THE LANCET
Haematology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem cell transplantation recipients: an observational cohort study. *Lancet Haematol* 2021; published online Jan 19. https://doi.org/10.1016/S2352-3026(20)30429-4.

Supplementary Data

Study Protocol

1.0 Hypothesis:

Patients receiving hematopoietic cell transplantation and cellular therapy (TCT) are severely
immunocompromised and, therefore, distinctively susceptible to COVID-19 related mortality.
We hypothesize that the severity of COVID-19 illness varies based on the immunosuppressed state of the TCT recipients and is associated with inferior survival after infection irrespective of the time since TCT.

2.0 Specific Aims

2.1 Describe the characteristics of TCT patients with a COVID-19 infection
2.2 Describe the severity of COVID-19 infection in TCT patients
2.3 Describe the treatment approaches for COVID-19 in TCT patients
2.4 Describe the survival of TCT patients after infection with COVID-19

3.0 Scientific Impact/Justification:

Patients who have undergone a hematopoietic cell transplant or cellular therapy (TCT) are at a high risk of poor outcomes from COVID-19 owing to their immunocompromised state. New management approaches are being developed rapidly but it is unclear which, if any, of these approaches will be effective in these highly immunocompromised patients. The Center for International Blood and Marrow Transplant Research (CIBMTR) is collecting data on clinical presentation, diagnosis, management, and outcomes of respiratory viral infections (including SARS-CoV-2) in TCT recipients. Analysis and rapid dissemination of these data will be pivotal to expand knowledge about this novel coronavirus as a whole and potentially impact treatment decisions for future patients.

The pandemic of Coronavirus Disease 2019 (COVID-19) caused by a novel coronavirus - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is continuing to cause substantial loss of life and economic damage globally. Epidemiological studies have indicated that majority cases are mild and recover spontaneously. However, some patients do develop severe illness and may succumb to their disease. Most patients who have poor outcomes after developing COVID-19 are reported to be older, have other comorbidities or are immunocompromised.[1-3]

A few recent studies have assessed the incidence and risk of COVID-19 in patients with cancer. In a nationwide study from China, compared to patients without cancer, patients with cancer (N=18) were found to be at a significantly higher risk of developing severe events such as invasive ventilation, ICU admission or death (Hazard ratio 3.56, 95% confidence interval 1.65-7.69).[2] Another large-scale study from Italy assessed the patient characteristics of 355 fatal COVID-19 cases[3] of whom, 72 (20.3%) had active cancer. He W, *et al*. further described a case fatality

rate (CFR) of 62% (8 of 13 died) in a cohort of 128 admitted patients with hematological malignancies of which 10% (n=13) developed COVID-19.[4] While it is known from previous literature that patients undergoing hematopoietic cell transplant and cellular therapy recipients are at a higher risk of morbidity and mortality from viral illnesses compared to others, the incidence and outcomes of COVID-19 in TCT recipients have not yet been reported. With a rapidly growing number of COVID-19 cases worldwide, there is an imminent need to study these data in patients undergoing hematopoietic cell transplant or cellular therapy.

The CIBMTR is a research collaboration between the National Marrow Donor Program (NMDP)/ Be The Match and the Medical College of Wisconsin. The CIBMTR conducts prospective and observational research through a large network of transplant centers worldwide and a clinical database of more than 540,000 patients. The CIBMTR started collecting data regarding the diagnosis, treatment, and outcomes of COVID19 infections starting 3/27/2020. To date, there have been 81 cases of COVID19 reported to the CIBMTR, out of which 13 have died. It is paramount to characterize these patients in relation to patient, disease, and transplant and cellular therapy related factors in order to inform the global scientific community.

4.0 Study Population

Inclusion

All patients who have received a hematopoietic cell transplant or cellular therapy and have been reported to the CIBMTR as having confirmed COVID-19 infection. All diagnoses, donor choice/ graft sources, and conditioning regimen will be included.

Exclusion

Patients who have not provided consent for research
Patients from embargoed centers

5.0 OUTCOMES

5.1 **Overall survival**: This will be calculated as the time from COVID-19 infection
5.2 **Severity of infection:** This will be determined as a frequency of patients requiring mechanical ventilation vs supplemental oxygen without mechanical ventilation vs neither
5.3 **Duration of COVID-19 infection**: Median, range
5.4 **Time from TCT to COVID-19 infection**: Median, range
5.5 **Time from acute GVHD onset to COVID-19 infection**: median, range
5.6 **Time from chronic GVHD onset to COVID-19 infection:** median, range
5.7 **Cause of death:** COVID-19 (as primary or contributing COD) vs other

6.0 VARIABLES TO BE DESCRIBED

Patient related

- Patient age at transplant (in decades ≤ 10, 11-20, 21-30, 31-40, 41-50, 51-60, ≥ 60)

- Patient gender
- Patient race/ethnicity
- Karnofsky performance at transplant: <90% vs. ≥90%
- Region of residence: NE vs South vs Midwest vs West vs non-US

Disease/Transplant Related

- Disease
- Disease risk index
- Time from diagnosis to TCT
- Recipient HCT-CI
- Conditioning intensity: myeloablative vs. reduced-intensity/non-ablative
- TBI-based conditioning: yes vs. no
- GVHD prophylaxis
- T-cell depletion, either *ex vivo* or *in vivo*: yes vs no
- Donor type: matched related vs haplo-identical (≥ 2 Ag/allele mismatch) vs matched unrelated vs mismatched unrelated vs cord
- Stem cell source: peripheral blood vs. marrow

Infection Related

- Diagnosis of acute GVHD II-IV prior to time of COVID-19: yes vs no
- Diagnosis of chronic GVHD, any severity prior to time of COVID-19: yes vs no
- Use of Immunosuppressive agents in the 6 months prior to COVID-19 diagnosis: yes vs no vs unknown/not available, list of agents
- IgG level in the 6 months prior to COVID-19 diagnosis: yes vs no vs unknown/not available; median, range
- CD4 count in the 6 months prior to COVID-19 diagnosis: yes vs no vs unknown/not available; median, range
- Method of diagnosis of COVID-19: Nasal swab/wash vs imaging vs unknown
- WBC count at diagnosis of COVID-19: median, range
- Absolute lymphocyte count at diagnosis of COVID-19: median, range
- Treatment received for COVID-19: list of treatments, median duration of each treatment
- Status of infection: based upon most recent assessment

7.0 Study Design

Patient-, disease- and transplant- related factors will be described as frequency for categorical variables and median (range) for non-categorical variables and time dependent outcomes. The probability of overall survival will be calculated using the Kaplan Meier estimator, with the variance estimated by Greenwood's formula.

References:

1. Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. *Cancer Discov* 2020; **10**(6): 783-91.
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21**(3): 335-7.
3. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* 2020.
4. He W, Chen L, Chen L, et al. COVID-19 in persons with haematological cancers. *Leukemia* 2020; **34**(6): 1637-45.

Supplemental Table 1. Characteristics of hematopoietic cell transplant recipients with a PCR confirmed COVID-19 diagnosis and a minimum 10-day follow-up.

Characteristic	AlloHCT N = 113	AutoHCT N = 88
No. of centers	58	45
Region - no. (%)		
US – Northeast	54 (48)	44 (50)
US – Midwest	16 (14)	15 (17)
US – South	15 (13)	14 (16)
US – West	11 (10)	7 (8)
Canada	3 (3)	2 (2)
Europe	3 (3)	0
Central/South America	10 (9)	5 (6)
Middle East/Africa	1 (1)	1 (1)
Patient-related		
Age (years) - no. (%)		
Median (range)	48 (<1-76)	60 (5-76)
≤ 10	9 (8)	2 (2)
11 – 20	5 (4)	0
21 – 40	32 (29)	7 (8)

Characteristic	AlloHCT N = 113	AutoHCT N = 88
41 – 60	43 (38)	40 (45)
≥ 61	24 (22)	39 (45)
Sex, Male - no. (%)	65 (58)	51 (58)
Race - no. (%)		
Caucasian	89 (79)	44 (50)
African-American	8 (7)	25 (28)
Asian	6 (5)	5 (6)
More than one race	1 (1)	0
Missing	9 (8)	14 (16)
Ethnicity - no. (%)		
Hispanic or Latino	28 (25)	21 (24)
Non-Hispanic or non-Latino	69 (61)	58 (66)
Non-resident of the U.S.	15 (13)	7 (8)
Missing	1 (1)	2 (2)
HCT-CI score pre-HCT - no. (%)		
0	25 (22)	18 (20)
1 – 2	41 (36)	22 (25)
3 – 4	31 (27)	33 (37)
≥ 5	12 (11)	15 (17)

Characteristic	AlloHCT N = 113	AutoHCT N = 88
Not reported	4 (4)	0
Disease-related		
HCT indication - no. (%)		
AML	41 (36)	0
ALL	27 (24)	0
CML	6 (5)	0
MDS/MPN	17 (15)	0
Other acute leukemia	1 (1)	0
Non-Hodgkin lymphoma	7 (6)	25 (28)
Hodgkin lymphoma	3 (3)	2 (2)
Plasma cell disorder/Multiple Myeloma	3 (3)	58 (66)
Solid Tumors	0	3 (3)
Other malignancy	2 (2)	0
Severe aplastic anemia	2 (2)	0
Sickle cell anemia	2 (2)	0
Immune disorders (SCID, other inherited immunodeficiency, autoimmune disease)	2 (2)	0
Refined disease risk index - no. (%)		
Low	8 (7)	N/A

Characteristic	AlloHCT N = 113	AutoHCT N = 88
Intermediate	59 (53)	N/A
High	15 (13)	N/A
Very high	4 (4)	N/A
N/A - < 18 years old or no DRI for sub-disease	25 (23)	N/A
Missing	2 (2)	N/A
Conditioning intensity (as reported by center) - no. (%)		
MAC	49 (43)	N/A
RIC/NMA	61 (54)	N/A
Not reported	3 (3)	N/A
TBI-based conditioning- no. (%), Yes	50 (44)	N/A
GVHD prophylaxis - no. (%)		
Ex-vivo T-cell depletion	3 (3)	N/A
CD34 selection	5 (4)	N/A
PTCy + other(s)	19 (17)	N/A
PTCy alone	1 (1)	N/A
TAC/CSA + MMF ± other(s) (except PTCy)	18 (16)	N/A
TAC/CSA + MTX ± other(s) (except MMF, PTCy)	52 (46)	N/A
TAC/CSA + other(s) (except MMF, MTX, PTCy)	2 (2)	N/A
TAC/CSA alone	8 (7)	N/A

Characteristic	AlloHCT N = 113	AutoHCT N = 88
Other(s)/None Given	3 (3)	N/A
Missing	2 (2)	N/A
ATG/Alemtuzumab use at the time of HCT		
No	62 (55)	N/A
Yes	19 (17)	N/A
Not reported	32 (28)	N/A
Donor type - no. (%)		
HLA-identical sibling	44 (39)	N/A
Haploidentical (≥2 MM)	8 (7)	N/A
Other related (1 antigen mismatched or fully matched but not identical)	14 (12)	N/A
Well-matched unrelated (8/8)	24 (21)	N/A
Partially-matched unrelated (7/8)	8 (7)	N/A
Unrelated (matching unknown)	7 (6)	N/A
Cord blood	8 (7)	N/A
Graft type - no. (%)		
Bone marrow	17 (15)	0
Peripheral blood	88 (78)	88
Umbilical cord blood	8 (7)	0

Characteristic	AlloHCT N = 113	AutoHCT N = 88
Year of Transplant		
1999 - 2010	6 (5)	2 (2)
2011 - 2014	16 (15)	6 (7)
2015 – 2017	21 (18)	31 (35)
2018 – 2020	70 (62)	49 (56)

Abbreviations: ALL indicates acute lymphoblastic leukemia, AML: acute myeloid leukemia, ATG: anti thymocyte globulin, CML: chronic myeloid leukemia, CSA: cyclosporine A, DRI: disease risk index, HCT: hematopoietic cell transplant, HCT-CI: hematopoietic cell transplant-comorbidity index, HLA: human leukocyte antigen, MAC: myeloablative conditioning, MDS: myelodysplastic syndrome, MMF: mycophenolate mofetil, MPN: myeloproliferative neoplasm, NMA: non myeloablative conditioning, PTCy: post-transplant cyclophosphamide, RIC: reduced intensity conditioning, SCID: severe combined immunodeficiency syndrome, TAC: tacrolimus, TBI: total body irradiation and US: United States.

Supplemental Table 2: Patient characteristics at diagnosis and clinical features of COVID-19 including patients with PCR confirmed diagnosis and a minimum 10-day follow-up.

Characteristic	AlloHCT N = 113	AutoHCT N = 88
Time from HCT to COVID-19		
Median, months (range)	18 (1 – 243)	23 (1 – 121)
Interquartile range, months	8 - 46	7 - 46
Acute GVHD II-IV prior to COVID-19 - no. (%)		
No	61 (54)	N/A
Yes	40 (35)	N/A
Not reported	12 (11)	N/A
Chronic GVHD prior to COVID-19 - no. (%)		
No	67 (59)	N/A
Yes	46 (41)	N/A
On immunosuppression in 6 months prior to COVID-19 diagnosis - no. (%)		
No	75 (66)	N/A
Yes	24 (21)	N/A
Not reported	14 (12)	N/A
WBC count at COVID-19 diagnosis – no. (%)		

Characteristic	AlloHCT N = 113	AutoHCT N = 88
No/Not reported	22 (19)	21 (34)
Reported	91 (81)	67 (76)
Median, x10^9/L (range)	6 (0-21)	4 (0-23)
Absolute lymphocyte count at COVID-19 diagnosis – no.(%)		
No/ Not reported	24 (21)	24 (27)
Reported	89 (79)	64 (73)
Median, ×10^9/L (range)	1 (0-5)	1 (0-5)

Abbreviations are as in Supplemental Table 1, additionally GVHD indicates graft versus host disease and WBC: white blood cell count.

Supplemental Table 3: Overall survival of hematopoietic cell transplant recipients including patients with PCR confirmed diagnosis and a minimum 10-day follow-up.

	AlloHCT (N = 113)		AutoHCT (N = 88)	
Outcomes	**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**
Overall Survival	113		88	
14 days	64	81 (73 – 88)%	64	90 (83 – 96)%
30 days	36	68 (57 – 77)%	27	71 (58 – 82)%

Supplemental Table 4: Multivariable analysis for risk factors associated with death from COVID-19 including patients with PCR confirmed diagnosis and a minimum 10-day follow-up.

Parameter	Number Events/Evaluable	Hazard Ratio (95% CI)	p-value
Allogeneic HCT			
Age			
< 50	10/62	1.00	
≥ 50	25/51	2.57 (1.18 – 5.63)	0.018
Sex			
Female	8/48	1.00	
Male	27/65	2.94 (1.25 – 6.90)	0.013
Time from HCT to COVID-19			
> 12 months	14/71	1.00	
≤ 12 months	21/42	2.59 (1.27 – 5.26)	0.009

Other factors tested and not found to be statistically significant: immunosuppression within 6 months of diagnosis, race, ethnicity, pre-HCT comorbidity score

Parameter	Number Events/Evaluable	Hazard Ratio (95% CI)	p-value
Autologous HCT			
Disease for HCT[1]			
Plasma cell disorder/Myeloma	10/58	1.00	
Lymphoma	9/27	2.33 (0.94 – 5.76)	0.067

[1]N=3 other malignancies were excluded from multivariable analysis

No factors were found to be significant in multivariable analysis for autoHCT.

Other factors tested: age, sex, time from HCT to COVID-19, race, ethnicity, pre-HCT comorbidity score