LETTER

The outcome of hematopoietic stem cell transplantation patients with COVID-19 infection

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To the Editor:

Data concerning the impact of COVID-19 on hematopoietic stem cell transplant (HSCT) patients are scarce and variable. It is thought that HSCT patients may be at higher risk of COVID-19-associated complications secondary to immunosuppressive therapy, and the subsequent delayed immune reconstitution at the post-transplant phase [1].

In this report, we describe the clinical course of seven stem cell transplant recipients at the Nasser's Institute for Research and Treatment Hospital who survived a diagnosis of COVID-19. Patients were identified as being SARS-CoV-2 positive by real-time polymerase chain reaction. Nasopharyngeal swabs were performed in the context of symptoms (fever, cough, dyspnea, and fatigue), radiological findings, or contact with a documented SARS-CoV-2 positive individual. The median age of patients was 30 years (range, 3–43 years), two patients (28%) were females and five (72%) were males, and the median time from stem cell infusion to the diagnosis of COVID-19 was 8 months (range, 3–113 months).

All patients received allogeneic stem cell transplantation (allo-SCT) from human leukocyte antigen (HLA) 10/10-matched related donors. All patients received myeloablative conditioning regimens. Four patients (66%) received post-transplant cyclophosphamide (PTCy), and one patient received antithymocyte globulin rabbit for primary graft-versus-host disease (GvHD) prophylaxis. None of our patients had a relapse at the point of being diagnosed with a

COVID-19 infection. All patients were receiving immunosuppressant therapy at diagnosis, with a stable graft function before COVID-19 positivity. Immunosuppressants were continued after the diagnosis of COVID-19 was confirmed. All patients not previously receiving corticosteroids were given prednisone at a dose of 0.5 mg/kg/day PO for 10 days (0.4 mg/kg/day methylprednisolone equivalent), azithromycin 500 mg/day PO for 6 days (10 mg/kg/day for pediatrics), voriconazole 200 mg PO q12h for 1 month (7 mg/kg/dose q12h PO for pediatrics), and high-dose cotrimoxazole for PCP coverage (15 mg/kg/day trimethoprim PO for 2 weeks). Adult patients were given rivaroxaban 20 mg/day PO according to their platelet counts for one month.

All patients were lymphopenic with a median absolute lymphocyte count of $0.76 \times 10^9/L$ (range, 0.31 – $0.97 \times 10^9/L$). The median platelet count was $115 \times 10^9/L$ (range, 80 – $230 \times 10^9/L$) at the diagnosis of COVID-19. Only one patient (14%) had acute grade II GvHD of the skin and gut (overall grade II per Glucksberg criteria) and was receiving prednisone (2 mg/kg/day PO) and mycophenolate. Two patients had chronic GvHD of the skin and liver; one patient was receiving prednisone 1 mg/kg/day PO, while the other patient was receiving cyclosporine, mycophenolate, and prednisone (0.5 mg/kg/day PO). Except for systemic corticosteroids, none of our patients received specific treatment for COVID-19. Patients' characteristics and their outcome are summarized in Table 1.

Regarding COVID-19 symptoms, four patients (57%) experienced mild lower respiratory tract symptoms, three (43%) experienced high-grade fever, and all of them had chest infiltrates on both chest radiographs and computed tomography scans. The median follow-up was 82 days (range, 77–112) from the onset of COVID-19.

Our observations are inconsistent with those reported by Kanellopoulos et al., where they reported a mortality rate of 43%. However, their patients' characteristics were different. The median age in their patient population was 61 years, half of the allo-SCT were HLA 10/10-matched unrelated donor transplants, two (34%) had a haploidentical

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Table 1 Patients' baseline characteristics and outcome.

Patient	Age (years)	Diagnosis	Gender	Conditioning	Months	Status	GvHD	IS	Plt ($\times 10^9/L$)	Lymph ($\times 10^9/L$)	CT-scan findings	Clinical course	Outcome	Follow-up (days)
Patient 1	5	Shwachman–Diamond	Female	Bu/Cy/PTCy	10	CC	None	MMF, CS	112	0.95	GGO, unifocal, inferior lobe of right lung	Mild (cough, low-grade fever, symptoms improved after 5 day)	Survived	112
Patient 2	22	T-ALL (CR-3)	Male	TBI/Cy	24	CR	Chronic (skin and lung)	CS	210	1.1	GGO, multifocal, bilateral	Severe (cough, dyspnea and high-grade fever. The patient was admitted to ward and received oxygen (7 L/min) for SaO ₂ of 80% and IV fluids for vomiting and diarrhea, patient symptoms improved within 9 days and became oxygen independent)	Survived	81
Patient 3	43	AML (CR-2)	Male	Flu/Bu/PTCy	6	CR	None	CSA	230	0.4	Subpleuritic left lung nodule with basal GGO	Mild (cough, fatigue, symptoms improved after 7 days)	Survived	79
Patient 4	38	AML	Female	Flu/Bu/PTCy	8	CR	None	CSA, CS	145	0.7	GGO, multifocal subpleuritic small nodules	Mild (cough, fatigue, symptoms improved after 8 days)	Survived	84
Patient 5	30	B-ALL (ph+)	Male	TBI/Cy	113	CR	Chronic (liver)	CSA, MMF, CS	115	0.5	GGO, multifocal, bilateral, subpleural bands	Moderate (cough, high-grade fever (39 °C, myalgia, anosmia and arthralgia. Symptoms improved within 8 days)	Survived	89
Patient 6	3	BTM	Male	Bu/Cy/ATG	8	CC	Acute (skin and gut)	CS, MMF	80	0.3	GGO, multifocal, bilateral	Severe (Cough, dyspnea and tachypnea. The patient was admitted to ward and received oxygen (5 L/min) for SaO ₂ of 86%, patient symptoms improved and patient was discharged after 15 days)	Survived	82
Patient 7	30	SAA	Male	Flu/Cy/PTCy	3	CC	None	CSA, CS	96	0.7	GGO, unifocal, inferior lobe of right lung	Mild (cough, myalgia, sore throat, and anosmia, symptoms improved after 7 days)	Survived	77

AML Acute Myeloid Leukemia, *ALL* Acute Lymphoblastic Leukemia, *ATG* Antithymocyte Globulin, *BTM* Beta-Thalassemia Major, *Bu* Busulfan, *CC* Complete Chimeraism, *CR* Complete Remission, *CS* Corticosteroid, *CSA* Cyclosporine A, *Cy* Cyclophosphamide, *Flu* Fludarabine, *GGO* Ground-Glass Opacity, *GvHD* Graft-versus-Host Disease, *IS* Immunosuppressant, *Lymph* absolute lymphocyte count, *MMF* Mycophenolate Mofetil, *Months* Months from stem cell infusion to COVID-19 diagnosis, *Plt* Platelet count at diagnosis, *PTCy* Post-transplantation cyclophosphamide, *Ph+* Philadelphia chromosome-positive, *SAA* Severe Aplastic Anemia, *TBI* Total Body Irradiation.

transplant, one (16%) had an HLA 9/10-matched unrelated donor transplant, and no patient received a myeloablative allo-SCT. Of note, out of the three patients who received PTCy, only one patient (64 years) died due to CNS bleeding secondary to AML relapse [2].

Our observations also differ from those reported by Malard et al. from the hematology department of Saint Antoine hospital in Paris, where they reported 52% of their patients developed ARDS and a 1-month mortality rate of 40%. Remarkably, only one out of three patients who received cyclophosphamide-based regimens died. Half of their patients were older than 65 years of age, and all patients who died were older than 65 years. This suggests that COVID-19 mortality risk factors in HSCT patients may be similar to those in the general population [3].

We propose a few remarks for consideration. First, despite receiving myeloablative conditioning regimens, we had no mortality among our patients secondary to COVID-19. Second, we observed that all patients who received PTCy for GvHD prophylaxis experienced mild COVID-19 symptoms. Cytokine release syndrome (CRS) that is frequently associated with haploidentical HSCT and mitigated by PTCy shares similar pathophysiology with severe COVID-19-associated CRS [4, 5]. We hypothesize that PTCy might have a protective role against COVID-19-associated CRS.

We recommend controlled studies with a greater number of patients and longer follow up periods—with special attention to the impact of cyclophosphamide on COVID-19

outcome—to reach a definite conclusion concerning the outcome of COVID-19 in HSCT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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