, Sellas Life Sciences, and Servier and on a scientific advisory board for NexImmune; has ownership interests in NexImmune and Omeros; has received research support for clinical trials from Incyte, Kite Pharma, Miltenyi Biotec, and Novartis; and serves in a volunteer capacity as a member of the Board of Directors of the American Society for Transplantation and Cellular Therapy and Be The Match (National Marrow Donor Program), as well as on the CIBMTR Cellular Immunotherapy Data Resource Executive Committee. G.L.S. has received research funding from Amgen and Janssen. B.G. has received research funds for clinical trials from Actinium. The other authors have no conflicts of interest to disclose.

#### SUPPLEMENTARY MATERIALS

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