COVID-19 infection in adult and paediatric recipients of allogeneic stem cell transplantation: the UK experience.

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Running title

COVID-19 in UK allogeneic stem cell transplant recipients

Summary

COVID-19 is associated with increased morbidity and mortality amongst allogeneic haematopoietic stem cell transplantation (HSCT) recipients. Cytokine-mediated response to COVID-19 in the immunosuppressed population has not been described. In this observational study, we describe the UK experience of COVID-19 in HSCT recipients, and investigate the cytokine response in prospectively-recruited patients.

Ninety-two patients receiving an HSCT for any indication were recruited between May 2020 and June 2021, comprising 10 patients recruited at the time of COVID-19 diagnosis to the prospective cohort, and a further 82 patients to the retrospective cohort. Mortality by day 30 after COVID-19 diagnosis was 30% in the prospective cohort, 17% in the retrospective. Interleukin-6 concentration was elevated in 50% of patients tested, but there was no evidence for a multi-cytokine driven pro-inflammatory response. In the retrospective cohort, univariate analysis identified older age at COVID-19 infection, and shorted time between HSCT and COVID-19 diagnosis amongst risk factors for death. Our analysis of HSCT recipients who contracted COVID-19 confirms a high risk of death in this vulnerable cohort. Basic biochemical data at disease onset could help identify patients at higher risk of death. Interleukin-6 seems to play a major role in driving the inflammatory response in immunosuppressed patients.

Introduction

The impact of COVID-19 on recipients of allogeneic haematopoietic stem cell transplantation (HSCT) has been reported by multiple studies for both adults and children (El Fakih et al., 2021, Xhaard et al., 2021, Passamonti et al., 2020, Schaffrath et al., 2022). The largest European and US studies describe an increased risk of mortality for the HSCT recipient population, with risk factors for severe disease including older age, reduced performance status, time from HSCT over 12 months and lymphopenia (Ljungman et al., 2021, Sharma et al., 2021).

An excessive, proinflammatory viral response has been described in the general population and linked to poorer outcome following COVID-19 infection, (Blanco-Melo 2020, Ren 2021) but the role of cytokine activation in the immunocompromised patient following HSCT has not been investigated. We present a combined prospective and retrospective national study, run through the UK IMPACT trial network, to characterise the clinical and immunological features of COVID-19 in adult and paediatric recipients of HSCT in the United Kingdom

Materials and methods

Allogeneic HSCT recipients of any age and transplanted for any indication, with an RT-PCR-proven SARS-CoV-2 infection, were eligible for this study. Patients recruited within 72 hours of COVID-19 diagnosis, who had not received cytokine-targeted treatment, were included in a prospective cohort. All other patients were eligible for a retrospective cohort.

The primary outcome was death due to any cause at day 30 and day 100 after COVID-19 diagnosis. Secondary outcomes included respiratory support requirement, delayed SARS-CoV-2 viral clearance, and inflammatory profile. Clinical data was collected in a centralised database hosted by REDCap and

managed by the IMPACT trial network hub. Clinical information was requested at disease onset and patients were followed up at 30 and 100 days from disease onset.

In the prospective cohort blood samples for cytokine analysis (interleukin (IL)-2, IL-4, IL-6, IL-10, tumour necrosis factor (TNF)-alpha, interferon (IFN)-gamma), and lymphocyte subsets were taken within 72 hours of diagnosis and analysed in a centralised immunology lab at Great Ormond Street Hospital.

The study received approval by UK Research Ethics Committee and was registered as NCT04349540.

Statistical analysis

Eligible patients recruited into the prospective and retrospective cohorts were analysed separately; combined analysis is not permissible because of the different eligibility criteria. Due to the exploratory nature of the study no sample size calculation was undertaken and hence the study was not powered, but instead the target recruitment reflects the number of patients that could be practicably recruited, influenced by the general prevalence of COVID-19 in the HSCT recipient population. Given the study is non-interventional and exploratory in nature the analysis is largely descriptive. Descriptive summary data are therefore provided with categorical data being presented as counts and percentages and continuous data being presented as means with standard deviations or medians with ranges, as appropriate. The primary outcome of all cause mortality at day 30 and day 100 is presented as mortality rates alongside 95% confidence intervals. Secondary outcomes include requirement for mechanical ventilation, incidence of haemophagocytic lymphohistiocytosis (HLH), prevalence of COVID-19 at day 30 and inflammatory biomarker profile at disease onset. Additional analysis includes assessment of the primary outcome by immunosuppression, all-cause mortality by invasive mechanical ventilations, overall survival and time to COVID-19 negativity. All secondary outcomes and additional analysis are presented descriptively as previously described. Overall survival and time to COVID-19 negativity are assessed using Kaplan Meier curves with estimates provided at relevant time points along side 95% confidence intervals. Further non-pre-specified analysis of blood measures by mortality status is assessed using Mann-Whitney U tests, as well as univariate logistic regression for the outcome of day 100 mortality status and a multivariate logistic regression model of the same outcome to assess clinically relevant characteristics in the retrospective cohort.

Results

Between May 2020 and June 2021, 100 patients were recruited to the study from 16 sites across the UK. Eight patients were subsequently found to be ineligible, thus 92 patients are evaluable for analysis: 10 for the prospective and 82 for the retrospective cohorts of the study (Supplementary Figure 1 patient flow diagram). Patient and transplant characteristics are summarised in Table 1.

Prospective cohort

Patients recruited to the prospective cohort (within 72 hours of COVID-19 diagnosis) had a median time from HSCT of 8 months (range 0 to 56 months). Seven (70%) of the cohort were on immunosuppression at COVID-19 diagnosis. Comorbid conditions at the time of COVID-19 onset are included in Table 1.

Symptoms at the time of COVID-19 diagnosis were most commonly fever (7 patients, 70%), cough (5 patients, 50%), and shortness of breath (4 patients, 40%); diarrhoea and vomiting were each experienced by 3 patients (30%). Evidence of a concomitant infection was reported for 4 patients (40%). Laboratory findings at diagnosis are summarised in Table 2.

At COVID-19 diagnosis, 1 patient (10%) required continuous positive airway pressure (CPAP) respiratory support, 4 patients (40%) required supplementary oxygen (including 3 at a rate over 5L/min); the remaining 5 patients (50%) demonstrated adequate oxygen saturation in room air. At baseline, none of the prospective cohort required vasopressor support or renal replacement therapy. By day 30 following COVID-19 diagnosis, 1 patient (10%) had progressed to requiring mechanical ventilation. At baseline COVID-19 diagnosis, 2 patients (20%) had received dexamethasone and 1 (10%) remdesivir treatment, no one had cytokine targeting agents.

Within 30 days post-COVID-19 diagnosis: 2 patients (20%) developed significant thrombocytopenia (platelet count below 50 $x10^9$/L for more than 14 days), no one developed significant neutropenia (neutrophil count below 0.5 $x10^9$/L for more than 14 days); no graft rejection, HLH or thrombotic microangiopathy (TMA) were reported; no severe neurological complications were reported.

In the prospective cohort, 3 patients (30%) had died by day 30 after COVID-19 diagnosis; all deaths were attributed to COVID-19. No further deaths were reported at day 100.

Viral clearance of SARS-CoV-2 was estimated using the time of first negative respiratory swab RT-PCR result, in relation to the first positive result. The median time to SARS-CoV-2 negativity was 52 days (range 2 to 135 days).

Cytokine evaluation at baseline (within 72 hours of COVID-19 diagnosis) is depicted in Figure 1. IL-6 was the most commonly elevated cytokine. IL-2, IL-4 and TNF-alpha were also tested; none of the available samples demonstrated levels outside the normal range. Samples were available at respiratory deterioration for 3 patients and showed no significant difference compared with baseline (not shown).

Retrospective cohort

Patients identified more than 72 hours after their COVID-19 diagnosis were recruited to the retrospective cohort, with a median time from HSCT of 11 months (range 0 to 292 months). Forty (49%) of this cohort were on immunosuppression at COVID-19 diagnosis. Comorbidities at the time of COVID-19 onset are reported in Table 1.

Symptoms at the time of COVID-19 diagnosis were most commonly fever (39 patients, 48%), cough (38 patients, 46%), and shortness of breath (16 patients, 20%); a minority of patients presented with gastrointestinal symptoms, including diarrhoea (6 patients, 7%) and vomiting (5 patients, 6%). Concomitant infection was reported in 15 patients (18%) at COVID-19 diagnosis, and suspected in a further 7 patients (9%). Laboratory findings at diagnosis are summarised in Table 2.

At the time of COVID-19 diagnosis, 1 patient (1%) required invasive mechanical ventilation, 9 patients (11%) required supplementary oxygen (including 4 (5%) at a rate over 5L/min), whereas 71 patients (87%) were self-ventilating in room air. Two (2%) of this cohort required vasopressor support, and 1 patient (1%) received renal replacement therapy. By day 30 following COVID-19 diagnosis, 5 patients (6%) had received invasive ventilation, and 4 patients (5%) were treated with CPAP. At baseline, 4

patients (5%) had received dexamethasone and 3 (4%) had received remdesivir for the treatment of COVID-19.

By day 30 post COVID-19 diagnosis, no patient had developed graft rejection, HLH or TMA, 4 patients (5%) had significant neutropenia, and 10 patients (12%) significant thrombocytopenia.

In the retrospective cohort, 14 patients (17%) died within 30 days of COVID-19 diagnosis, of which 10 deaths (71%) were due to COVID-19. By day 100, a total of 21 patients (26%) had died, including 14 deaths (67%) due to COVID-19. The median time to SARS-CoV-2 PCR negativity in this cohort was 37 days (range 1 to 405).

Univariate logistic regression showed that increased mortality risk was associated with: older age, shorted time between HSCT and COVID-19 diagnosis, higher CRP concentration, higher creatinine concentration, lower platelet count and lower albumin concentration at COVID-19 diagnosis, and requirement for mechanical ventilation (Supplementary Table 1). Multivariate modelling did not reveal any independently predictive risk factors or mortality, but was limited by the number of patients and the event rate (Supplementary Table 2).

Discussion

To our knowledge, this is the only study reporting national data for the UK describing the acute clinical course of COVID-19 in recipients of allogeneic HSCT. As the study was enrolling patients between May 2020 and June 2021, it captured the first and second COVID-19 waves of pandemic in the UK (the second mostly driven by the Alpha variant) (www.ons.gov.uk).

In line with the largest European and US studies on COVID-19 in the post-HSCT population, we confirm a high mortality rate for this group of patients. Significantly, no patients below the age of 16 died in our cohort (comprising 4 prospective and 12 retrospective patients), consistent with previous UK data demonstrating that paediatric HSCT recipients mostly experience mild disease (Lucchini et al, BJH).

Univariate analysis of our data support previous findings that age and time from HSCT to COVID-19 are predictors of mortality in this cohort. Our data suggest that simple baseline assessment (such as platelet count, and albumin and creatinine concentrations) could identify “at risk” patients with a higher risk of death, however this would require further investigation and validation in a larger set of patients.

Our data are encouraging with regard to transplant-related complications in the acute COVID-19 setting. Indeed we did not document any evolution to HLH, TMA or any graft rejection. A limited number of patients developed severe neutropenia or thrombocytopenia but these were not contributors to early death in our cohort of patients.

The limited data available for our patients suggest that a significant number of patients developing COVID-19 disease after HSCT do not show a multi-cytokine driven inflammatory response in the very early (within 72 hrs) phase of disease. Indeed IL-2, IL-4- IL-10, IFN-gamma and TNF-alpha were normal in the vast majority of the patients. IL-6 was raised in 5/10 patients in our cohort. The role of cytokine storm in the population of non-immunosuppressed individuals affected by severe COVID-19 has been well documented and represents the target of a number of biological lines of treatment (Yang, Signal Transduction and Targeted Therapy (2021)). IL-6 has been the prominent targeted cytokine in this

setting but our limited data suggest that the wider cytokine involvement in patients post-HSCT could be different. Notably, 70% of patients contributing samples for cytokine analysis in this study were on active post-HSCT immunosuppression, and the influence of pre-COVID-19 immunosuppression on cytokine response and clinical outcomes is worthy of further evaluation.

Data on the COVID-19 immunisation status of participants of this study are not known. The COVID-19 immunisation programme started in the UK from December 2020, and quickly moved to an extended 12-week interval for delivery of the 2 doses comprising the primary vaccination course. Since the time that this study was open, a primary vaccination course in the immunocompromised is now considered to require 3 doses. Whilst we are unable to assess any potential impact of vaccination on the study outcomes, only a minority of patients would have received a 2-dose course, and none would have completed a 3-dose primary vaccination course. Moreover, the efficacy of COVID-19 vaccination in this population is likely to be lower than for the general population (Ni 2022). Overall, the concurrent COVID-19 immunisation programme is unlikely to have substantially affected the outcomes of this study, which are similar to those reported previously from earlier in the pandemic (Ljungman, Sharma).

An important limitation of the study is that it recruited only limited number of patients to the prospective cohort. This can be attributed to the substantial pressure NHS services were under during the pandemic, and a time when clinical research personnel and resources were re-directed to providing front-line clinical care to patients.

In conclusion, our study adds to and supports prior evidence that COVID-19 in non-immunised recipients of allogeneic HSCT is a severe and life-threatening infection, especially for adults early post-transplant. This population might not share the characteristics of the general population with regard to the inflammatory mechanism leading to severe COVID-19 disease, and this warrants further studies to identify the most appropriate targetable pathways in this population of patients.

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Conflict of interest

Giovanna Lucchini –
Elena Cozma –
Aimee Jackson –
Kimberly Gilmour – no conflicts
Rachel Protheroe –
Keith Wilson –
Karl Peggs –

Victoria Potter –
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Robert Wynn –
Emma Nicholson –
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Alexander M Martin –
Josu de la Fuente –
Graham McIlroy – No conflict of interest
Rebecca Bishop –
Rebecca Collings –
Ellie Williams –
Persis Amrolia –

Authorship statement

GL, AJ, KG, RP, RB, RC, EW and PA designed and conducted the study. GL, RP, KW, KP, VP, APa, APe, AT, RW, EN, CC, DM, CP, SP, OM-D, AMM and JdlF recruited patients and collected data. EC and AJ performed statistical analyses. KG performed laboratory analyses. GL, AJ and GM interpreted the results and wrote the first draft of the manuscript. All authors were involved in revisions of the manuscript; all authors approve the final version of the paper.

References

<To be added after co-author review>