JACC: CARDIOONCOLOGY VOL. 5, NO. 6, 2023

ORIGINAL RESEARCH

Incidence of MACE in Patients Treated With CAR-T Cell Therapy

A Prospective Study

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ABSTRACT

BACKGROUND Previous retrospective studies have shown that chimeric antigen receptor T (CAR-T) cell therapy may be associated with major adverse cardiovascular events (MACE), especially in the context of cytokine-release syndrome (CRS) events.

OBJECTIVES The aim of this prospective observational study was to define the occurrence of MACE in adults undergoing treatment with CAR-T cell therapy and identify associated risk factors.

METHODS Vital signs, blood samples, and an echocardiogram were collected prior to and 2 days, 1 week, 1 month, and 6 months after CAR-T cell infusion, and charts were consulted at 12 months. In the event of CRS, echocardiography was repeated within 72 hours. MACE were defined as cardiovascular death, symptomatic heart failure, acute coronary syndrome, ischemic stroke, and de novo cardiac arrhythmia.

RESULTS A total of 44 patients were enrolled (mean age 58 ± 11 years, 77% men). The median follow-up duration was 487 days (Q1-Q3: 258-622 days). There were 24 episodes of CRS in 23 patients (52%) (13 grade 1, 10 grade 2, and 1 grade 3), with a median time to CRS of 4 days. Two patients had MACE (heart failure with preserved ejection fraction and atrial fibrillation) within 1 year and 6 and 7 days after CAR-T cell infusion. There was no change in left ventricular ejection fraction, but a modest decrease in global longitudinal strain was noted.

CONCLUSIONS There were few cardiac effects associated with contemporary CAR-T cell therapy. As MACE occurred after CRS episodes, aggressive treatment and close follow-up during CRS events are essential. (J Am Coll Cardiol CardioOnc 2023;5:747-754) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Guilherme H. Oliveira, MD, served as the Guest Associate Editor for this paper. Kathryn J. Ruddy, MD, MPH, served as the Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 18, 2023; revised manuscript received July 19, 2023, accepted July 31, 2023.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2023.07.009

JACC: CARDIOONCOLOGY, VOL. 5, NO. 6, 2023
DECEMBER 2023:747–754

ABBREVIATIONS AND ACRONYMS

ALL = acute lymphoblastic leukemia

CAR-T = chimeric antigen receptor T

CRS = cytokine-release syndrome

CV = cardiovascular

GLS = global longitudinal strain

HF = heart failure

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular event(s)

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Over the past several years, chimeric antigen receptor T (CAR-T) therapy has proved to be a promising therapeutic strategy in adult and pediatric patients with certain types of hematologic malignancies, including B-cell lymphoma and lymphoblastic leukemia.[1-3] CAR-T cell therapy is remarkably successful; in patients with relapsed or refractory diffuse large B-cell lymphoma, recurrence-free survival was 65% at 1 year.[4,5] In CAR-T cell treatment, the patient's T cells are harvested, genetically engineered to express synthetic receptors (chimeric antigen receptors) to target and eliminate cancer cells expressing specific target antigens, and reinjected into the patient.[6]

Despite its remarkable successes, CAR-T cell treatment has also been linked to potentially fatal toxicities.[7-9] One of the most commonly reported adverse effects of CAR-T cell therapy is cytokine-release syndrome (CRS), characterized by a systemic inflammatory response to CAR-T cell therapy occurring hours to days after the initial infusion, ranging from mild symptoms to life-threatening conditions.[7,10] The increased levels of inflammatory cytokines released in CRS can induce fever, vascular leakage, hypotension, hypoxia, possible direct myocardial injury, multiorgan dysfunction, and potential progression to death.[11,12] CRS is thought to be mediated predominantly by interleukin-6; therefore, treatment focuses on the use of interleukin-6 receptor-blocking agents such as tocilizumab in addition to corticosteroids.[7]

Cardiovascular (CV) adverse events following CAR-T cell treatment are of significant concern and are less well characterized because of the paucity of data in the literature.[1] Adult patients undergoing CAR-T cell treatment often have CV comorbidities and are also more likely to develop CV complications as a result of exposure to multiple prior potentially cardiotoxic therapies.[11,13] The CV adverse effects of CAR-T cell therapy in adult and pediatric populations have been reported in retrospective studies only.[11,14-16] In 137 patients receiving CAR-T cell therapy, CV events including heart failure (HF), arrhythmias, and cardiac death occurred in 12% of patients, more prominently in association with CRS.[14] In a previous study from our group, major adverse CV events (MACE) developed in 31 of 145 adult patients (21%) at a median time of 11 days after CAR-T cell therapy. Moderate or severe CRS was independently associated with MACE.[11]

The present prospective observational study was designed to define the CV effects of CAR-T cell treatment and to assess the relationships among clinical factors, echocardiographic parameters, laboratory values, and CV outcomes.

METHODS

The study was conducted at the Hospital of the University of Pennsylvania and was approved by its Institutional Review Board. All consecutive adult patients (≥18 years of age) with CD19$^+$ malignancies treated with commercial CAR-T 19 cells at the Hospital of the University of Pennsylvania between July 2019 and February 2022 were identified and approached. After enrollment, an echocardiogram and blood samples including cardiac biomarkers were obtained prior to CAR-T cell therapy and repeated 2 days (visit 1), 1 week (visit 2), 1 month (visit 3), and 6 months (visit 4) after CAR-T cell infusion. The 6-month visit became optional because of the COVID-19 pandemic. In the event of a CRS episode, an echocardiogram was obtained within 72 hours of the diagnosis. At each visit, patients were queried about CV events or symptoms, their medical records were reviewed, and their vital signs were collected. All patients' charts were analyzed 1 year following infusion to identify any further MACE or clinical events.

DEFINITIONS AND ENDPOINTS. MACE included 1 or several of the following conditions: symptomatic HF, nonfatal acute coronary syndrome, nonfatal ischemic stroke, new-onset cardiac arrhythmia, and cardiac death. Each chart was reviewed separately to determine the presence of MACE, and the American College of Cardiology/American Heart Association definitions provided for clinical trials were used to report and categorize MACE.[17] CV events were adjudicated by 2 independent cardiologists (B.L. and T.O.), who were blinded to all other clinical and echocardiographic information. In the event of discordance, a third cardiologist (Y.K.) adjudicated. Atrial fibrillation was detected on 12-lead electrocardiography (performed on the basis of symptoms or vital sign derangement). The use of continuous telemetry was left to the discretion of the treating team.

Symptomatic HF was reported if 3 or more of the following 4 criteria were present: 1) at least 1 symptom of HF (shortness of breath at rest or during exercise, decrease in exercise capacity, and symptoms suggesting volume overload); 2) 2 or more signs on physical examination (peripheral edema, ascites in the absence of hepatic disease, pulmonary crackles or

rales, elevated jugular venous pressure, S3 gallop, and significant and rapid weight gain associated with fluid retention); 3) laboratory or imaging findings of HF such as B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide, Kerley B-lines or pulmonary edema, pleural effusion, and reduced left ventricular ejection fraction (LVEF); and 4) new treatment for HF (eg, initiation of medications such as diuretic agents and/or mechanical support). De novo cardiac arrhythmias such as atrial fibrillation and atrial flutter were reported on the basis of the electrocardiogram. Atrial fibrillation, atrial flutter, and HF occurring in the presence of sepsis were not included in MACE.

CRS was scored into 4 grades according to the American Society for Transplantation and Cellular Therapy consensus grading for CRS. All grades required fever, defined as temperature ≥38.0 °C. Grade 1 was defined as no life-threatening symptoms, grade 2 as symptoms that required and responded to moderate interventions, grade 3 as hypotension requiring aggressive intervention with 1 vasopressor and/or hypoxia with high-flow oxygen supplementation, and grade 4 as hypotension requiring aggressive intervention with more than 1 vasopressor and/or hypoxia with treated with positive pressure or intubation. Time from infusion to CRS events and administration of tocilizumab or corticosteroids for the treatment of CRS were reported.

Baseline characteristics such as age, sex, body mass index, CV risk factors, and disease such as hypertension, diabetes mellitus, dyslipidemia, history of smoking, coronary artery disease, atrial fibrillation, HF, and stroke as well as CV medication history were manually retrieved from medical charts and confirmed with patients. Hypertension, diabetes mellitus, and dyslipidemia were reported if both diagnosis and treatment were present in the medical chart. Data regarding types of cancer and previous cancer treatments, including anthracyclines, radiotherapy, and stem cell transplantation, were also collected. Vital signs were assessed, and laboratory samples were collected at each visit and in case of CRS or MACE. Deaths due to septic shock, multiorgan failure, or progression of cancer were recorded as noncardiac deaths.

ECHOCARDIOGRAPHY ANALYSIS. All measurements were reported from the average of 3 consecutive cardiac cycles by a single cardiologist (B.L.) blinded to the clinical data and outcomes. LVEF was calculated using the modified Simpson biplane method, and left atrial volume was calculated using the biplane method. Global longitudinal strain (GLS) was assessed at a rate of at least 30 frames/s by an independent cardiologist (T.O.) blinded to clinical characteristics and outcomes using an offline vendor-independent analysis program (2D Cardiac Performance Analysis, TomTec Imaging Systems).

STATISTICAL POWER AND ANALYSIS. Continuous data are shown as mean ± SD for normally distributed continuous variables, as median (Q1-Q3) for nonparametric continuous variables, and as total counts with percentages for categorical variables. The study was powered using an enrollment of 50 patients; assuming a rate of events of 20%[11] and an SD of 2% for GLS, the 10 occurring events would have allowed us to detect a difference of 2% (in absolute value, eg, −18% vs −20%) in baseline GLS between patients with and those without MACE with power of 0.85 and a type II error rate of 0.05. The COVID-19 pandemic had a profound impact on the willingness of patients to participate. As the number of events was also lower than expected, the study was ended prematurely. The differences between patients developing or not developing MACE were not analyzed, because of the small number of events (n = 2). Differences at baseline between patients developing or not developing CRS were analyzed using the unpaired Student's *t*-test for normally distributed continuous variables or the Mann-Whitney *U* test for non-normally distributed continuous variables and the chi-square or Fisher exact test for categorical variables. To compare the longitudinal changes in the whole cohort and in patients with CRS events, a generalized linear model was fit using the generalized estimating equation method. Differences between variables at baseline and during CRS in the subgroup of patients who developed CRS were analyzed using Student's paired *t*-tests or the Wilcoxon signed rank test as appropriate.

Data were analyzed using SPSS version 16.0 (SPSS). A P value <0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PATIENTS. A total of 44 patients were enrolled (mean age 58 ± 11 years, 77% men). Baseline characteristics at the time of CAR-T cell infusion are presented in **Table 1**. Forty-three patients were diagnosed with lymphoma and 1 patient with acute lymphoblastic leukemia (ALL). Prior to CAR-T treatment, 84% of patients (37 of 44) were treated with anthracyclines, 32% (14 of 44) received radiation to the chest, and 25% (11 of 44) received stem cell transplantation. Baseline

TABLE 1 Baseline Clinical Characteristics of Patients Treated With Chimeric Antigen Receptor T Cell Therapy

	All (n = 44)	MACE (n = 2)
Demographics		
Age, y	58 ± 11	73 ± 21
Male	34 (77)	2
Race		
White	40	2
Black	3	0
Other	1	0
Ethnicity		
Not Hispanic or Latino	43	2
Hispanic or Latino	1	0
BMI, kg/m^2	28.7 ± 5.9	24.8 ± 2.9
Duration of follow-up, d	487 ± 264	424 ± 80
Heart rate, beats/min	79 ± 13	78 ± 9
SBP, mm Hg	120 ± 14	141 ± 29
DBP, mm Hg	72 ± 9	78 ± 11
CRS	23 (52)	2
Cardiovascular history		
Dyslipidemia	19 (43)	2
Hypertension	19 (43)	2
Diabetes	13 (30)	1
Obesity	15 (34)	0
Current/previous smoker	19 (43)	2
Heart failure	2 (4)	0
Coronary artery disease	4 (9)	0
Atrial fibrillation/flutter	6 (13)	1
Chronic kidney disease	3 (7)	0
Cerebrovascular disease	2 (4)	0
DVT/pulmonary embolism	6 (14)	1
Cardiovascular medications		
Beta-blockers	7 (16)	0
ACEIs/ARBs	11 (25)	1
CCBs	6 (14)	0
Aspirin	5 (11)	1
Anticoagulant agents	6 (14)	0
Diuretic agents	2 (4)	0
Oral antidiabetic agents	7 (16)	1
Insulin	2 (4)	1
Statins	13 (30)	2
Cancer history		
Previous cancer	17 (39)	1
Anthracycline	37 (84)	2
Radiotherapy	14 (32)	0
Stem cell transplantation	11 (25)	0
Laboratory values		
CRP, mg/dL	1.5 ± 2.3	1.2 ± 1.5
Ferritin, ng/mL	192 (107-345)	8.2 (1)
Troponin elevation	2	1
NT-proBNP, pg/mL	67 (28-299)	24 and 478
IL-6, pg/dL	6 ± 9.9	2.2 ± 0.2
Hemoglobin, g/dL	11.2 ± 2.2	12.05 ± 1.65
WBCs, ×10^3/μL	4.2 ± 2.2	5.7 ± 3.8
Lymphocytes, ×10^3/μL	6.0 ± 7.8	4.8 ± 2.7
Platelets, ×10^3/μL	182.4 ± 124.9	111.0 ± 79.2
Creatinine, mg/dL	1.0 ± 0.4	0.8 ± 0.3
eGFR, mL/min/1.73 m^2	87 ± 30	84 ± 21
Uric acid, mg/dL	4.5 ± 1.5	4.2 ± 2.3
LDH, U/L	181.1 ± 75.4	145.5 ± 6.4
Fibrinogen, mg/dL	432 ± 158	357 ± 145

Values are mean ± SD, n (%), or median (Q1-Q3).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CCB = calcium channel blocker; CRP = C-reactive protein; CRS = cytokine-release syndrome; DBP = diastolic blood pressure; DVT = deep vein thrombosis; eGFR = estimated glomerular filtration rate; IL = interleukin; LDH = lactate dehydrogenase; MACE = major adverse cardiovascular events; SBP = systolic blood pressure; WBC = white blood cell.

echocardiographic findings are listed in **Table 2**. LVEF and GLS were 62% ± 5% and −21.1% ± 2.0% prior to CAR-T cell treatment.

LONGITUDINAL FOLLOW-UP OF PATIENTS: CRS, MACE, AND MORTALITY. CRS. There were 24 episodes of CRS in 23 patients (52%) (13 grade 1, 10 grade 2, and 1 grade 3). No patient had grade 4 CRS. The median time to CRS was 4 days (range: 1-11 days; Q1-Q3: 2-6 days). Seven patients were treated with tocilizumab, and 6 patients received corticosteroids. The median time between the diagnosis of CRS and treatment with tocilizumab was 1 day (range: 0-6 days; Q1-Q3: 0-5 days).

There were no clinical or echocardiographic baseline differences in patients who subsequently developed or did not develop CRS (Supplemental Table 1). During CRS, patients had a higher mean heart rate (109 ± 20 beats/min vs 81 ± 14 beats/min; $P < 0.001$), higher mean C-reactive protein values (9.4 ± 7.6 pg/dL vs 1.4 ± 1.9 mg/dL; $P < 0.001$), and higher median ferritin (512 ng/mL [Q1-Q3: 291-1,011 ng/mL] vs 204 ng/mL [Q1-Q3: 118-336 ng/mL]; $P = 0.001$) than at baseline. In 14 patients (61% of those with CRS) in whom NT-proBNP was measured during CRS episodes, median NT-proBNP was higher than at baseline (362 pg/mL [Q1-Q3: 118-2,698 pg/mL] vs 63 pg/mL [Q1-Q3: 25-404 pg/mL]; $P = 0.001$). There were no significant changes in LVEF, GLS, or other echocardiographic parameters on the echocardiogram obtained within 72 hours of CRS (Supplemental Table 2).

MACE. MACE occurred in 2 patients with lymphoma: 1 patient developed HF with preserved ejection fraction 6 days after CAR-T cell infusion, and another patient had de novo atrial fibrillation 7 days after CAR-T cell infusion. The patients who developed MACE were 71 and 74 years of age (the average age of the cohort was 58 years). Both patients had CRS (1 grade 2 and 1 grade 1), and the

TABLE 2 Baseline Echocardiographic Characteristics

	All (n = 44)	MACE (n = 2)
LVEDD, cm	4.7 ± 0.5	4.1 ± 0.6
LVESD, cm	3.2 ± 0.5	2.3 ± 0.0
LVEF, %	62 ± 5	64 ± 6
RV basal dimension, cm	3.6 ± 0.5	2.9 ± 0.2
TAPSE, cm	2.4 ± 0.4	2.3 ± 0.5
RV S′, mm/s	14 ± 3	14 ± 6
Mitral E/e′ ratio	8.8 ± 2.8	11.4 ± 3.8
LAVi, mL/m^2	26 ± 9	17 ± 3
GLS, %	−21.1 ± 2.0	−22.2 ± 2.1

Values are mean ± SD.

GLS = global longitudinal strain; LAVI = left atrium volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MACE = major adverse cardiovascular event; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

mean time from CRS diagnosis to MACE was 3.5 days. No other MACE were noted at the 1-year follow-up time point or thereafter.

Mortality. The median follow-up duration was 487 days (range: 42-1,039 days; Q1-Q3: 258-622 days). In total, 12 patients died (27%), with a median time to death of 378 days (range: 51-717 days; Q1-Q3: 185-588 days).

ECHOCARDIOGRAPHIC CHARACTERISTICS OF PATIENTS TREATED WITH CAR-T CELL THERAPY. No changes in the LVEF were noted among study visits (Table 3). There was a modest and temporary decrease in GLS at visits 2 and 3 ($P = 0.003$) (Table 3). Similar changes were noted in the subgroup of patients with CRS. Furthermore, a slight decrease in right ventricular S′ was noted at visits 3 and 4 compared with baseline ($P = 0.003$) in patients with CRS. Tricuspid annular plane systolic excursion was unchanged (Supplemental Table 3).

DISCUSSION

In this first prospective study presenting the CV effects of CAR-T cell treatment in 44 adult patients with CD19$^+$ malignancies, the occurrence of MACE was rare (n = 2). The patients developed subtle cardiac dysfunction, indicated by modest declines in left ventricular GLS on serial echocardiographic examinations; however, the declines were mostly reversible. The 2 MACE occurred early after infusion (6 and 7 days after infusion) and after CRS episodes (mean time 3.5 days after CRS diagnosis). Although the MACE were closely related in time to the CAR-T cell infusion and CRS, it is conceivable that CRS may not have been involved and that the MACE were related to the advanced age and high CV risk factors of the 2 patients (Central Illustration).

The study population reflects the current indications of CAR-T cell therapy in adults.[5,18-21] Although patients with ALL can be treated with CAR-T cell therapy, the majority of adults treated with CAR-T cell therapy have lymphoma.[5,9,18,21-23] The baseline characteristics of patients were consistent with previous studies in adult patients undergoing CAR-T cell treatments in terms of age, sex distribution, and baseline CV risk profile.[8,11,14,18,23-25] The prevalence of CV risk factors and CV diseases in our study is higher than in the general population at a similar age,[26-29] which may reflect shared risk factors between cancer and CV disease and the effect of previous cardiotoxic treatments.[30-32]

The incidence of MACE was lower in the present study compared with previous investigations in adult

TABLE 3 Echocardiographic Changes Compared Among Visits

	Baseline (n = 44)	Visit 1 (n = 44)	Visit 2 (n = 42)	Visit 3 (n = 37)	Visit 4 (n = 27)	*P* Value
Heart rate, beats/min	79 ± 13	85 ± 15[a]	88 ± 15[a]	78 ± 14[b,c]	73 ± 74[b,c]	<0.001
SBP, mm Hg	120 ± 14	117 ± 17	117 ± 18	119 ± 14	120 ± 19	0.63
DBP, mm Hg	72 ± 9	71 ± 10	71 ± 9	72 ± 9	71 ± 9	0.76
Echocardiography						
LVEDD, cm	4.6 ± 0.5	4.7 ± 0.5	4.6 ± 0.4	4.5 ± 0.5	4.5 ± 0.6	0.43
LVESD, cm	3.2 ± 0.5	3.2 ± 0.4	3.2 ± 0.6	3.2 ± 0.7	3.0 ± 0.6	0.26
LVEF, %	62 ± 5	63 ± 5	61 ± 6	61 ± 6	62 ± 4	0.25
TAPSE, cm	2.4 ± 0.5	2.4 ± 0.5	2.3 ± 0.6	2.4 ± 0.4	2.5 ± 0.5	0.66
RV S′, mm/s	13.9 ± 3.0	14.7 ± 4.4	14.0 ± 3.9	13.0 ± 3.1	13.3 ± 3.7	0.14
E/e′ ratio	8.8 ± 2.8	8.1 ± 2.1	8.6 ± 4.0	8.8 ± 3.5	8.7 ± 2.8	0.63
LAVi, mL/m^2	26 ± 9	24 ± 12	27 ± 11	24 ± 10	25 ± 6	0.31
GLS, %	−21.0 ± 2.7	−20.2 ± 2.6	−19.9 ± 2.5[a]	−19.5 ± 2.9[a]	−20.2 ± 2.7	0.005

Values are mean ± SD. *P* values were obtained using a generalized estimating equation model. [a]$P < 0.05$ compared with baseline. [b]$P < 0.05$ compared with visit 1. [c]$P < 0.05$ compared with visit 2.

Abbreviations as in Tables 1 and 2.

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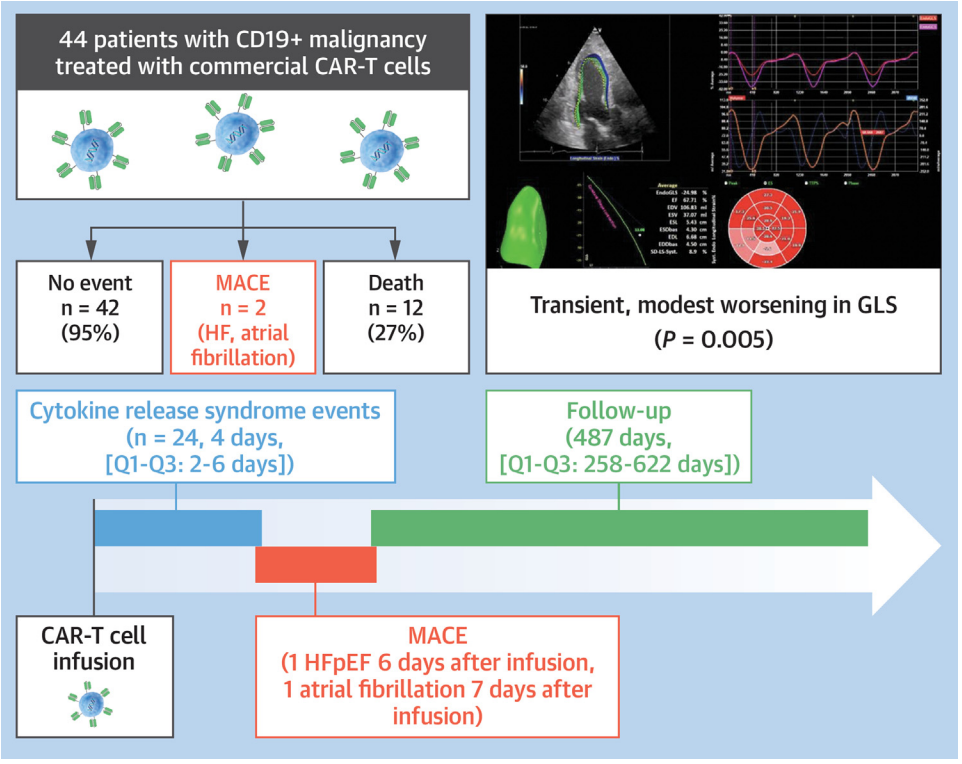
CENTRAL ILLUSTRATION **Cardiovascular Events of Contemporary CAR-T Cell Therapy in Adults With CD19^{+} Malignancies**



Lefebvre B, et al. J Am Coll Cardiol CardioOnc. 2023;5(6):747–754.

As major adverse cardiovascular events (MACE) occurred soon after cytokine release syndrome (CRS) onset, this suggests that CRS can at least contribute to the occurrence of MACE in patients treated with anti-CD19 chimeric antigen receptor T (CAR-T) cell therapy and supports earlier intervention and treatment in the case of CRS. GLS = global longitudinal strain; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

patients receiving CAR-T cells. In the 2 largest retrospective studies of adult patients treated with CAR-T cell therapy, rates of MACE of 21% and 12% were noted.[11,14] The previous retrospective study on 145 patients in our institution with a similar age and follow-up period demonstrated that 21% of patients developed MACE. The lower occurrence of MACE in the present study cannot be explained by higher mortality, as mortality was lower (27% vs 42% in the prior study).

In the present study, 98% of patients had non-Hodgkin B-cell lymphoma and only 2% had ALL, while in the retrospective investigation from our institution, only 29% carried diagnoses of lymphoma. However, in the retrospective study, cancer subtype did not influence the risk for MACE.[11] In the other large retrospective study, 88% of patients enrolled had lymphoma, and MACE were noted in 12%.[14]

An important difference between the retrospective studies and the present study is the rate and grade of CRS. CV dysfunction is associated with the development and severity of CRS following CAR-T cell infusion.[3,14,22,23,33] The occurrence of grade 3 and 4 CRS is known to be strongly associated with MACE.[11] In the study by Alvi et al,[14] all adults undergoing CAR-T therapy who developed CV events and cardiac injury (indicated by elevated troponins) had CRS grades ≥2. In the present study, 52% of patients developed CRS (compared with 72% in our previous retrospective study), of whom 95% had CRS

grades ≤2. Only 1 patient experienced CRS grade 3. The lower rates of CV events in our cohort compared with the earlier retrospective studies may therefore be at least partially attributable to the lower rate and grades of CRS experienced by the patients.

The exact mechanism explaining the association between CRS and MACE is not clearly understood. It is possible that CRS could result in reduced myocardial function and capillary leak, as indicated by higher NT-proBNP values during CRS episodes than baseline. In addition, patients with CRS usually receive large amounts of intravenous fluids, which can worsen the volume-overload state.[11]

The reasons for the lower rate and grades of CRS may be several. In the previous retrospective studies, CAR-T cell therapy was often used in clinical trials or as the third, fourth or fifth line during cancer therapy; patients in the present study were likely less sick from an oncologic standpoint and thus less likely to develop CRS.[11,13,34] Furthermore, as the body of evidence is growing, CRS is now treated more aggressively, as indicated by the number of patients who received tocilizumab and corticosteroids and how quickly they were administered (median time from CRS to tocilizumab 1 day; range: 0-6 days). CRS events are being identified and treated at earlier stages, resulting in lower grades and lower rates of related adverse events. Tocilizumab use at lower grades of CRS has become more prevalent in real-world practice and may reduce the likelihood of subsequent progression to grade 3 or 4 CRS.[35-37] In earlier studies, tocilizumab was administrated to patients with CRS grade 2 or higher, but current consensus encourages the earlier use of tocilizumab in patients with significant comorbidities or in those with prolonged CRS.[14,38]

There were no significant changes in LVEF among study visits. Although GLS demonstrated modest and mostly reversible changes, these variations are unlikely to greatly affect clinical prognosis.

STUDY LIMITATIONS. Although the low occurrence of MACE is reassuring, the population studied is small. The duration of follow-up (median 487 days) cannot eliminate longer term MACE. As the patients treated with CAR-T cell therapy were referred from multiple locations, lifetime total dose of anthracyclines and total radiation dose to the chest were not always known. Also, the use of continuous telemetry for the detection of arrhythmia was left to the discretion of the treating team, which could have led to an underestimation of the incidence of atrial fibrillation. Another limitation is the lack of more sensitive imaging assessment such as cardiac magnetic resonance imaging, which may have shown subtler decreases in LVEF. The post hoc pairwise comparisons in the comparisons among serial visits must be interpreted with caution, as no multiple-comparison adjustment was applied. Finally, assessment of MACE did not consider competing risks due to mortality, which could affect the analysis of MACE at longer follow-up time.

CONCLUSIONS

In this prospective study of patients receiving CAR-T cell therapy under strict CV surveillance, the incidence of MACE was <5%, and MACE occurred in patients with CRS within 7 days of therapy. The comparison with the higher occurrence of MACE in earlier retrospective studies with higher rates of CRS supports that earlier intervention, aggressive treatment, and close follow-up during CRS events are essential.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded through by National Heart, Lung, and Blood Institute grant R01 130539 (to Dr Scherrer-Crosbie). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE AND PATIENT CARE: Our findings provide insight into the rare cardiac side effects of contemporary CAR-T cell therapy and the modest impact on left and right ventricular function. As all MACE occurred after CRS episodes, aggressive management of CRS episodes in early stages and close follow-up during CRS events are essential.

TRANSLATIONAL OUTLOOK: Further larger prospective studies are needed to confirm the incidence of MACE in patients receiving CAR-T cell therapy. More sensitive imaging assessment may be used to show subtler decreases in left ventricular and right ventricular function.

JACC: CARDIOONCOLOGY, VOL. 5, NO. 6, 2023
DECEMBER 2023:747–754

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KEY WORDS cardiovascular, CAR-T cells, cardio-oncology

APPENDIX For supplemental tables, please see the online version of this paper.