Severe presentations and high mortality from SARS-CoV-2 in patients undergoing Chimeric Antigen Receptor (CAR-T) therapy: a UK NCCP analysis.

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CAR-T therapy for relapsed/refractory (r/r) B-cell cancers confers heightened susceptibility to infection due to cytopenias, impaired T-cell immune reconstitution, B-cell aplasia and hypogammaglobulinemia [1]. To date, the impact of SARS-CoV-2 in CAR-T patients has been described in case reports and a single European series [2–4]. Here we retrospectively evaluate the clinical sequalae of COVID-19 in adult CD19CAR-T patients at 9 UK CAR-T centers as an NCCP-registered service evaluation.

More than 168 patients per year with r/r B-cell cancers are now approved for CAR-T therapy in the UK. We collected baseline and outcome data for all UK patients on the CAR-T pathway, known to have acquired SARS-COV-2 infection between January 2020 and April 2021. Patients were separated into two groups: Group A (SARS-CoV-2+ between CAR-T approval and infusion), and Group B (SARS-CoV-2+ post-CAR-T infusion). We further separated groups by WHO COVID-19 severity at presentation [5]. Severe/critical COVID-19 was defined by oxygen saturation <90% on air; respiratory rate >30 breaths/minute, respiratory failure, shock or multiorgan dysfunction. Non-severe COVID-19 was defined by the absence of any criteria for severe/critical COVID-19.

Clinical management, SARS-CoV- 2-specific therapies, laboratory parameters and clinical outcomes are illustrated in Table 1. Time to SARS-CoV-2 clearance was the interval from first positive qPCR to the first (of two) negatives, or date of death without confirmed clearance. COVID-19-related deaths include death from respiratory/other organ failure ascribed to COVID-19. Wilcoxon-Mann Whitney, Chi-squared or Fisher's exact tests were performed in STATA version16.1 (STATA-corp, Texas) ($p<0.05$=significance).

A total of 29 patients undergoing CAR-T therapy were diagnosed with COVID-19 during the study. The median age was 61 (IQR, 40-71; range, 22-74) and 17 (59%) were male. Patient analyses and COVID-19 outcomes are provided in Table 1 and Figure 1 respectively. All patients were unvaccinated as the time of data cut-off fell outside the UK

SARS-CoV-2 vaccine roll-out

Ten patients tested positive for SARS-CoV-2, pre-CAR-T cell infusion (Group A). Severe/critical COVID-19 occurred in 4/10 (40%) patients and was associated with two deaths. One patient required 19 days of ICU respiratory support, received Remdesivir and REGN-COV2, cleared SARS-CoV-2 at 62 days, and underwent CAR-T infusion 134 days post-approval. Non-severe COVID-19 occurred in 6/10 (60%) and all received outpatient management. Of the eight patients who recovered from COVID, two patients did not proceed with CAR-T cell infusion due to deterioration in ECOG and subsequent death from PD. Eventually, 6/10 (60%) patients reached CAR-T infusion at a median interval from CAR-T approval to infusion of 99 days (range, 64-134), compared with 57 days (IQR, 47-71) in the main UK CAR-T dataset, reflecting the adverse impact of SARS-CoV-2 infection on the feasibility of CAR-T delivery, particularly in rapid progressors.

Nineteen patients developed SARS-CoV-2 infection following CAR-T infusion (Group B). Five cases (26%) occurred within 3 months of CAR-T; 5 (26%) between 3-6 months, and 9 (47%) at >6 months. At the time of infection, 16/19 (84%) patients had documented disease response to CAR-T (12 Complete response (CR) and 4 Partial Response (PR)). Low ALC (N=15/16 (94%)) and raised CRP (≥5 mg/L, N=12/15(80%)) was observed in both non-severe and severe/critical presentations. Six patients required at least weekly GCSF support in the month prior to COVID-19, and 4 of these patients were neutropenic ($<1.0x10^9$/L) at the time of diagnosis. Additional data on immune reconstitution was available for 9 patients at presentation: 6/9 (67%) had undetectable/low CD19 (($<0.1x10^9$/L) and 5/9 (56%) had both low CD4/CD8 ratio (<1.0) and IgG levels (<4g/L), with three patients receiving monthly intravenous immunoglobulin (IVIG).

Severe/critical COVID-19 occurred in 14/19 (74%) patients post-CAR-T. All were symptomatic, requiring hospital admission for a median of 23 days (range, 11-54). Eight patients (64%) required organ support in ICU (8/8 respiratory; 2/8 cardiovascular; 1/8 renal)

for a median of 12 days (range, 5-21). COVID-19 directed therapies included Corticosteroids in 11/14 patients (79%), Remdesivir in 8/14 (57%) and Tocilizumab in 5/14 (36%). Only one patient in this cohort received convalescent plasma and a further one patient received REGN-COV2. Twelve (86%) patients died of COVID-19 sequelae, at a median of 29.5 days (range, 2-151) following diagnosis and 177.5 days (range, 88-309) following CAR-T infusion. Only 2 patients with severe/critical COVID-19 post-CAR-T survived to be discharged from hospital at 10- and 15-days post-infection. The first patient remained SARS-CoV-2-positive at 80 days. The second received REGN-CoV-2 and cleared SARS-CoV-2 35 days following diagnosis but remains dyspneic on long-term home oxygen.

Non-severe COVID-19 presentations occurred in 5/19 (26%) patients post CAR-T. Three patients were asymptomatic, and only one patient was hospitalized for 8 days, requiring ward-based oxygen support. None required SARS-CoV-2-directed therapies or died from COVID-19. The majority (4/5 patients) cleared SARS-CoV-2 at a median of 30.5 days (range, 8-69). One patient remains SARS-CoV-2 positive at 252 days post-infection.

We show that non-severe COVID-19 pre- or post-CAR-T is associated with a predominantly mild course and survival, albeit with critical delays in CAR-T infusion in the pre-CAR-T cohort. We report two deaths from PD in this group. In contrast, CAR-T patients with severe/critical presentations in both groups had higher rates of hospitalization/ICU admissions, limited viral clearance and 15/18 (83%) died from sequelae of COVID-19 despite COVID directed therapies. Aligned with previous reports of poor COVID-19 outcomes with increasing age [2] we note a trend towards older age in severe/critical presentations (median 39 vs 64.5 years, p=0.052) in post CAR-T patients.

We observed that 94% of patients post CAR-T were lymphopenic at the time of COVID-19 diagnosis and more than 50% had CD19, CD4 and IgG levels below normal limits. Defects in humoral and cellular immunity post CAR-T cell therapy are associated with an increased susceptibility to infections and contribute to 4-8% of non-relapse mortality

rates [1,6]. We demonstrate that severe SARS-CoV-2 infection in patients post CAR-T had a devastating mortality impact: 86% (12/14) of patients died and notably 92% (11/12) were in CR or PR at the time of death.

In our cohort, median duration of shedding was 29 days for all patients with documented viral clearance, longer than estimates from pre-morbidly healthy patient groups (median 14 days) [7], but comparable to other immunocompromised groups [2,8,9]. Prolonged shedding from immunocompromised patients poses a risk of intra-host viral evolution with the potential for emergence of variants of concern [9,10]. Observing worldwide de-isolation protocols, SARS-CoV-2+ CAR-T patients are advised to continue isolating to mitigate for viral transmission [11] .

Targeting SARS-CoV-2 spike protein using REGN-COV2 can reduce viral load in SARS-CoV-2 antibody negative patients [12] and reduce mortality [13], critical for B-cell deficient, SARS-CoV-2 antibody negative CAR-T patients. REGN-COV2 was not approved in the UK during this study, but two patients treated via compassionate access schemes are currently alive with viral clearance.

Data from the CoV-VACC [14] and PROSECO [15] studies demonstrate low seroconversion rates post-COVID-19 vaccination in B-cell cancers, with CAR-T patients at particularly high risk. Vaccination cannot currently be considered a robust risk mitigation strategy for CAR-T patients, who remain a highly vulnerable clinical group.

Limitations of this analysis include the retrospective design, small patient numbers and limited power to assess risk factors for severe disease. Additional data on predictors of severe disease and vaccination response may allow further risk stratification of CAR-T patients with COVID-19. Prospective trials reviewing the mortality benefits of REGN-COV2 and other novel therapies in CAR-T patients are desirable, alongside approaches to improve upon current vaccination/therapeutic strategies. Until then, continued shielding and protective precautions should be recommended for all patients undergoing CAR-therapy.

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AUTHORSHIP CONTRIBUTIONS:

K.C., C.R., A.P., R.S., A.A.K. designed the research, collected the data, analyzed the data, and wrote the manuscript; T.M., E.T., S.C., A.M., B.U., J.R., D.I., R.J., E.N., J.B., W.T., A.K.,
M.O. contributed to collecting the data and writing the manuscript.

CONFLICT OF INTEREST:

A.K., S.C. A.P., and C.R. have served on advisory boards and received honoraria from Kite/Gilead, Novartis and BMS. K.C. and A.A.K. received honoraria from Kite/Gilead. R.S., D.I., B.U., E.T. and M.O. have served on advisory boards and received honoraria from Kite/Gilead and Novartis. T.M has served on advisory boards and received honoraria from Kite/Gilead, Novartis, BMS, Janssen, Roche, Servier, Pfizer, Amgen. W.T. has received honoraria and consultancy fees from Kite, BMS, and Roche.

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