Cardiovascular events in patients treated with chimeric antigen receptor T-cell therapy for aggressive B-cell lymphoma

Raphael E. Steiner,[1*] Jose Banchs,[2*] Efstratios Koutroumpakis,[2**] Melody Becnel,[1**] Cristina Gutierrez,[3] Paolo Strati,[1] Chelsea C. Pinnix,[4] Lei Feng,[5] Gabriela Rondon,[6] Catherine Claussen,[1] Nicolas Palaskas,[2] Kaveh Karimzad,[2] Sairah Ahmed,[1] Sattva S. Neelapu,[1] Elizabeth Shpall,[6] Michael Wang,[1] Francisco Vega,[7] Jason Westin,[1#] Loretta J. Nastoupil[1#] and Anita Deswal[2#]

[1]Lymphoma and Myeloma, MD Anderson Cancer Center; [2]Cardiology, MD Anderson Cancer Center; [3]Critical Care& Respiratory Care, MD Anderson Cancer Center; [4]Radiation Oncology, MD Anderson Cancer Center; [5]Biostatistics, MD Anderson Cancer Center; [6]Stem Cell Transplantation, MD Anderson Cancer Center and [7]Hematophathology, MD Anderson Cancer Center, Houston, TX, USA

*RES and JBcontributed equally as co-first authors.
**EK and MB contributed equally as co-second authors.
#JW, LJN and AD contributed equally as co-senior authors.

Abstract

Standard of care (SOC) chimeric antigen receptor (CAR) T-cell therapies such as axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are associated with multisystem toxicities. There is limited information available about cardiovascular (CV) events associated with SOC axi-cel or tisa-cel. Patients with CV comorbidities, organ dysfunction, or lower performance status were often excluded in the clinical trials leading to their Food and Drug Adminsitration approval. An improved understanding of CV toxicities in the real-world setting will better inform therapy selection and management of patients receiving these cellular therapies. Here, we retrospectively reviewed the characteristics and outcomes of adult patients with relapsed/refractory large B-cell lymphoma treated with SOC axi-cel or tisa-cel. Among the 165 patients evaluated, 27 (16%) developed at least one 30-day (30-d) major adverse CV event (MACE). Cumulatively, these patients experienced 21 arrhythmias, four exacerbations of heart failure/cardiomyopathy, four cerebrovascular accidents, three myocardial infarctions, and one patient died due to myocardial infaction. Factors significantly associated with an increased risk of 30-d MACE included age ≥60 years, an earlier start of cytokine release syndrome (CRS), CRS ≥ grade 3, long duration of CRS, and use of tocilizumab. After a median follow-up time of 16.2 months (range, 14.3-19.1), the occurrence of 30-d MACE was not significantly associated with progression-free survival or with overall survival. Our results suggest that the occurrence of 30-d MACE is more frequent among patients who are elderly, with early, severe, and prolonged CRS. However, with limited follow-up, larger prospective studies are needed, and multidisciplinary management of these patients is recommended.

Introduction

Patients with relapsed/refractory aggressive large B-cell lymphoma (LBCL) can achieve durable remissions with anti-CD19 chimeric antigen receptor T (CAR-T) cell therapies.[1-5] Multicenter clinical trials led to US Food and Drug Administration (FDA) approval of the CAR-T cell products axicabtagene ciloleucel (axi-cel) in October 2017, tisagenlecleucel (tisa-cel) in May 2018, and Lisocabtagene maraleucel in February 2021 for relapsed or refractory LBCL after two or more lines of systemic therapy.[6-8] In the trials leading to their FDA approval, patients with cardiovascular (CV) comorbidities, organ dysfunction, or lower performance status were often excluded.

These CAR-T cell therapies are associated with significant toxicities. Notably, cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS) are commonly observed.[9] In addition, CAR-T cell therapy has been associated with cardiotoxicity, which may result in prolonged length of hospital stay, admission to the intensive care unit for vasopressor support, or cardiac death.[10] Early diagnosis and management of CV complica-

tions may occur in patients with CRS and require awareness and multidisciplinary collaboration.[11,12]

The exact mechanisms of CAR-T cell-associated cardiac dysfunction are unclear. Potential hypotheses include interleukin-6–mediated myocardial stunning[13] during CRS.[14] With the increased utilization of CAR-T cell therapy outside of clinical trials, more data characterizing the CV toxicities of standard of care (SOC) CAR-T cell therapy among LBCL adults are needed to assist clinical decisions. An adequate cardiac reserve is required to withstand the clinical manifestations of CRS. Second, many adults, including elderly patients treated with CAR-T cell therapy, especially outside of clinical trials, have pre-existing CV disease in addition to prior cardiotoxic chemo- or radiation therapy. These different factors can predispose patients to a higher risk for CV events after CAR-T therapy. Hence, we report the results from a contemporary cohort of patients with relapsed or refractory LBCL treated at our institution with SOC axi-cel and tisa-cel and describe the clinical, CV characteristics and outcomes and their relation to CRS.

Methods

Patient selection

The study cohort consists of 165 consecutive adult patients (≥18 years old) with relapsed or refractory LBCL after ≥2 lines of systemic therapy, treated with SOC axi-cel and tisa-cel at the University of Texas MD Anderson Cancer Center (MDACC), between January 2018 and April 2020. The study excluded patients with unapproved indications such as Richter syndrome and post-transplant lymphoproliferative disorders because of their different biology and outcomes.

SOC was defined as the administration of commercial products outside of any clinical trial.[9] Follow-up data were collected through February 19, 2021. The study was approved by the Institutional Review Board (IRB) of MDACC and conducted in accordance with our institutional guidelines and the principles of the Declaration of Helsinki.[9] The IRB approved the request of waiver of informed consent and a waiver of authorizations as the study does not involve diagnostic or therapeutic intervention or any type of direct patient contact.

Covariates, definitions, and response assessment

Data on the covariates were extracted retrospectively from the electronic medical records.[15]

A cardiologist reviewed all electrocardiogram (EKG) (EK) and echocardiogram studies (JB). Cardiac testing was performed at the discretion of the treating team at any time and was not pre-specified.

Myocardial infarction (MI) was defined as angina or anginal equivalent symptoms with cardiac enzyme elevation, with or without EKG/echocardiographic changes. New or worsening cardiomyopathy (CMP) was defined as a reduction in left ventricular ejection fraction (LVEF) >10% from baseline to <50% during the hospitalization for CAR-T cell therapy.[14] Major adverse cardiovascular events (MACE) were defined as a composite of arrhythmias requiring an intervention, new or worsening CMP, exacerbation of heart failure (HF), cerebrovascular accident (CVA), MI, or CV death. CV death was defined as death due to HF, cardiogenic shock, arrhythmia, MI, or cardiac arrest.[16]

CRS and ICANS were prospectively graded for up to 30 days (30-d) after CAR-T cell infusion according to the CAR toxicity (CARTOX) grading system from January 2018 to April 2019 and ASTCT criteria from May 2019 onward.[17,18] CRS and ICANS were managed according to our institutional CARTOX guidelines. Notably, patients requiring tocilizumab received 8 mg/kg dosing for a maximum of four doses. All MACE were treated by cardiologists per disease guidelines and clinical expertise. Of note, all patients receiving CAR-T cell therapy are monitored by telemetry at our institution. Lymphoma response status was determined by the Lugano 2014 classification.[19]

Statistical methods

Fisher's exact test or Chi-square test was used to evaluate associations between categorical variables. The Wilcoxon rank sum test was used to evaluate differences in continuous variables between patient groups. Multivariable logistic regression models were fitted to estimate the effects of important covariates on 30-day (30-d) MACE. The variables with a *P*-value <0.2 from the univariable analysis were included in the full multivariable model, and a backward selection method was used for the final model.

Progression-free survival (PFS) time was calculated from the start of CAR-T cell infusion to the progression of disease or death, whichever occurred first. Patients without event were censored at the last follow-up. Overall survival (OS) was calculated from the start of CAR-T cell infusion to death or last follow-up. A multidisciplinary committee determined the cause of death, including a cardiologist, intensivist, and medical oncologist. The Kaplan-Meier method was used to estimate PFS and OS. The Cox proportional hazards models were used for multivariable analysis. The Schoenfeld residual was used to check the proportional hazards assumption. The variables with a *P*-value <0.2 from the univariable analysis were included in the initial full model. A backward selection method was used, and a significant level of 0.1 was set as the criterion for a covariate to stay in the model. Landmark analysis for PFS/OS by 30-d MACE post-infusion was performed using the landmark time of 30 d. The patients with follow-up time less than 30-d were excluded from this analysis. 30-d MACE was forced

in the final model to assess its effect on PFS/OS with the adjustment of other covariates in the model.

Results

Baseline patient characteristics

The baseline characteristics of the study cohort of 165 patients with relapsed or refractory LBCL are shown in Table 1. Patients had a median age of 60 years (range, 18-88 years), and the majority were male (72%) and white (74%). They had received a median number of three previous therapy lines, a median cumulative dose of anthracycline of 300 mg/m^2, and 12% had a history of radiotherapy of the chest. Overall, 9% of patients had a history of coronary artery disease (CAD), and 8% had a history of HF. Most patients received axi-cel (94%; median age 60 years; range, 18-85 years), and ten patients received tisa-cel (6%; median age 66 years; range, 28-88 years).

Description of 30-day major adverse cardiovascular events

Overall, 27 patients (16%) developed at least one 30-d MACE, with a total of 33 30-d MACE (Figure 1A). Of all MACE, 64% were arrhythmias that triggered a medical intervention even if asymptomatic, 12% were CVA, 12% were new or exacerbated prior HF or worsening of CMP, 6% were non-fatal MI, and one was a CV death due to possible MI. Figure 1B shows the distribution of the first and subsequent MACE by patients. The timing of the 30-day MACE is depicted in Figure 1C. The first MACE occurred at a median of 7 days (range, 0-29 days) after CAR-T cell infusion (day 0), and 91% of all events occurred within the first 16 days after the infusion. Six patients had one recurrence of 30-d MACE, with five of these six events occurring in patients who had an arrhythmia as the initial event (Figure 1B).

The baseline characteristics between patients who did and did not develop a MACE are shown in Table 1. Patients that developed MACE were older (median age 69 years)) compared with patients that did not develop MACE (median age 59 years). However, younger patients also presented with severe non-arrhythmic CV events. Non-arrhythmic CV events include MI, cerebrovascular accident, heart failure, cardiomyopathy, and CV-related death. Although the prevalence of CV risk factors and pre-existing cardiac disease was numerically higher in patients with MACE compared to those without MACE, these differences did not reach statistical significance (trend towards significance for coronary artery disease).

Among the patients who developed arrhythmias triggering an intervention, the median age was 68 years (range, 42-82 years). Almost half these arrhythmias (48%) were short runs of non-sustained ventricular tachycardia (NSVT), with

a median number of eight beats (range, 3-11), and only one event was associated with symptoms of palpitations. Episodes of NSVT were detected, given patients were monitored on telemetry as standard practice. In the ten (48%) patients with at least one episode of atrial fibrillation (AF), the median age was 70 years (range, 54-83 years), and among them, only two had a prior history of AF before CAR-T cell therapy. Of the ten patients treated with tisa-cel, two patients aged 71 and 81 years old developed a 30-d MACE, an episode of AF, and NSVT, respectively. All the patients who presented with at least one episode of arrhythmia had a rapid resolution of the event, and 55% of them were discharged with a new cardiac medication such as metoprolol and/or amiodarone.

Of the three patients with MI, the median age was 77 years (range, 60-83 range), two had a prior history of CAD, and all had a least one CV risk factor. One patient required cardiac catheterization without revascularization; the two other patients could not get aspirin because of grade 4 thrombocytopenia and did not undergo invasive cardiac evaluation. The CV death also occurred in an elderly patient, 76 years old, with a history of diabetes mellitus and hypertension, in the setting of transient CRS maximal grade 1, requiring tocilizumab. He developed a cardiac arrest due to suspected inferior MI on day 15 post-CAR-T cell infusion.

Three patients developed clinical HF, and one patient developed a worsening CMP with further reduction in LVEF without symptomatic HF (median age of patients with HF or cardiomyopathy was 62 years). Of the three patients with symptomatic HF post-CAR-T cell therapy, at baseline, one patient had a history of mild asymptomatic ischemic CMP, one patient had a history of HF with preserved LVEF, and one patient had a history of AF with preserved LVEF. All patients with symptomatic HF developed a significant reduction in LVEF. These patients had a median baseline LVEF of 50% (range, 47-63%). None of the HF exacerbations or CMP were related to CAD or MI.

Among the four patients with clinical HF/worsening CMP, three presented with progression of LBCL at day 30, and one died of multiple etiologies at day 50.

Among the four patients who presented a CVA (median age 61 years), three had at least one CV risk factor, and two of them had AF. A young 24-year-old patient without risk factors was postulated to have CVA-like brain injury possibly related to ICANS. Of note, among all the patients who presented a 30-d MACE, only one was readmitted in the following 6 months for a CV reason: atrial fibrillation with rapid ventricular rate.

Echocardiographic characteristics

Overall, 129 patients (78%) had a baseline echocardiogram before CAR-T cell therapy infusion, with a median baseline LVEF of 54% (range, 38-75%). Although numerically lower

in patients with 30-d MACE (median LVEF 53%), the difference in LVEF compared to patients without MACE (58%) was not statistically significant, *P*=0.131 (Table 1). Moreover, 67% of non-arrhythmic MACE occurred in patients with a baseline LVEF of at least 50%, as shown in Figure 2. Baseline diastolic function could be reported in 123 patients: normal in 51%, grade 1 (mild/impaired relaxation) in 57 (46%), and grade 2 (moderate/pseudonormal)
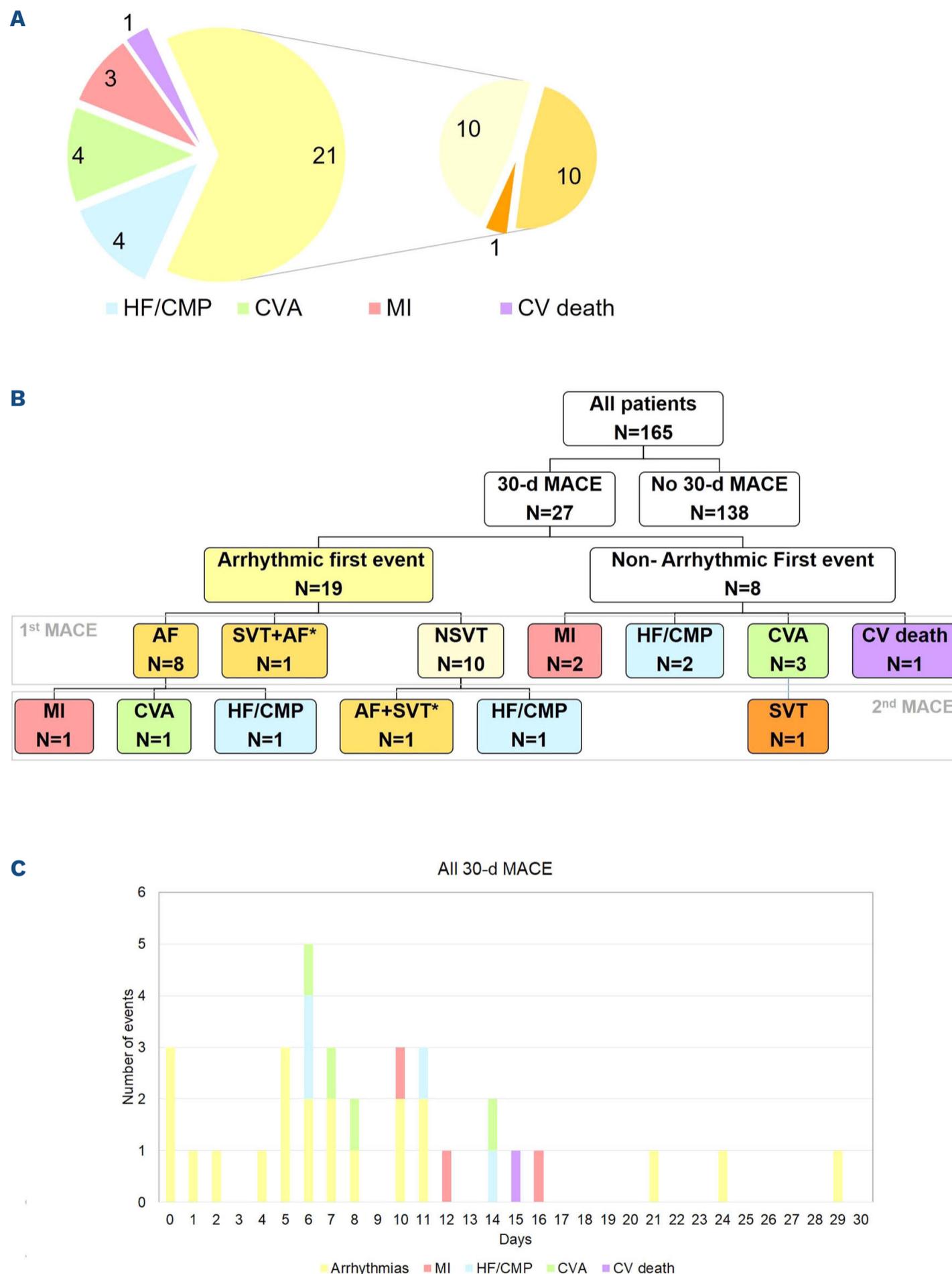
Figure 1. Nature, recurrences, and timing of 30-day major adverse cardiovascular events (A) Cumulative occurrences of 30-day major adverse cardiovascular event (30-d MACE). (B) Nature and recurrences of 30-d MACE. *Events happened on the same day, counted as 1 atrial fibrillation (AF) event. The patients who presented clinical heart failure had a decrease in left ventricular ejection fraction. (C). Timing of 30-d MACE. Day 0 represents the day of chimeric antigen receptor T-cell therapy infusion. AF: atrial fibrillation; CMP: cardiomyopathy; HF: heart failure; CV: cardiovascular; CVA: cerebrovascular accident; MI: myocardial infarction; NSVT: non-sustained ventricular tachycardia; SVT: supraventricular tachycardia.

Table 1. Baseline patient characteristics and association with 30-day major adverse cardiovascular events

Characteristics/ Outcomes	All patients (N= 165)	Patients who did not present 30-d MACE (N = 138)	Patients who presented at least one 30-d MACE (N = 27)	P	Patients who presented at least one 30-d MACE (N = 27)	
					Arrhythmic event(s) only (N = 15)	At least one non-arrhythmic event (N = 12)
Cohort						
Age, median [range], y	60 [18-88]	59 [18-88]	69 [24-83]	**0.001**	68 [42-82]	70 [24-83]
Age >60 years	87 (53%)	66 (48%)	21 (78%)	**0.004**	13 (48%)	8 (30%)
Age <60 years	78 (47%)	72 (52%)	6 (22%)		2 (7%)	4 (15%)
Male	118 (72%)	97 (70%)	21 (78%)	0.431	11 (41%)	10 (37%)
Race						
Asian	8 (5%)	6 (4%)	2 (7%)	0.212	1 (4%)	1 (4%)
African American	13 (8%)	13 (9%)	0 (0%)		0 (0%)	0 (0%)
White	123 (74%)	100 (73%)	23 (86%)		13 (48%)	10 (37%)
Hispanic	21 (13%)	19 (14%)	2 (7%)		1 (4%)	1 (4%)
ECOG performance status >1	129 (78%)	21 (15%)	5 (19%)	0.772	2 (7%)	3 (11%)
HCT-CI						
NA	26 (16%)	25 (18%)	7 (26%)	0.897	1 (4%)	6 (22%)
0	37 (22%)	31 (22%)	6 (22%)		5 (19%)	1 (4%)
1-2	55 (33%)	44 (32%	11 (41%)		3 (11%)	8 (30%)
≥3	47 (28%)	38 (28%)	9 (33%)		6 (22%)	5 (19%)
Previous treatment						
Previous therapies, median [range], N	3 [2-11]	3 [2-11]	3 [2-6]	0.915	2 [2-6]	3 [2-5]
Previous ASCT	42 (26%)	37 (27%)	5 (19%)	0.472	3 (11%)	2 (7%)
Cum dose anthracycline, mg/m², median [range], N	300 [0-632]	300 [0-632]	300 [50-370]	0.660	300 [50-300]	225 [80-370]
History of radiotherapy of chest	20 (12%)	17 (12%)	3 (11%)	1.000	1 (4%)	2 (7%)
CV risk factors and baseline CVD						
Hypercholesterolemia	39 (24%)	34 (25%)	5 (19%)	0.623	2 (7%)	3 (11%)
Smoking (history or active)	58 (35%)	46 (34%)	12 (44%)	0.280	9 (33%)	3 (11%)
Diabetes Mellitus	37 (23%)	29 (21%)	8 (30%)	0.336	3 (11%)	5 (19%)
Hypertension	70 (43%)	55 (40%)	15 (56%)	0.139	7 (26%)	8 (30%)
History of coronary artery disease	14 (9%)	9 (7%)	5 (19%)	0.057	2 (7%)	3 (11%)
Heart failure	13 (8%)	9 (7%)	4 (15%)	0.231	2 (7%)	2 (7%)
History of coronary artery disease or heart failure	22 (13%)	16 (12%)	6 (22%)	0.141	3 (33%)	3 (11%)
Baseline echocardiographic features#						
Left ventricular ejection fraction, median [range]	58% [38-75]	58% [38-75]	53% [39-68]	0.131	58% [39-66]	50% [44-68]
Presence of diastolic dysfunction	49%	43%	82%	**0.004**	89%	75%
CAR-T cell therapy						
Axi-cel	155 (94%)	130 (94%)	25 (93%)	0.669	13 (48%)	12 (44%)
Tisa-cel	10 (6%)	8 (6%)	2 (7%)		2 (7%)	0 (0%)

Values are n (%) except as noted. % values reflect the proportion of patients who had no 30-d MACE, at least one 30-d MACE, and all the patients. *P*-value reflects the comparison of patients who did not present a 30-d MACE with patients who had at least one MACE. Bold numbers indicate a significant *P*-value. CAR-T cell: chimeric antigen receptor T cell; ASC: autologous stem cell transplant; CAR: chimeric antigen receptor; cum: cumulative; CV: cardiovascular; CVD: cardiovascular disease; d: day; ECOG: Eastern Cooperative Oncology Group; HCT-CI: Hematopoietic Cell Transplantation–Specific Comorbidity Index[15]; MACE: major adverse cardiovascular event; n: number of patients; NA: not available; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; y: years. Non-arrhythmic events include myocardial infarction, cerebrovascular accident, heart failure, cardiomyopathy, and cardiovascular-related death. #not done in all patients.

in three patients (3%). Patients who presented with any baseline diastolic dysfunction were more at risk for 30-d MACE (82% in the 30-d MACE group *vs* 43% in the non-MACE group, *P*=0.004).

Among the 27 patients who had at least one repeat echocardiogram during the 30-d following CAR-T cell therapy, only six patients had a decrease of LVEF of at least 10% (range, 10-21%); however, only four of them experienced a decrease of LVEF under 50%. Among the latter, one patient had documented rapid resolution of the LVEF decrease but died of lymphoma progression on day 53 (Figure 3). Another patient had no documented recovery of LVEF and died of lymphoma progression on day 49. The two latter patients did not have a documented repeat echocardiogram to date but had clinical recovery of HF in less than a month.

Inflammation and 30-day major adverse cardiovascular events

Overall, 151 (92%) patients had CRS, and 100 (61%) had ICANS of any grade. As shown in Table 2, patients with 30-d MACE were more likely to have an earlier manifestation of CRS and longer and more severe episodes of CRS requiring tocilizumab (especially patients with non-arrhythmic events) than patients who did not have 30-d MACE (*P*=0.016). There was no significant association between 30-d MACE and ICANS, the requirement for ste-

roids, stay in the ICU, use of vasopressive and inotropic support, and intubation/mechanical ventilation. Moreover, among the three patients who presented a 30-d MACE requiring intubation, only one patient was intubated for CV reasons (cardiac arrest). Compared with patients without 30-d MACE (n=138), 30-d MACE was not associated with higher median peak ferritin, CRP, or time to the first peak of CRP or ferritin.

### Independent predictors of major adverse cardiovascular events

On multivariable analyses, the only two independent predictors of 30-MACE were age (odds ratio 3.98, 95% confidence interval [CI]: 1.47-10.78 for MACE in patients > 60 years *vs.* those <60 years) and development of grade 3 or higher CRS (odds ratio 4.66, 95% CI: 1.68-12.95; *Online Supplementary Tables S1 and S2, Online Supplementary Appendix*).

Outcome of patients with major adverse cardiovascular events

After a median follow-up time of 16.2 months (range, 14.3-19.1 months) for censored observations, the occurrence of 30-d MACE was not significantly associated with hospital survival, PFS (12-month PFS 38% if 30-d MACE *vs.* 42% without 30-d MACE, *P*=0.552, log-rank test, Figure 4), or with OS (12-month OS 58% if 30-d MACE *vs.* 62% without
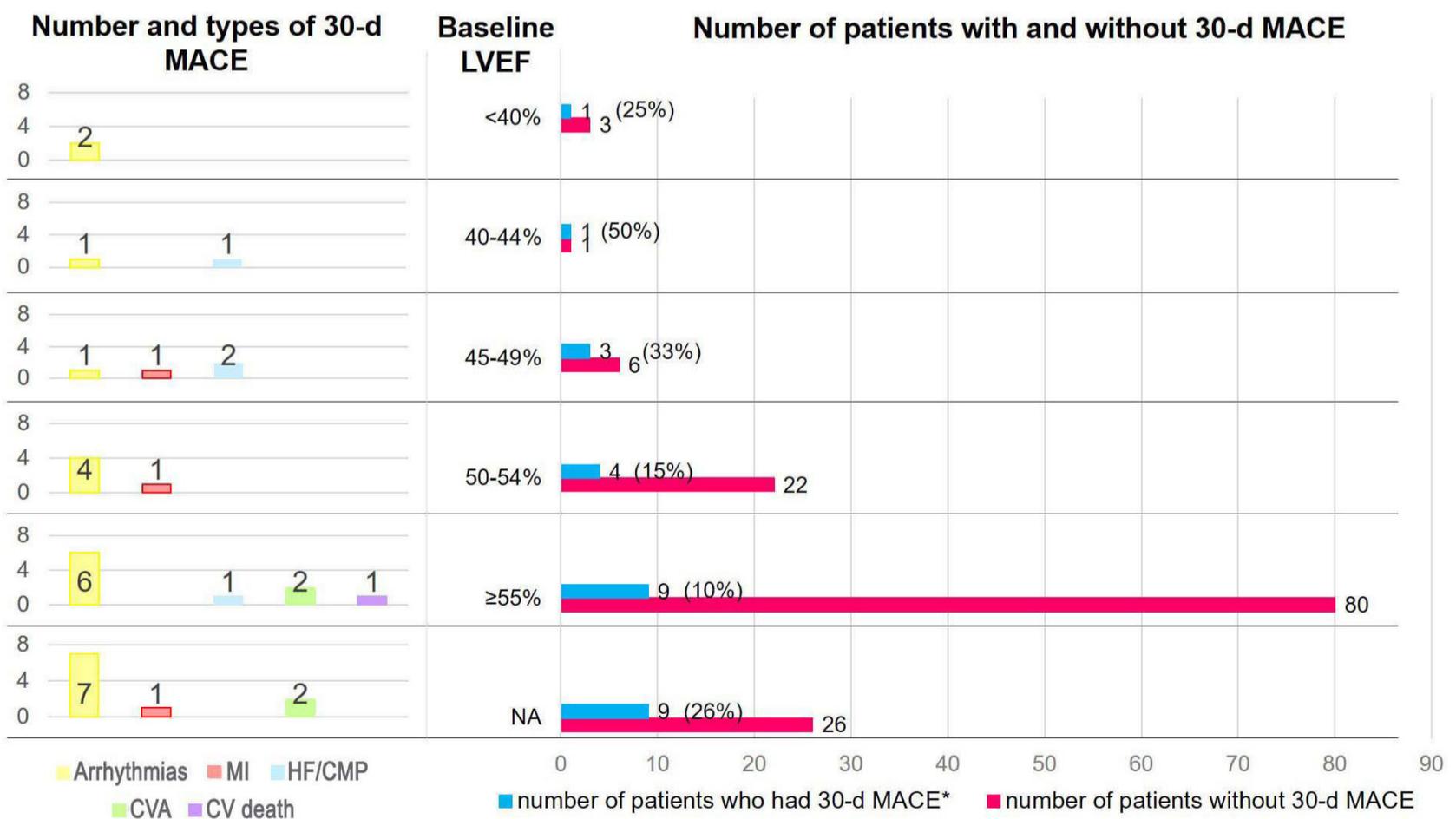
Figure 2. Baseline left ventricular ejection fraction and occurrence of 30-day major adverse cardiovascular events. *The numbers between parentheses represent the proportion of patients who had at least a 30-day major adverse cardiovascular event (30-d MACE) within the represented range of baseline left ventricular ejection fraction (LVEF). CMP: cardiomyopathy; CV: cardiovascular; CVA: cerebrovascular accident; d: day; HF: heart failure; MI: myocardial infarction.
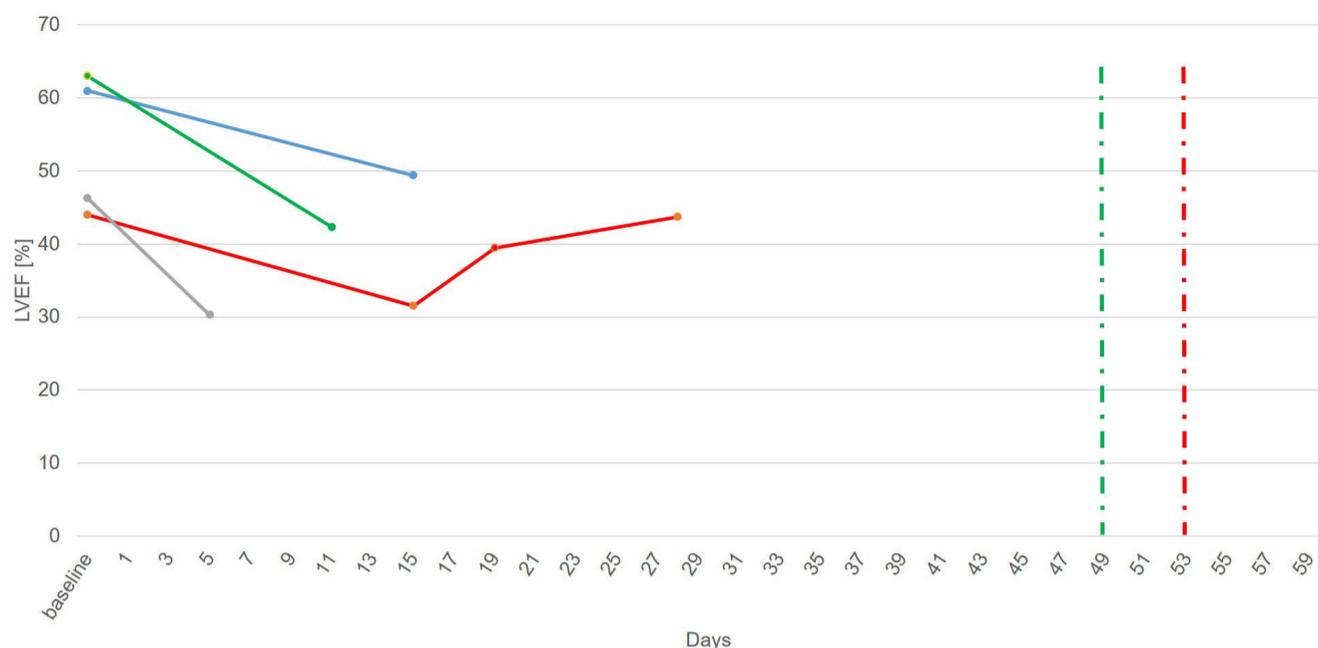
Figure 3. Evolution of left ventricular ejection fraction of patients who presented a drop of ejection fraction of at least 10% during day 0-30. LVEF: left ventricular ejection fraction. Day 0 represents the day of chimeric antigen receptor T-cell therapy infusion. The colored dashed lines indicate the day of death for the patient of the corresponding color.

30-d MACE *P*=0.519, log-rank test) in a landmark analysis using the landmark time of 30 days. The multivariable analyses also demonstrated no significant association of: 30-d MACE with OS or PFS. Moreover, the association between arrhythmias, non-arrhythmic MACE, and the outcome was not significant for either PFS or OS. Of note, among the 15 patients with 30-d MACE who died, eight died of lymphoma progression, two of sepsis, two of multifactorial etiologies, two of unknown causes, and only one died of a CV cause (MI death).

Discussion

This large, single-institution cohort study describes the incidence and baseline clinical and echocardiographic correlates of MACE in a population of contemporary patients with relapsed or refractory LBCL treated with SOC CAR-T cell therapy axi-cel or tisa-cel.

Our key findings in real-world patients treated outside of clinical trials include i) 16% patients developed at least one 30-d MACE; ii) almost two-thirds of the 30-d MACE were cardiac arrhythmias which were managed easily with standard therapy; iii) of all patients, only 7% developed non-arrhythmic CV events, with one CV death; iv) development of 30-d MACE did not impact intermediate or longer-term global outcomes of OS or PFS.

Notably, amongst the 9% of patients that developed arrhythmias triggering treatment changes, almost half were short runs of asymptomatic NSVT, which were only noted because of the routine use of telemetry. Whether any treatment, usually in the form of beta-blockers, is even needed in these patients is unclear at this time. As new CAR products gain FDA approval with more manageable

toxicity profiles and institutions gain experience managing these toxicities, increased outpatient CAR administration and monitoring can be expected.[20] Given the strong association of age with MACE, especially with arrhythmias, further multicenter studies are needed to evaluate the clinical usefulness of routine telemetry, particularly in patients younger than 60 years without cardiac comorbidities. Also, given the strong association of MACE with higher grades of CRS, closer monitoring could be triggered by the development of higher grades of CRS.

In a prior retrospective study by Alvi *et al.* of 137 lymphoma and myeloma patients treated with CAR-T cell therapy (almost half as part of clinical trials), 17 CV events occurred (6 CV deaths, 6 decompensated HF, and 5 arrhythmias).[16] They did not include asymptomatic drops in LVEF, asymptomatic NSVT, or CVA in the count of CV events. If we evaluate comparable events in our cohort, it is reassuring to note that only 18 such CV events were observed in a larger SOC cohort (165 patients) with only one CV death. This is further notable given that patients in our cohort had more CV risk factors and CV comorbidities at baseline compared to those of Alvi *et al.* and were of comparable age. Although not definitive, given the overall lower number of events, the lower number of CV deaths in our cohort could be associated with increased recognition and improved management of CRS, including increased use of tocilizumab (65% in our cohort *vs.* 41% in the prior cohort).[16]

In our study, age of 60 years or older and ≥ grade 3 CRS were independent predictors of 30-d MACE. Although baseline CV risk factors and disease were numerically higher in patients with CV events described in the results, these may not have been statistically significant given an overall lower number of events, especially non-arrhythmic

Table 2. Inflammation and 30-day major adverse cardiovascular events

Characteristics/Outcomes	All patients (n= 165)	Patients who did not present 30-d MACE (n = 138)	Patients who presented at least one 30-d MACE (n = 27)	P	Patients who presented at least one 30-d MACE (n = 27)	
					Arrhythmic event(s) only (n = 15)	At least one non-arrhythmic event (n = 12)
CRS						
Time to CRS onset, d	3 [0-15]	3 [0-15]	2 [0-9]	**0.025**	2 [0-9]	2 [0-7]
≥grade 3 CRS	23 (14%)	14 (10%)	9 (33%)	**0.002**	3 (11%)	6 (22%)
Duration between first and last day of CRS any grade, median [range], d	6 [0-48]	5 [0-48]	11 [0-48]	**0.036**	7 [1-20]	17 [0-48]
Tocilizumab use Time to first dose, median [range], d Cumulative number of doses median [range]	107 (65%) 6 [0-40] 1 [1-4]	84 (61%) 6 [0-40] 1 [1-4]	23 (85%) 5 [3-10] 1 [1-4]	**0.016** 0.403 0.789	12 (44%) 5 [3-10] 1 [1-3]	11 (41%) 5 [3-10] 1 [1-4]
ICANS						
ICANS any grade	100 (61%)	80 (58%)	20 (74%)	0.105	10 (37%)	10 (37%)
time to ICANS onset, median [range], d	6 [0-18]	6 [0-18]	5 [1-14]	0.443	5 [3-10]	5 [1-14]
≥grade 3 ICANS	51 (31%)	41 (30%)	10 (37%)	0.451	3 (11%)	7 (26%)
Duration between first and last day of ICANS any grade, d [range]	5 [0-82]	4.5 [0-82]	7 [0-49]	0.220	5 [0-24]	7 [3-49]
Corticosteroid use* Time to first dose, median [range], d Median cumulative dose, mg	91 (55%) 7 [1-16] 170 [8-13,043]	72 (52%) 6 [1-16] 180 [8-13,043]	19 (70%) 7 [4-15] 140 [10-11,750]	0.082 0.914 0.653	8 (30%) 7 [4-8] 106 [10-494]	11 (40%) 7 [5-15] 200 [20-11,750]
Intensive care management						
ICU stay	60 (36%)	47 (34%)	13 (48%)	0.164	4 (15%)	9 (33%)
Required vasopressive and/or inotropic support	13 (8%)	12 (9%)	1 (4%)	0.696	1 (4%)	0
Mechanical ventilation	12 (7%)	9 (7%)	3 (11%)	0.4485	0	3 (11%)
Inpatient stay						
Length of inpatient stay, median [range], d	17 [7-99]	16 [7-99]	23 [10-54]	0.073	16 [10-54]	30 [16-54]
Inflammatory markers						
First peak of CRP, median [range], mg/L	117 [5-490]	109 [5-490]	121 [6-296]	0.098	109 [6-257]	164 [97-296]
Time to first peak of CRP, median [range], d	5 [1-371]	5 [1-371]	5 [3-10]	0.769	5 [3-10]	5 [3-10]
First peak of Ferritin, median [range], mg/L,	1902 [83-100,001]	2005 [102-100,001]	1752 [83-34,513]	0.939	1567 [83-12,287]	2053 [266-34,513]
Time to first peak of Ferritin, median [range], d	9 [1-40]	9 [1-40]	9 [2-19]	0.697	9 [2-19]	11 [6-18]

Values are n (%) except as noted. % values reflect the proportion of patients who did not experience a 30-day major adverse cardiovascular events (30-d MACE), at least one 30-d MACE, and all the patients. *P*-value reflects the comparison of patients who did not experience a 30-d MACE with patients who experienced at least one MACE. Bold numbers indicate a significant *P*-value. CRS: cytokine release syndrome; Cum.: cumulative; d: day; ICANS: immune cell-associated neurotoxicity syndrome; ICU: intensive care unit; n: number; CRP: c-reactive protein. *Dexamethasone or dexamethasone equivalent. Non-arrhythmic events include myocardial infarction, cerebrovascular accident, heart failure, cardiomyopathy, and cardiovascular-related death.

events. In another retrospective study by Ganatra *et al.* with 187 patients with relapsed refractory follicular lymphoma and LBCL, the median age was 63 years. Patients who developed cardiomyopathy were older and had a greater prevalence of hyperlipidemia and CAD.[14] In the retrospective study of Lefebvre *et al.* with 145 adult patients undergoing anti-CD19 CAR-T cell therapy with a median age of 60 years, age was not associated with MACE (*P*=0.431). Overall, 31 patients had MACE (41 events) at a median time of 11 days (interquartile range, 6-151 days) after CAR-T cell infusion (median follow-up period was 456 days [Interquartile range, 128-1,214 days]). However, the population was not limited to LBCL treated SOC CAR-T cell therapy and included ALL and CLL patients.[21] Advanced age is a risk factor for increased comorbidities and complications. However, in a subgroup analysis of the trial ZUMA-1[2,4] of Neelapu *et al.*, axi-cel induced a high rate of durable responses with a manageable safety profile, regardless of age, suggesting that age alone should not limit

CAR-T cell therapy, although it may prompt pre-therapy optimization and closer monitoring after infusion.[22] The occurrence of 30-d MACE was associated with the earlier start of CRS in our study and with a more extended duration of CRS, and expectedly with higher use of tocilizumab. Our population consisted exclusively of LBCL patients treated with SOC axi-cel and tisa-cel, and comparisons with other studies may be challenging given the use of different noncommercial products and heterogeneous populations. In the study of Nastoupil *et al.*, the overall incidence of CRS was comparable to the trial ZUMA-1. Still, grade ≥3 CRS was slightly lower at 7% *versus* 11% in ZUMA-1.[1] This difference might be accounted for by greater use of tocilizumab and corticosteroids[23] (62% and 55%, respectively) in the study of Nastoupil *et al.* compared with the trial ZUMA-1 (43% and 27%, respectively) in line with evolving practice patterns for toxicity management. CRS may result in depressed myocardial function, even if transient, explaining the association with MACE.
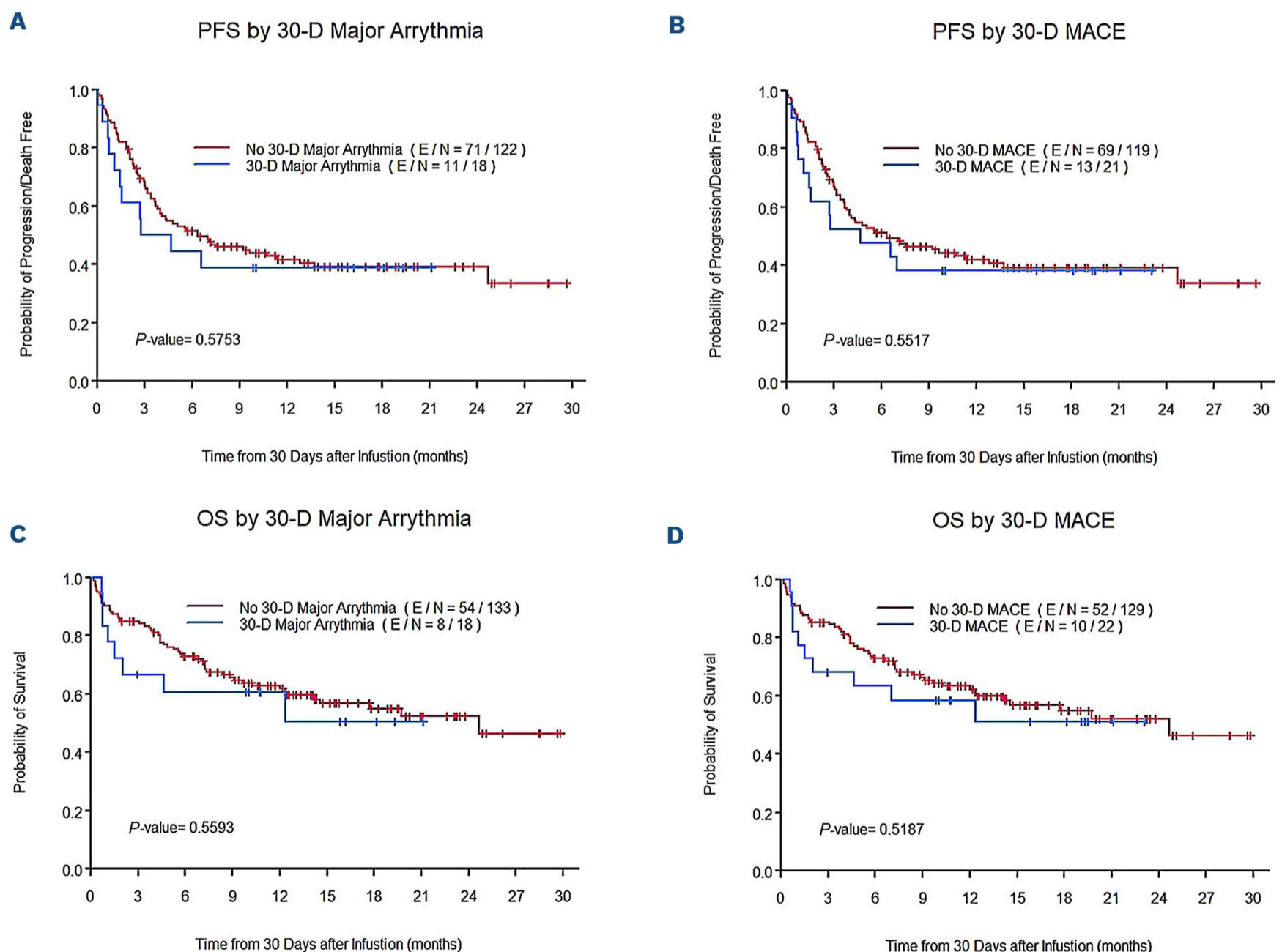
Figure 4. Association between 30-day major adverse cardiovascular and arrhythmic events and survival. (A) Progression-free survival (PFS) of patients with and without 30-day arrhythmia requiring intervention. (B) PFS of patients with and without 30-day major adverse cardiovascular event (30-d MACE). (C) Overall survival (OS) of patients with and without 30-d arrhythmia requiring intervention. (D) OS of patients with and without 30-d MACE.

Further, it is possible that patients with CRS, especially with hypotension and tachycardia, which are cardiac stressors and in which patients receive large quantities of intravenous fluids, can worsen the volume overload state and precipitate myocardial ischemia.[21]

Our data did not show a statistically significant association between baseline LVEF and 30-d MACE. The median baseline LVEF of our study population was 54% (range, 38.1-75%), compared to 60% (range, 35-75%) in the study of Ganatra *et al*.[14] In the latter study, baseline LVEF was not associated either with new or worsening cardiomyopathy (*P*=0.23). In addition, a lower baseline LVEF was not associated with poorer outcomes in our study. Nevertheless, the number of patients with low baseline LVEF was small, and further studies are needed to evaluate such a population's safety to undergo CAR-T cell therapy.

We noted that patients who presented with any baseline diastolic dysfunction were at increased risk for 30-d MACE (*P*=0.004). However, diastolic dysfunction is prevalent with increasing age.[24] In a subset analysis in patients for whom baseline echocardiogram data was available, baseline diastolic dysfunction did not prove to be an independent risk factor for 30-d MACE (*P*=0.109). Therefore, diastolic dysfunction may be a marker of older age and comorbidities, such as hypertension. In contrast, in the study by Lefebvre *et al.*, there was no association between diastolic dysfunction and MACE (*P*=0.866).[21] Of note, the evaluation of left ventricular diastolic function with echocardiographic methods may not always be standardized, and there have been two significantly different guideline statements in terms of criteria published from the same cardiology society since 2009.[25,26] In our study, diastolic function on echocardiography was examined by uniformly standardized criteria for this analysis. Future studies examining larger cohorts may be needed to further study the association of diastolic dysfunction with MACE. Among the 27 patients of our study who had at least one repeat echocardiogram during the 30 days following CAR-T cell therapy, only four patients had a decrease in LVEF of at least 10% to LVEF under 50%. None of these patients presented grade ≥3 CRS, and the drop in EF was diagnosed after CRS resolution. However, echocardiograms were only done as clinically indicated, and the actual proportion of patients with a decrease of LVEF is unknown. In the study of Ganatra *et al.*, around 10% of patients develop cardiomyopathy in the context of high-grade CRS following CAR-T cell therapy.[14] Among them, 50% had persistent cardiac dysfunction (median follow-up of 168.5 days). These results emphasize the need for baseline workup with echocardiogram before CAR-T cell infusion for every patient and repeat echocardiogram in case of clinical suspicion of cardiac dysfunction. Moreover, additional studies are needed to evaluate the long-term evolution of these post-CAR-T cell cardiomyopathies and the role of

earlier or more frequent use of tocilizumab to avoid some of these events.

Finally, 30-d MACE was not significantly associated with hospital survival, PFS, or OS in our study. This may be related to relatively fewer non-arrhythmic MACE and the relatively higher competing risk of oncologic disease progression and related death.

We acknowledge the limitations of our single-center study, including the retrospective nature of the analysis, the absence of long-term follow-up after MACE, and the lower frequency of follow-up cardiac imaging available in the follow-up period. We recognize the need for future prospective studies to confirm the findings of our study SOC cohorts. Another limitation to our study is that pre-therapy and post-therapy cardiac serologic biomarkers were measured only as clinically indicated and did not yield specific predictive information regarding 30-d MACE.[27] The strengths of our study are a large cohort, prospectively assigned toxicity grading, and comprehensive multidisciplinary evaluation, including EKG, echocardiogram, serologic markers, and telemetry.

In conclusion, 30-d cardiac events were noted in 16% of patients after axi-cel and tisa-cel infusion in patients with LBCL, with CV death being rare. Age was the only independent predictor of MACE prior to infusion, although the development of grade 3 or higher CRS was associated with MACE after infusion. Excluding patients solely because of advanced age or cardiac comorbidities may be inappropriate since the majority of CV events appear to be non-life-threatening arrhythmias, treatable and/or reversible, and the prognosis of elderly patients is not inferior in regards to oncologic disease progression.[28] Closer monitoring may be appropriate in elderly patients and those with underlying CV disease. More aggressive treatment of CRS with tocilizumab at our site may be a reason for lower comparable CV events compared to prior studies.

Further studies are needed to predict response better, mitigate CRS, and increase response.[29] In the future, machine learning may assist in CV event prediction in an initially asymptomatic population.[30] This may be especially relevant to select patients able to receive CAR-T cell therapy in the outpatient setting.

References

1. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US lymphoma CAR T Consortium. J Clin Oncol. 2020;38(27):3119-3128.

2. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42.

3. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.

4. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.

5. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.

6. https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma access date 01 21 2020 FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma. Yescarta (axicabtagene ciloleucel).

7. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma access date 01 20 20. FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma.

8. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-relapsed-or-refractory-large-b-cell-lymphoma access date 07/11/2021. FDA approves lisocabtagene maraleucel for relapsed or refractory large B-cell lymphoma.

9. Strati P, Nastoupil LJ, Westin J, et al. Clinical and radiologic correlates of neurotoxicity after axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv. 2020;4(16):3943-3951.

10. Burns EA, Gentille C, Trachtenberg B, Pingali SR, Anand K. Cardiotoxicity associated with anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy: recognition, risk factors, and management. Diseases. 2021;9(1):20.

11. Ganatra S, Carver JR, Hayek SS, et al. Chimeric antigen receptor T-cell therapy for cancer and heart: JACC council perspectives. J Am Coll Cardiol. 2019;74(25):3153-3163.

12. Patel NP, Doukas PG, Gordon LI, Akhter N. Cardiovascular toxicities of CAR T-cell therapy. Curr Oncol Rep. 2021;23(7):78.

13. Pathan N, Hemingway CA, Alizadeh AA, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet. 2004;363(9404):203-209.

14. Ganatra S, Redd R, Hayek SS, et al. Chimeric antigen receptor T-cell therapy-associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. Circulation. 2020;142(17):1687-1690.

15. Berro M, Arbelbide JA, Rivas MM, et al. Hematopoietic cell transplantation-specific comorbidity index predicts morbidity and mortality in autologous stem cell transplantation. Biol Blood Marrow Transplant. 2017;23(10):1646-1650.

16. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). J Am Coll Cardiol. 2019;74(25):3099-3108.

17. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.

18. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

19. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.

20. Alexander M, Culos K, Roddy J, et al. Chimeric antigen receptor T cell therapy: a comprehensive review of clinical efficacy, toxicity, and best practices for outpatient administration. Transplant Cell Ther. 2021;27(7):558-570.

21. Lefebvre B, Kang Y, Smith AM, Frey NV, Carver JR, Scherrer-Crosbie M. Cardiovascular effects of CAR T cell therapy: a retrospective study. JACC CardioOncol. 2020;2(2):193-203.

22. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2020;135(23):2106-2109.

23. Strati P, Ahmed S, Furqan F, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. Blood. 2021;137(23):3272-3276.

24. Kuznetsova T, Herbots L, López B, et al. Prevalence of left ventricular diastolic dysfunction in a general population. Circ Heart Fail. 2009;2(2):105-112.

25. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-1360.

26. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10(2):165-193.

27. Shalabi H, Sachdev V, Kulshreshtha A, et al. Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies. J Immunother Cancer. 2020;8(2).

28. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. Blood Adv. 2020;4(13):3024-3033.

29. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv. 2020;4(13):3123-3127.

30. Ambale-Venkatesh B, Yang X, Wu CO, et al. Cardiovascular event prediction by machine learning: the Multi-Ethnic Study of Atherosclerosis. Circ Res. 2017;121(9):1092-1101.