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Abstract Background
Patients with high-risk haematological malignancies often progress and succumb to their disease without a timely haematopoietic stem cell transplantation (HCT). However, in patients undergoing HCT following acute Coronavirus disease 2019 (COVID-19) infection, there is a significant morbidity and mortality risk. Few recent reports suggest that allogeneic and autologous HCT may be feasible in patients who have recovered from COVID-19, but there is little data on the optimal timing and safety of HCT following the infection. High rates of COVID-19 community transmission were observed in a highly-vaccinated population of Singapore between September 2021 and April 2022, affecting many HCT recipients. In this study at the largest tertiary transplant centre in Singapore, we analyzed the outcome of patients who underwent HCT following COVID-19 infection in the preceding 120 days or with active COVID-19 infection during transplant.

Methods
We conducted a retrospective analysis of consecutive patients admitted to Singapore General Hospital for planned HCT from September 2021 and April 2022. Written informed consent was obtained, and patients were followed up for transplant-related outcomes. The date of diagnosis of COVID-19 was based on the first positive SARS-CoV-2 PCR nasopharyngeal swab. Patients who were diagnosed with COVID-19 within 120 days prior to stem cell infusion were included in the study.

Results
We studied 10 allogeneic and 1 autologous HCT patients, with acute myeloid leukaemia (n=3), acute lymphoblastic leukaemia (n=2), chronic myeloid leukaemia (n=2), myelofibrosis (n=1), severe aplastic anaemia (n=1), Hodgkin lymphoma (n=1) and multiple myeloma (n=1). Median interval between diagnosis of COVID-19 to HCT infusion was 53 days (range 1-118). 6 were tested negative by PCR and 2 were prolonged low-level viral shedders detectable by PCR, prior to HCT. 3 patients were diagnosed with COVID-19 immediately prior to HCT infusion, at Days -1, -3 and -5 respectively. Median duration of COVID-19 infection defined by time to negative PCR was 20 days.

All allogeneic HCT patients had 2 doses of COVID-19 mRNA vaccines (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273) prior to infection, and the autologous HCT patient was unvaccinated. Median receptor binding domain IgG serology titre (Abbott assay) in vaccinated patients was 1301 AU/ml at the time of COVID-19 diagnosis. COVID-19 disease severity by WHO guidelines was mild in 9, moderate in 1 and critical in 1 patient. 8 patients received antivirals; 5 of them had concurrent monoclonal antibodies (sotrovimab, n=4; casirivimab-imdevimab, n=1).

Median age at HCT was 53 years (range 26-70); 64% of patients had low-risk HCT-comorbidity index, 45% were male, and 55% were of high-risk by the disease risk index. Allogeneic HCT patients received peripheral blood stem cells from matched siblings donors (MSD, n=3), matched unrelated donors (MUD, n=2) or haploidentical donors (n=5). 50% of patients received myeloablative conditioning regimen (n=5); and prophylaxis for graft-versus-host disease (GvHD) included calcineurin inhibitors and/or mycophenolate mofetil. Haploidentical transplant patients received post-transplant cyclophosphamide (PTCy, n=3) or ex-vivo TCRalpha-beta depleted grafts (n=2). A relapsed AML patient received haploidentical TCRalpha-beta depleted graft without conditioning regimen. A median of 5.5 x 10^6 CD34+ cells/kg (range 2.9-10.1) was infused.
Median time to neutrophil and platelet engraftment were 10 days (range 10-17) and 12 days (range 10-20) respectively, in both MSD and MUD recipients (Table 1), comparable to that of non-COVID-19 cohorts. 2 patients died of non-relapse pulmonary complications on D+43 and D+50 post HCT respectively. 2 out of 10 allogeneic HCT patients developed grade II acute GvHD of skin, but none grade III-IV acute GvHD. Median follow up was 103 days (range 43-208), and GvHD-free/reapse-free survival (GRFS) among surviving patients at D+100 was 78%. There was no evidence of COVID-19 reinfection or late complications, or increase in viral reactivation of CMV, EBV and HHV6.

Discussion

Our study suggests that timely HCT can be safely performed with favourable outcome for patients with haematological malignancies, following acute COVID-19 infection in a fully-vaccinated cohort. Immunization, viral therapeutics and a careful disease risk-benefit assessment play a crucial role.

| Patient | Haematological Diagnosis | Interval Between COVID-19 and HCT (Days) | SARS-CoV-2 IgG (nCd) AU/mL | Type of HCT | Donor Source for Allogeneic HCT | Conditioning Regimen | ANC Engraftment (Days) | Platelet Engraftment (Days) |
|---------|------------------------|------------------------------------------|-----------------------------|-------------|-------------------------------|----------------------|------------------------|--------------------------|
| 1       | Multiple myeloma       | 99                                       | 6444.2                      | Autologous  | NA                            | Mel                  | 10                     | 13                      |
| 2       | Ph+ B-ALL             | 57                                       | 809.6                       | Allogeneic | MSD                           | Fludarabine, Mel    | 10                     | 10                      |
| 3       | Ph+ B-ALL             | 54                                       | 513.0                       | Allogeneic | MSD                           | CY, TBI              | 15                     | 16                      |
| 4       | AML                   | 1                                        | 178.3                       | Allogeneic | MUD                           | Fludarabine, Bu, ATG| 10                     | 10                      |
| 5       | AP-CML                | 3                                        | 2244.7                      | Allogeneic | Haploidentical                | TT, Fludarabine, Mel, PTCy | 26                     | 30                      |
| 6       | AML                   | 5                                        | 1514.0                      | Allogeneic | Haploidentical                | NA                   | NA                     | 9                       |
| 7       | AML                   | 28                                       | >400000                     | Allogeneic | Haploidentical                | TT, Fludarabine, Mel, TBI, Thymoglobulin | 11                     | 10                      |
| 8       | SAA                   | 51                                       | 4294                        | Allogeneic | MSD                           | Fludarabine, Cy, Campath | 10                     | 14                      |
| 9       | Hodgkin lymphoma      | 53                                       | 2836.4                      | Allogeneic | Haploidentical                | Fludarabine, Cy, TBI, PTCy | 22                     | 41                      |
| 10      | AP-CML                | 73                                       | 1088                        | Allogeneic | MUD                           | Bu, Cy, ATG         | 17                     | 20                      |
| 11      | Myelodysplasia        | 138                                      | 71.9                        | Allogeneic | Haploidentical                | Fludarabine, Mel, PTCy | 18                     | 19                      |

Ph, Philadelphia chromosome; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AP-CML, accelerated phase chronic myeloid leukaemia; SAA, severe aplastic anaemia; HCT, haematopoietic stem cell transplantation; MSD, matched sibling donor; MUD, matched unrelated donor; Mel, melphalan; Fludarabine; Cy, cyclophosphamide; TT, thiopeta; Bu, busulfan; ATG, anti-thymocyte globulin; TBI, total body irradiation; Thymoglobulin.

Figure 1.

Disclosures Chen: Amgen: Honoraria; Janssen: Honoraria; Novartis: Honoraria; Takeda: Honoraria.

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