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Covid-19 in Bone Marrow Transplant Recipients: Reflecting on a Single Centre Experience

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Running Title: Single Stem Cell Transplant Centre experience in SARS-CoV-2 infection

Covid-19 disease is caused by a novel SARS-CoV-2 virus and has been declared a pandemic on the 9th of March by WHO. Hallmark of COVID-19 management is supportive care and there is still no convincing evidence on 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 (Liang *et al*; 2020, Guan *et al*; 2019). There is a paucity of data on Covid-19 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 positive for SARS-CoV-2 RNA on RT-PCR from nasopharyngeal swabs done in the context of symptoms (fever, cough, dyspnea, 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-CoV2 via real time PCR based technique.

Out of the seven patients n=6 (86%) received an Allograft (allo-SCT) and one (14%) an Autograft (auto-SCT). Half (n=3/6) of the allo-HSCT were HLA 10/10 matched unrelated donor transplants, whereas two (34%) had haplo-identical transplant and one (16%) had HLA 9/10 matched unrelated donor transplant. No patient underwent a myeloablative allo-SCT. N=4/7 patients (66%) received post-transplant

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cyclophosphamide (PTCy) for primary graft versus host disease (GvHD) prophylaxis. N=5/7 (71%) were in complete remission from underlying disease, and two of them (29%) had relapsed acute myeloid leukemia with bone marrow chimerism 79% and 27% donor at COVID-19 diagnosis. The median Hematopoietic 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 1.

All patients were profoundly lymphopenic with median absolute lymphocyte count 0.36 x 10^9/L (range 0.01 x10^9/l-0.67 x 10^9/l) at diagnosis and median CRP 80mg/l (range 7-240). Only one (14%) suffered from steroid refractory post-DLI stage III Gut and Stage III liver GvHD (overall grade IV-Glucksberg criteria) and another one had mild upper GI tract GVHD under low dose prednisolone (5mg-prolonged course over 8 weeks). Notably, n=3/7 (43%) patients developed the virus well into inpatient stay whereas the rest 4/7 were shielded but had to attend Day Care Unit at least once weekly for line care or blood products. With regards to COVID-19 symptoms n=4/7 (57%) manifested with mild lower respiratory tract symptoms whereas three (29%) were tested for SARS-CoV-2 because of isolated fever (43%). As of the 7th of May 2020, with a median follow up of 22 days (range18-30) since the identification of Covid-19, four patients (57%) were alive (three discharged home) and the rest three (43%) have died. The cause of death was bilateral pulmonary emboli secondary to Covid-19 (n=1/7, 14%), ARDS to Covid-19 plus uncontrollable GVHD (n=1/7, 14%) whereas the third allo-SCT patient died of accidental intracranial bleed amidst thrombocytopenia to relapsed AML eleven 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 1) received specific antiviral treatment (five day Hydroxychloroquine course).

Our findings are comparable to that reported from Haematology Department in Saint Antoine hospital in Paris. (Mallard et al 2020). The French study included five autografts and one allograft recipients. Present study focuses on seven hematopoietic 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 all allograft recipients in this series who have had non myeloablative conditioning with PTCy have exhibited mild COVID-19 in spite of comorbid conditions such as BMI>35, or DM in some of them, as shown on table 1. 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 (Walter et al., 2018, Mehta *et al;* 2020, Cupps *et al;* 1982, Tay *et al*; 2020, Zhang *et al*; 2020). Moreover, non-myeloablative conditioning causes less tissue damage and possibly fewer risks for severe COVID-19 associated CRS early post allograft. Next to this, it preserves more than myeloablative chemotherapy

recipients' innate immunity, which is the first line of antiviral defense and essential for immunity against coronaviruses (Channappanavar et al, 2019).

Secondly, in line with other reports, we propose that asymptomatic health care professionals in the care of 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 as shown in table 1(Gandhi *et al,* 2020).

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

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Author Contributions

AK and MN conceived the study. AK, MZ and MN performed data analysis and wrote the manuscript. BK, SP, 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.

Conflict of Interest

The authors declare no conflict of interest.

References:

Channappanavar, R., Fehr, A.R., Zheng, J., Wohlford-Lenane, C., Abrahante, J.E., Mack, M., Sompallae, R., McCray, P.B., Meyerholz, D.K., and Perlman, S. (2019). IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J. Clin. Invest. 129, 3625–3639.

Cupps, T.R., Edgar, L.C. and Fauci, A.S., 1982. Suppression of human B lymphocyte function by cyclophosphamide. *The Journal of Immunology*, *128*(6), pp.2453-2457.

Gandhi, M., Yokoe, D.S. and Havlir, D.V., 2020. Asymptomatic transmission, the Achilles' heel of current strategies to control COVID-19

Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S. and Du, B., 2020. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*, *382*(18), pp.1708-1720.

He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, Wu D, Liang B, Lu X, Ma Y, Li L, Wang H, Chen Z, Li Q, Gale RP. COVID-19 in patients with haematological cancers Leukemia. 2020 Apr 24. doi: 10.1038/s41375-020-0836-7

Liang, W., Guan, W., Chen, R., Wang, W., Li, J., Xu, K., Li, C., Ai, Q., Lu, W., Liang, H. and Li, S., 2020. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncology*, *21*(3), pp.335-337.

Malard F, Genthon A, Brissot E, van de Wyngaert Z, Marjanovic Z, Ikhlef S, Banet A, Lapusan S, Sestilli S, Corre E, Paviglianiti A, Adaeva R, M 'Hammedi-Bouzina F, Labopin M, Legrand O, Dulery R, Mohty M.COVID-19 outcomes in patients with haematology disease. Bone Marrow Transplant. 2020 May 6.

Tay, M.Z., Poh, C.M., Rénia, L., MacAry, P.A. and Ng, L.F., 2020. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology, pp.1-12.

Walter, J.M., Helmin, K.A., Abdala-Valencia, H., Wunderink, R.G., and Singer, B.D. (2018). Multidimensional assessment of alveolar T cells in critically ill patients. JCI Insight 3.

Zhang, C., Wu, Z., Li, J.W., Zhao, H. and Wang, G.Q., 2020. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *International Journal of Antimicrobial Agents*, p.105954.

Table 1: Patient Clinical Characteristics and Outcome

Abbreviations: 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

	Age	Sex	Comor	Dx	HCT-CI	Date of HSCT	Type of allo-SCT	Condit	Day	Symptom /Source Of infection	Disease status at Covid	GvHD	Immuno-suppres-sion	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	Azacyti-dine	Alive
Patient 3	59	F	BMI>35 Depres-sion 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 Neuropa-thy 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