STIMULUS REPORT

blood advances

COVID-19 and CAR T cells: a report on current challenges and future directions from the EPICOVIDEHA survey by EHA-IDWP

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Key Points

- The EHA-IDWP developed an observational registry collecting data on COVID-19 infection in patients who received CAR T-cell therapy.
- Prevalence of COVID-19 was 4.8%, and overall mortality was 50%, highlighting the need for prevention of infection in these patients.

Introduction

Since it was first reported in China, coronavirus disease 2019 (COVID-19) has spread rapidly around the world, and the number of cases has increased exponentially.[1] Initial reports suggested that patients with cancer have an estimated twofold increased risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with the general population.[2] More importantly, it is expected that COVID-19 will be particularly life threatening in patients with hematological malignancies because of their immune dysfunction. Recent studies have reported an overall COVID-19–related mortality of 29% to 42%[3-8] in patients with hematological disease, depending on the type of malignancy, in contrast to the 2% to 7% observed in the general population. Regrettably, there remains a lack of studies about COVID-19 in patients receiving cellular therapies, including chimeric antigen receptor (CAR) T cells.[9,10] CAR T cells are genetically modified autologous T cells, which have shown great promise in the treatment of advanced malignant hematological disorders, including non-Hodgkin lymphoma, acute lymphoblastic leukemia, and multiple myeloma.[11] CAR T-cell recipients have significant B-cell aplasia requiring immunoglobulin G replacement therapy and may also develop delayed cytopenias, leaving them unable to mount any humoral response to viral infections.[12] Shah et al[10] demonstrated that the seroconversion rate in a small cohort of patients treated with hemopoietic stem cell transplantation (HSCT) and CAR T-cell therapy did not exceed 66%.

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According to these observations, the outcomes of COVID-19 in patients treated with CAR T cells remain unclear. The aim of this study was to describe the clinical outcomes of patients developing COVID-19 after treatment with CAR T cells.

Methods

In this retrospective observational multicenter study, we collected data on all consecutive adult patients who received CAR T-cell therapy with symptomatic COVID-19 between January 2020 and February 2021 across 18 European centers (Spain, n = 6; France, n = 3; Italy, n = 2; and Belgium, Croatia, Czechia, Slovakia, Sweden, Switzerland, and the United Kingdom, n = 1 each) participating in the survey promoted by the European Hematology Association (EHA) Scientific Working Group on Infection in Hematology (EPICOVIDEHA survey),[13] developed by the EHA Infectious Diseases Working Party (IDWP). Confirmed cases of COVID-19 were defined by positive reverse transcription polymerase chain reaction assays of specimens collected on nasopharyngeal swabs. Each institutional review board independently approved the study. The study was conduct in accordance with the Declaration of Helsinki. Researchers at each center collected data using an online questionnaire hosted at www.clinicalsurveys.net. The EPICOVIDEHA trial was registered at www.clinicaltrials.gov as #NCT04733729. Only deidentified data have been entered and analyzed. We obtained demographic data, comorbidities, and underlying hematological disease, including clinically significant outcomes (hospital and intensive care unit [ICU] admission and vital status) and management strategies of COVID-19. The severity of COVID-19 at admission was graded according to the China Centers for Disease Control and Prevention definitions: mild (nonpneumonia and mild pneumonia), severe (dyspnea, respiratory frequency ≥30 breaths per minute, oxygen saturation ≤93%, or ratio of arterial oxygen partial pressure/fractional inspired oxygen of 50%), and critical (respiratory failure, septic shock, or multiple organ dysfunction or failure).

SPSS v25.0 was employed for statistical analyses (IBM Corp., Chicago, IL). Categorical variables are presented using frequency and percentage, and continuous variables are shown by median, interquartile range (IQR), and absolute range. Additionally, overall mortality was evaluated by employing a Cox proportional hazards model. Univariable Cox regression model was performed with variables suspected to play a role in the mortality of patients with COVID-19 receiving CAR T-cell therapy. Variables with a P value ≤.1 were considered for multivariable analysis. Multivariable Cox regression model was calculated with the Wald backward method, and only statistically significant variables were reported. A P value ≤.05 was considered statistically significant.

Results and discussion

Overall, 459 patients received CAR T-cell therapy, of whom 30 met the criteria for diagnosis of COVID-19. Median age at COVID-19 diagnosis was 57 years (IQR, 51-64; range, 18-74); 13 patients (43.3%) were female, and 17 patients (56.7%) were male. Demographic and clinical characteristics of CAR T-cell recipients with COVID-19 are summarized in Table 1. Patients received CAR T cells for the treatment of large B-cell lymphoma (n = 28), multiple myeloma (n = 1), and acute lymphoblastic leukemia (n = 1). A majority of patients received CAR-T therapy in 2020 (n = 17), 3 in 2018, 9 in 2019, and 1 in 2021. CAR T cells were tisagenlecleucel (Kymriah) in 16 cases and axicabtagene (Yescarta) in 13 cases, and 1 patient with multiple myeloma was treated with CAR T cells targeting B-cell maturation antigen. A majority of patients received bridging therapy (n = 21 of 30) and fludarabine plus cyclophosphamide as lymphodepletion conditioning (n = 29 of 30). Severe (grade ≥3) CRS after receiving CAR T cells was observed in 1 patient only. No patient received COVID-19 vaccine. Seventeen patients (56.7%) developed COVID-19 within 6 months from CAR T-cell infusion, and 13 patients (43.3%) developed it after 6 months. Prevalence of COVID-19 in our patients was 4.8%, based on the total number of CAR T-cell recipients reported by participating centers in 2020 (n = 17 of 353).

Median time from CAR T-cell treatment to COVID-19 diagnosis was 169 days (IQR, 37-313; range, 1-635). Cellular and humoral immune reconstitution after CAR T cells showed that 90 days after infusion, median absolute neutrophil count and absolute lymphocyte count (ALC) were 1700/mm^3 (IQR, 1090-2700; range, 300-11 260) and 435/mm^3 (IQR, 200-775; range, 80-3500), respectively, whereas at the time of COVID-19 diagnosis, median absolute neutrophil count and ALC were 925/mm^3 (IQR, 495-2450; range, 18-11 510) and 370/mm^3 (IQR, 200-1250; range, 6-1750), respectively. Overall, 10% (n = 3), 20% (n = 6), and 66.7% (n = 20) of patients had asymptomatic, mild, or severe COVID-19, respectively. Comorbidities preceding diagnosis of COVID-19 were detected in 19 patients (76.7%), including chronic cardiopathy (n = 8; 23.3%), chronic pulmonary diseases (n = 7; 23.3%), smoking history (n = 6; 20.0%), and obesity (n = 5; 16.7%). In total, 13 patients (43.3%) required admission to ICU after COVID-19, and 9 of them (66.7%) required mechanical ventilation.

Patients received treatment for COVID-19 according to local policy; 15 patients were treated with convalescent plasma alone (n = 3) or convalescent plasma combined with remdesivir with or without steroids (n = 8), remdesivir with lopinavir/ritonavir and steroids (n = 1), and tocilizumab and steroids (n = 3); 5 patients were treated with steroids alone (n = 4) or steroids combined with remdesivir and tocilizumab (n = 1); 1 patient was treated with azithromycin; and 1 patient was treated with remdesivir alone. In total, 5 patients did not require any specific treatment; in 2 cases, this was because of poor general condition, and in 3 cases, treatment was unknown.

Median follow-up was 71 days (IQR, 44-142; range, 21-379) after CAR T-cell infusion, and at the last follow-up, 15 patients (50.0%) were alive and 15 patients (50.0%) had died. Ten patients (33%) died as a result of COVID-19 infection (associated with pulmonary embolism plus heart failure in 1 case and possible fungal infection in 1 case), and 5 patients died as a result of recurrent underlying disease (associated with COVID-19 infection in 3 patients). Seven (63.6%) of the 11 patients with relapsed/refractory disease and 7 (41.1%) of the 17 patients with complete remission/stable disease died as a result of COVID-19. In 2 patients, baseline malignancy status was unknown; 1 patient died, and 1 survived.

Severe (grade ≥3) CRS after CAR T cells was observed in 1 patient only, and in total, 8 (53.3%) of 15 patients who developed CRS after CAR T-cell infusion required treatment with tocilizumab with or without steroids. None of the parameters analyzed in the univariable analysis had a significant impact on patient outcomes. Only disease status at the time of COVID-19 was marginally significant for adverse outcome (P = .075), adjusted by sex (male vs female; P = .0092; Table 2).

Table 1. Characteristics of patients with COVID-19 receiving CAR T-cell therapy (n = 30)

Patient	Baseline hematological malignancy	Disease status at COVID-19 diagnosis	Time from CAR T cells to COVID-19, d	CAR T-cell construct	Bridging therapy	Lymphodepletion	Grade at CAR T-cell therapy		CRS/ICANS treatment		Reason for death (time after COVID-19 diagnosis, d)*
							CRS	ICANS	Tocilizumab	Steroids	
1	NHL LBCL	R/R	37	Axi-cel	X	Flu-Cyc	1	1			Malignancy (35)
2	NHL LBCL	CR	221	Axi-cel	X	Flu-Cyc	1	NA			NA
3	NHL LBCL	CR	240	Axi-cel		Flu-Cyc	2	NA	X	X	COVID-19 + other (52)
4	NHL LBCL	R/R	1	Tisa-cel	X	Flu-Cyc	2	NA	X	X	COVID-19 (25)
5	NHL LBCL	CR	85	Axi-cel		Flu-Cyc	1	2		X	NA
6	NHL LBCL	SD	14	Tisa-cel	X	Benda	2	1	X	X	COVID-19 + other (170)
7	MM	R/R	90	BCMA ARI-0002	X	Flu-Cyc	NA	NA			NA
8	NHL LBCL	R/R	42	Tisa-cel	X	Flu-Cyc	2	NA	X	X	Malignancy + COVID-19 (33)
9	NHL LBCL	R/R	397	Tisa-cel	X	Flu-Cyc	2	NA	X		NA
10	NHL LBCL	CR	313	Axi-cel	X	Flu-Cyc	1	NA	X		NA
11	ALL	Unknown	9	Tisa-cel		Flu-Cyc	NA	NA			NA
12	NHL LBCL	R/R	302	Axi-cel	X	Flu-Cyc	1	NA	X		COVID-19 (42)
13	NHL LBCL	CR	95	Tisa-cel	X	Flu-Cyc	NA	NA			NA
14	NHL LBCL	CR	457	Axi-cel	X	Flu-Cyc	1	NA			NA
15	NHL LBCL	R/R	158	Axi-cel	X	Flu-Cyc	1	NA	X	X	Malignancy (22)
16	NHL LBCL	R/R	65	Tisa-cel	X	Flu-Cyc	1	3	X	X	Malignancy + COVID-19 (21)
17	NHL LBCL	CR	270	Axi-cel	X	Flu-Cyc	3	NA	X	X	NA
18	NHL LBCL	Unknown	19	Tisa-cel		Flu-Cyc	2	NA	X		COVID-19 (50)
19	NHL LBCL	R/R	180	Tisa-cel		Flu-Cyc	1	NA	X	X	NA
20	NHL LBCL	CR	186	Tisa-cel		Flu-Cyc	1	NA			COVID-19 (51)
21	NHL LBCL	CR	348	Axi-cel		Flu-Cyc	2	2	X	X	NA
22	NHL LBCL	CR	19	Tisa-cel	X	Flu-Cyc	1	NA			NA
23	NHL LBCL	CR	605	Tisa-cel	X	Flu-Cyc	NA	NA			COVID-19 (46)
24	NHL NOS	CR	635	Axi-cel		Flu-Cyc	1	NA			COVID-19 (44)
25	NHL LBCL	R/R	180	Tisa-cel	X	Flu-Cyc	1	NA			Malignancy + COVID-19 (32)
26	NHL LBCL	CR	485	Axi-cel	X	Flu-Cyc	1	NA			COVID-19 (53)
27	NHL LBCL	CR	510	Axi-cel		Flu-Cyc	1	NA			COVID-19 (124)
28	NHL LBCL	CR	66	Tisa-cel	X	Flu-Cyc	1	NA	X		NA
29	NHL LBCL	R/R	12	Tisa-cel	X	Flu-Cyc	1	1			NA
30	NHL LBCL	CR	35	Tisa-cel	X	Flu-Cyc	NA	NA			NA

Other reasons for death: Patient #3, possible IFI; patient #6, pulmonary embolism and heart failure.

ALL, acute lymphoblastic leukemia; axi-cel, axicabtagene ciloleucel; BCMA, B-cell maturation antigen; benda, bendamustine; CR, complete remission; CRS, cytokine release syndrome; Flu-Cyc, fludarabine plus cyclophosphamide; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SD, stable disease; tisa-cel, tisagenlecleucel.

*Other reasons for death: patient 3, possible invasive fungal infection; patient 6, pulmonary embolism and heart failure.

Table 2. Univariable and multivariable analyses of factors associated with mortality of patients with COVID-19 receiving CAR T cells

	All patients						Time between CAR T-cell therapy and COVID-19, mo					
							≤6			>6		
	Univariable			Multivariable			Univariable			Univariable		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex												
Female	–	–	–	–	–	–	–	–	–	–	–	–
Male	2.682	0.849-8.474	.093	2.742	0.848-8.861	.092	4.897	0.591-40.604	.141	1.928	0.417-8.908	.401
Age, y												
<50	–	–	–	–	–	–	–	–	–	–	–	–
≥50	5.119	0.673-38.955	.115	–	–	–	1.809	0.222-14.742	.580	42.159	0.068-26 050.639	.254
Comorbidities, n												
None	–	–	–	–	–	–	–	–	–	–	–	–
1	3.093	0.772-12.393	.111	–	–	–	3.093	0.772-12.393	.111	3.438	0.482-24.537	.218
2	3.021	0.498-18.328	.229	–	–	–	3.021	0.498-18.328	.229	2.055	0.185-22.871	.558
≥3	1.880	0.413-8.562	.414	–	–	–	1.880	0.413-8.562	.414	6.111	0.820-45.529	.077
Malignancy status at COVID-19 diagnosis												
Controlled disease	–	–	–	–	–	–	–	–	–	–	–	–
Active disease	2.707	0.931-7.870	.067	2.652	0.907-7.754	.075	2.707	0.931-7.870	.944	1.121	0.133-9.446	.916
Unknown	1.579	0.188-13.238	.674	1.059	0.123-9.132	.958	–	–	.947	–	–	–
CAR T-cell construct												
Axi-cel	–	–	–	–	–	–	–	–	–	–	–	–
Tisa-cel	0.888	0.321-2.458	.820	–	–	–	0.479	0.092-2.494	.382	1.552	0.296-8.132	.603
Other	–	–	.986	–	–	–	–	–	.991	–	–	–
ICU stay	1.529	0.554-4.225	.413	–	–	–	0.887	0.211-3.729	.870	3.331	0.643-17.247	.152
Tocilizumab/steroids after CAR T cells	1.437	0.520-3.972	.484	–	–	–						
Time from CAR T cells to COVID-19, mo												
≤6	–	–	–	–	–	–						
>6	0.998	0.359-2.770	.996	–	–	–						
Neutrophils at COVID-19 diagnosis, n per mm^3												
≤500	–	–	–	–	–	–	–	–	–	–	–	–
>500	0.611	0.161-2.321	.469	–	–	–	0.761	0.167-3.472	.724	–	–	–
Lymphocytes at COVID-19 diagnosis, n per mm^3												
≤200	–	–	–	–	–	–	–	–	–	–	–	–
>200	0.551	0.164-1.846	.334	–	–	–	0.568	0.133-2.419	.444	0.872	0.089-8.511	.907

Axi-cel, axicabtagene ciloleucel; CI, confidence interval; HR, hazard ratio; tisa-cel, tisagenlecleucel.

In the present multicenter international study, we sought to evaluate COVID-19 outcomes in a cohort of 459 consecutive patients who received CAR T-cell therapy. Several studies have addressed clinical courses and outcomes of COVID-19 in patients with hematological disease as well as the presence of risk factors for more aggressive life-threatening disease.[4,7,14-16] Patients with hematological malignancies may be considered more vulnerable than the general population; however, the exact prevalence of SARS-CoV-2 infection in this setting is still unclear. We documented a 4.8% prevalence of COVID-19 in our study group, remarkably higher than the 0.1% reported in the general population, and median onset of COVID-19 was 169 days after CAR T-cell therapy. Several factors could explain the high rate of COVID-19 in patients receiving CAR T cells. Our study included a homogeneous group of heavily pretreated patients with large B-cell lymphoma who received at least 2 lines of treatment before CAR T-cell and lymphodepletion therapies. Delayed cytopenias and impaired immune reconstitution, leading to a significant risk of infectious complications, have been well documented after CAR T-cell therapy.[12] Consistent with findings seen in prior studies, we observed a low lymphocyte count 90 days after CAR T cells (median ALC, 435/mm^3) and at the time of COVID-19 diagnosis (median ALC, 370/mm^3; 23% of patients had <200 lymphocytes per mm^3), although the presence of both neutropenia and lymphocytopenia at COVID-19 diagnosis was not statistically significant in univariable analysis. In addition, it should be emphasized that the presence of relapsed/refractory disease in one-third of patients at the time of COVID-19 should be taken into account as a potential confounding factor. Regrettably, we were

unable to investigate in detail humoral or cellular immune reconstitution or whether worsening of lymphopenia during infection had an impact on survival. Notably, our results showed that half of the patients developed COVID-19 after the first 6 months post–CAR T-cell therapy, underscoring that prolonged delayed immune recovery may persist for a long period of time after cellular therapy.[17] Currently, there are few clinical trials evaluating the potential role of COVID-19 treatment in patients with cancer[18]; observational studies are also extremely limited. In our study, patients received a wide array of treatments, making difficult to draw any firm conclusions. Based on the presence of impaired humoral and cellular immune reconstitution after CAR T-cell therapy in a consistent number of patients, suboptimal responses to current treatments used in patients with COVID-19 are expected, although specific studies are urgently required to address this issue.

Mortality rates in patients receiving cellular therapy have been reported in few studies. Altuntas et al[9] evaluated 32 recipients of autologous and allogeneic grafts and found a 33% case fatality rate among patients still receiving immunosuppressive agents at the time of COVID-19 diagnosis. Similar results have been reported by the European Society for Blood and Marrow Transplantation group, with a mortality rate reaching 25%; older age, need for ICU admission, and moderate/high immunodeficiency index increased the risk for mortality.[19] The Center for International Blood and Marrow Transplant Research reported the results of 318 patients with COVID-19 who had undergone HSCT (allogeneic, n = 184; autologous, n = 134). Overall mortality was 22% among those who underwent allogeneic HSCT; age > 50 years, male sex, and time from HSCT to COVID-19 diagnosis <6 months were factors significantly associated with mortality.[20] Shah et al[10] evaluated 77 patients with COVID-19 who had been treated with HSCT (n = 72) and CAR T-cell therapy (n = 5); the overall death rate was 41%, roughly similar to that reported in our study, and was largely driven by patients with advance disease. The 50% mortality rate was remarkably high in our patients, considering that 10 of 15 deaths resulted from COVID-19 or COVID-19–related events. In this respect, it is worthwhile to keep in mind that two-thirds of our patients had severe infections, and 30% of our patients required mechanical ventilation. In addition, advanced disease status at the time of COVID-19 diagnosis should be considered a potential factor limiting favorable outcomes for patients, as emphasized by the univariable analysis. Several factors might explain the higher mortality rate observed in our study as compared with that reported in patients who had undergone HSCT. Patients with relevant comorbidities are usually excluded from HSCT programs, whereas comorbidities do not preclude CAR T-cell treatment in these vulnerable patients. Time interval from HSCT to COVID-19 has emerged as a factor associated with mortality in many studies, ranging from 13.7 to 18.9 months,[12,14,19,20] significantly longer than the median time from CAR T-cell therapy to COVID-19 reported in our series (median time, 169 days).

Preliminary data in patients who have undergone HSCT show that COVID-19 is associated with low lymphocyte counts, particularly in T-cell compartments; however, lymphopenia does not seem to impair immune reconstitution in recovery from COVID-19. Regrettably, we do not have data on lymphocyte subsets after COVID-19 in our cohort of patients, although protracted and profound lymphopenias after CAR T cells have been reported in several studies. In addition, whether differences in CAR T-cell products affect the kinetics of immunodeficiency recovery remains to be determined.

If prospective large studies corroborate our preliminary results, it seems wise to define strategies able to mitigate the adverse events occurring in patients receiving CAR T cells who develop COVID-19. Prioritization of COVID-19 vaccination in patients with hematological disease is of paramount importance; however, based on existing knowledge of the reduced immunogenicity in the immunocompromised host, CAR T-cell recipients are not expected to generate robust responses to COVID-19 vaccines. In this respect, additional preventive measures should be explored. It has been shown that cellular therapies may be safely administered throughout the COVID-19 pandemic when appropriate interventions are instituted, including antimicrobial stewardship programs, screening of donors and recipients, and safe delivery of cellular products. Appealing alternatives to vaccination are monoclonal antibodies or prophylaxis with oral agents (fluvoxamine and molnupiravir), although clinical trials in patients with hematological disease are urgently needed.

Our study is limited by its retrospective nature and small number of patients. Nevertheless, our results highlight a significant mortality rate in patients with COVID-19 who have received CAR T-cell therapy. Therapeutic strategies will need to be developed to ensure that CAR T-cell therapy can be delivered safely and successfully while COVID-19 remains endemic. Furthermore, data on vaccinations in this cohort are eagerly awaited to help formulate safe delivery.

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Authorship

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A complete list of the members of the EPICOVIDEHA Study Group appears in "Appendix."

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References

1. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720.
2. Miyashita H, Mikami T, Chopra N, et al. Do patients with cancer have a poorer prognosis of COVID-19? An experience in New York City. *Ann Oncol.* 2020;31(8):1088-1089.
3. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol.* 2020;7(10):e737-e745.
4. Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York hospital system. *Cancer Discov.* 2020; 10(7):935-941.
5. Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant.* 2020;55(11): 2180-2184.
6. Piñana JL, Martino R, García-García I, et al; Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH). Risk factors and outcome of COVID-19 in patients with hematological malignancies. *Exp Hematol Oncol.* 2020;9:21.
7. Martín-Moro F, Marquet J, Piris M, et al. Survival study of hospitalised patients with concurrent COVID-19 and haematological malignancies. *Br J Haematol.* 2020;190(1):e16-e20.
8. Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. *Leukemia.* 2020;34(9):2354-2363.

9. Altuntas F, Ata N, Yigenoglu TN, et al; Turkish Ministry of Health, Hematology Scientific Working Group. COVID-19 in hematopoietic cell transplant recipients. *Bone Marrow Transplant.* 2021;56(4):952-955.

10. Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Invest.* 2020; 130(12):6656-6667.

11. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J.* 2021;11(4):69.

12. Strati P, Varma A, Adkins S, et al. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. *Haematologica.* 2021;106(10):2667-2672.

13. Salmanton-García J, Busca A, Cornely OA, et al. EPICOVIDEHA: a ready-to use platform for epidemiological studies in hematological patients with COVID-19. *HemaSphere.* 2021;5(7):e612.

14. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. *Br J Haematol.* 2020;190(5):e279-e282.

15. Maia C, Martín-Sánchez E, Garcés JJ, et al. Immunologic characterization of COVID-19 patients with hematological cancer. *Haematologica.* 2020; 106(5):1457-1460.

16. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood.* 2020;136(25):2881-2892.

17. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica.* 2020;106(4):978-986.

18. Rivera DR, Peters S, Panagiotou OA, et al. Utilization of COVID-19 treatments and clinical outcomes among patients with cancer: a COVID-19 and cancer consortium (CCC19) cohort study. *Cancer Discov.* 2020;10(10):1514-1527.

19. Ljungman P, de la Camara R, Mikulska M, et al. COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey. *Leukemia.* 2021;35(10):2885-2894.

20. 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 [published correction appears in *Lancet Haematol.* 2021;8(6):e393]. *Lancet Haematol.* 2021;8(3):e185-e193.