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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplemental data.

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COVID-19 in bone marrow transplant recipients: reflecting on a single centre experience

Coronavirus disease 2019 (COVID-19) is caused by the novel SARS-CoV-2 virus and has been declared a pandemic on the 9th of March by the WHO. A hallmark of COVID-19 management is supportive care and there is still no convincing evidence for a treatment which will reduce mortality. Severe COVID-19-associated sepsis characterized by acute respiratory distress syndrome (ARDS), secondary bacterial pneumonias, thrombotic complications, myocarditis, and gastrointestinal involvement are more prevalent in those with comorbidities such as hypertension, diabetes, cardiac disease, cancer and age >70 years.[1,2] There is a paucity of data on COVID-19's impact on bone marrow transplant patients. Herein we reflect on the course of seven bone marrow transplant recipients in Birmingham Heartlands Hospital who have been found positive for SARS-CoV-2 RNA on real time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs done in the context of symptoms (fever, cough, dyspnoea, and fatigue) or inpatient contact. The median age was 61 years (range 40–74). Out of these, five (71%) were female and two (29%) were male. The median time from stem cell infusion to the diagnosis of SARS-CoV-2 virus was 61 days (range 7–343). Patients were screened for SARS-CoV-2 via an RT-PCR-based technique.

Table I. Patient clinical characteristics and outcome.

	Age	Sex	Comor	Dx	HCT-CI	Date of HSCT	Type of allo-SCT	Condit	Day	Symptom/Source Of infection	Disease status at COVID	GvHD	Immunosuppression	Outcome
Patient 1	64	F		AML	0	7/2/20	HLA 9/10 Non-MAC MUD	Flu/Cy/TBI with post Cy	+61	Mild Fever only/Self-isolating Contact from Clinic visits?	AML 80% Donor	Nil	Tacrol/MMF	Died of CNS bleeding Due to AML relapse
Patient 2	74	F		AML	0	5/7/19	HLA 10/10 RIC MUD	FMA	+287	Fever/Shielding but Frequent Day Unit Sessions	AML 27% Donor	Nil	Azacytidine	Alive
Patient 3	59	F	BMI> 35 Depression Asthma	MDS	5	6/3/20	Haplo-SCT Non-MAC	Flu/Cy/TBI/ PTCy	+55	LRTI/Very likely inpatient contact	CR	Nil	Tacrol	Alive Active Case for 21 days 0n O2 2lt
Patient 4	57	F	Brain Abscess, Severe Neuropathy PS 4	B-ALL	4	16/5/19	Haplo-SCT Non-MAC	Flu/Cy/TBI/ PTCy	+343	Fever/Inpatient with certainty (contact tracing)	CR	Gut Upper GI tract GvHD Mild but present	Prredn 5mg od	Alive
Patient 5	64	M	HTN, DM, subdural hemat BM> 35	AML	6	30/3/20	HLA 10/10 Non-MACMUD	Flu/Cy/TBI/ PTCy	+6	Fever/Inpatient with certainty as negative pre-admission	CR		Tacrol MMF	Alive
Patient 6	71	F		MF	3	19/7/19	HLA-10/10 RIC MUD	Bu2/Flu/A	+274	LRTI/Inpatient with certainty	CR	Grade IV Gut and liver GvHD SR	Methylpre infliximab	Death 13 days From COVID dx
Patient 7	40	M		NLPHL	0	10/1/20	Autograft	BEAM	+98	LRTI/Not clear source but was attending Day Unit for Platelets frequently	CR	N/A		Death 17 days from COVID dx

Comor, Comorbidities; Dx, Diagnosis; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; T, Type of BMT; Condit, Conditioning Regimen; Day, Days from stem cell infusion to COVID-19 diagnosis; RIC, Reduced Intensity Conditioning; Non-MAC, non-myeloablative; MUD, Matched Unrelated Donor; Haplo-SCT, Haploidentical Stem Cell Transplantation; AML, Acute Myeloid Leukaemia; MDS, Myelodysplasia; ALL, Acute Lymphoblastic Leukaemia; MF, Myelofibrosis; NLPHL, Nodular Lymphocyte Predominant Hodgkin Lymphoma; Flu/Cy/TBI2Gy/PTCy, Fludarabine/Cyclophosphamide/Total Body Irradiation 2Gy/Post-transplant Cyclophosphamide; FMA, Fludarabine/Melphalan/Alemtuzumab; Bu2/Flu/A, Busulfan two day/Fludarabine/Alemtuzumab; LRTI, Lower Respiratory Tract Infection; CR, Complete Remission; GvHD, Graft versus Host Disease; Tac, Tacrolimus; MMF, Mycophenolate Mofetil; Methylpredn, Methylprednisolone.

Out of the seven patients, six (86%) received an allograft stem cell transplantation (allo-SCT) and one (14%) an autograft (auto-SCT). Half ($n = 3/6$) of the allo-SCT were human leukocyte antigen (HLA) 10/10-matched unrelated donor transplants, whereas two (34%) had a haploidentical transplant and one (16%) had a HLA 9/10-matched unrelated donor transplant. No patient underwent a myeloablative allo-SCT. Altogether, $n = 4/7$ patients (66%) received post-transplant cyclophosphamide (PTCy) for primary graft *versus* host disease (GvHD) prophylaxis. Five out of seven (71%) were in complete remission from underlying disease, and two of them (29%) had relapsed acute myeloid leukaemia (AML) with bone marrow chimerism 79% and 27% donor at COVID-19 diagnosis. The median haematopoietic comorbidity index (HCT-CI) for allo-SCT recipients was 3·5 (0–6). Salient patient characteristics including comorbid conditions and their outcomes are summarized in Table I.

All patients were profoundly lymphopenic with median absolute lymphocyte count $0{\cdot}36 \times 10^9$/l (range $0{\cdot}01$–$0{\cdot}67 \times 10^9$/l) at diagnosis and median C-reactive protein (CRP) 80 mg/l (range 7–240). Only one (14%) suffered from steroid refractory post-donor leucocyte infusion (DLI) stage III gut and stage III liver GvHD (overall grade IV Glucksberg criteria) and another one had mild upper gastrointestinal tract GvHD under low dose prednisolone (5 mg prolonged course over eight weeks). Notably, $n = 3/7$ (43%) patients developed the virus well into inpatient stay whereas the remaining 4/7 were shielded but had to attend the day care unit at least once weekly for line care or blood products. With regard to COVID-19 symptoms, four patients (57%) manifested with mild lower respiratory tract symptoms whereas three (43%) were tested for SARS-CoV-2 because of isolated fever. As of 7 May 2020, with a median follow-up of 22 days (range 18–30) since the identification of COVID-19, four patients (57%) were alive (three discharged home) and the remaining three (43%) had died. The cause of death was bilateral pulmonary emboli secondary to COVID-19 ($n = 1/7$, 14%), ARDS due to COVID-19 plus uncontrollable GvHD ($n = 1/7$, 14%) whereas the third allo-SCT patient died of an accidental intracranial bleed amidst thrombocytopenia as a result of relapsed AML 11 days post SARS-CoV-2 identification but with no evidence of symptomatic COVID-19 apart from transient low-grade fever. Only patient number 5 (Table I) received specific antiviral treatment (a five-day hydroxychloroquine course).

Our findings are comparable to that reported from the Haematology Department in Saint Antoine hospital in Paris.[3] The French study included five autografts and one allograft recipient. The present study focuses on seven haematopoietic stem cell recipients who were diagnosed with SARS-CoV-2. Within the limitations of its small patient number and retrospective nature our study might be of interest for the reasons below:

Firstly, we have observed that all allograft recipients in this series who had had non-myeloablative conditioning with post-transplant cyclophosphamide (PTCy) have exhibited mild COVID-19 in spite of comorbid conditions such as body mass index (BMI) >35, or diabetes mellitus (DM) in some of them, as shown in Table I. PTCy is known to abrogate cytokine release syndrome (CRS) in haplo-identical stem cell transplantation which displays similarities in terms of pathophysiology with severe COVID-19-associated CRS. In addition, PTCy mediates allo-reactive T-cell direct elimination and thymic clonal deletion, together with an expansion in $FoxP3^+$ $CD4^+$ T-regulatory (T-reg) cells. In turn, T-reg cells have been shown to help resolve ARDS inflammation in mouse models.[4–7] Moreover, non-myeloablative conditioning causes less tissue damage and possibly fewer risks for severe COVID-19-associated CRS early post allograft. Next to this, more than myeloablative chemotherapy it preserves recipients' innate immunity, which is the first line of antiviral defence and essential for immunity against coronaviruses.[8]

Secondly, in line with other reports, we propose that asymptomatic health care professionals caring for immunosuppressed patients should be regularly PCR-tested for the novel coronavirus since all patients in this series are felt to have acquired SARS-CoV-2 during frequent day unit stays or prolonged inpatient stay.[9,10]

The present case series of haematopoietic stem cell transplant recipients diagnosed with SARS-CoV-2 demonstrated a mortality rate of 28% that can be directly attributed to COVID-19 with two out of three patients who had chest infiltrates on computed tomography and X-ray imaging progressing to ARDS. Prospect multicentre studies on the characteristics and outcomes of haematopoietic stem cell recipients with COVID-19 are a *sine qua non* to draw conclusions in terms of optimal transplant conditioning regimes and GvHD prophylaxis in the novel coronavirus era.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions

AK and MN conceived the study. AK, MZ and MN performed the data analysis and wrote the manuscript. BK, SP and RL reviewed the article. All other authors provided critical intellectual input, participated in data collection and were involved in the care of COVID-19 patients.

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Haemophagocytosis in bone marrow aspirates in patients with COVID-19

A 78-year-old man with haemorrhagic signs (epistaxis and purpura) presented with severe thrombocytopenia, lymphopenia and circulating neutrophil precursors. A bone marrow aspirate showed increased plasma cells and an increase in pleomorphic megakaryocytes, consistent with peripheral thrombocytopenia. A few macrophages showing haemophagocytosis were also revealed (Fig 1A). Considering the outbreak of COVID-19,[1,2] the combination of thrombocytopenia, lymphopenia and neutrophil precursors led to consideration and detection of SARS-CoV-2, although the patient did not have fever, cough, dyspnoea, diarrhoea, myalgia or headache. The diagnosis was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay and chest X-ray (CXR). Apart from thrombocytopenia and haemophagocytosis, this patient did not have other features of secondary haemophagocytic lymphohistiocytosis (sHLH). Clinical and laboratory features of the H-score[3] were not met (Table I). Numerous large megakaryocytes in the bone marrow aspirate and the presence of platelet antibodies led to a diagnosis of autoimmune thrombocytopenic purpura (ITP), potentially related to COVID-19.[4] The platelet count increased after treatment with intravenous immunoglobulin (from 6 to 87 $\times$ 10^9/l in 5 days). Corticosteroids were avoided in the context of COVID-19.[5]

Two other patients with severe COVID-19 confirmed by RT-PCR also had haemophagocytosis demonstrated in a bone marrow aspirate performed for cytopenia (Fig 1B,C). One of them (patient 2) was a 67-year-old obese woman with worsening of her general state, cough and fever, with a known SARS-CoV-2 contact. On admission, she had dyspnoea and tachycardia. CXR showed diffuse bilateral pulmonary infiltrates, and SARS-CoV-2 infection was confirmed by RT-PCR. A bone marrow aspirate also revealed increased