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Cardiovascular adverse events and outcomes after anti-BCMA CAR-T for relapsed and refractory multiple myeloma

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Relapsed and refractory multiple myeloma (RRMM) has a poor median overall survival (OS) of 13 months [1]. The two FDA-approved CAR-Ts targeting B-cell maturation antigen (BCMA) for RRMM are Idecabtagene Vicleucel (ide-cel) [2, 3] and Ciltacabtagene Autoleucel (cilta-cel), with subsequent real-world consortium data [4] showing improvement in overall survival and progression-free survival. However, similar to anti-CD19 CAR-Ts, the anti-BCMA CAR-Ts carry frequent and serious adverse events, such as cytokine release syndrome (CRS), characterized by fever and various degrees of hemodynamic compromise, and end-organ damage [5].

Cardiovascular adverse events (CVAE) of anti-CD19 CAR-T are also common (10-20%), such as arrhythmias, heart failure, myocarditis, acute myocardial infarction, and cardiovascular deaths [6–9] .We have previously shown that ide-cel also has a relatively frequent (14.1%) CVAEs [10], including arrhythmia, heart failure, and cardiovascular death. To date, there is no published literature investigating the incidence of CVAE among patients treated with cilta-cel. Thus, we aimed to determine the incidence, risk factors, and clinical outcomes of CVAE in RRMM patients treated with cilta-cel or ide-cel anti-BCMA CAR-T therapies.

This was a retrospective single-center observational study of patients with RRMM treated with standard-of-care (SOC) ide-cel or cilta-cel at H. Lee Moffitt Cancer Center & Research Institute. All patients treated with SOC ide-cel or cilta-cel from May 2021 to December 2023 were included with at least 6 months of follow-up. We routinely perform comprehensive baseline cardiovascular evaluation prior to CAR-T, as previously described [10] (Supplementary Methods). Chemotherapy-related cardiac dysfunction (CTRCD) was categorized as suggested by 2022 European Society of Cardiology Guideline on Cardio-Oncology [11]. CVAE was defined as CAD, CTRCD, arrhythmias, and cardiovascular death.

Competing risks analysis was performed using the cumulative incidence function (CIF) to account for competing types of death. Deaths were classified as myeloma-related or non-myeloma-related (CRS, cardiovascular death, or infection). A Gray's test was used to compare the CIF curves by CVAE.

Ethics Approval and Consent to Participate: All methods were performed in accordance with the University of South Florida and Moffitt Cancer Center's Institutional Review Board (IRB) and Scientific Review Committee (Pro 29257 and MCC 18991) and Declaration of Helsinki. We did not obtain informed consent from participants as this was a retrospective review.

A total of 164 patients were included (109 ide-cel and 55 cilta-cel). Baseline demographics are summarized in Table 1 and Supplementary Table 1. The mean age was 63.4 years (range 38–82), with 57% male. In total, 20 patients developed CVAE (12.2%), including 5 (3%) with non-sustained ventricular arrhythmias, 13 (7.9%) with atrial arrhythmias, 6 (3.7%) with CTRCD and 1 (0.6%) with cardiovascular death. Of the 6 CTRCD, 3 were in symptomatic heart failure (Supplemental Table 3). There was no difference in CVAE between ide-cel and cilta-cel (11.0% vs. 14.5%; $p = 0.69$).

Baseline demographics and oncologic characteristics are summarized in Table 1. There was no difference in age, sex, race or ethnicity between CVAE and no CVAE group (Table 1). Patients with CVAE had more advanced disease stage (R-ISS III; 52.9% vs. 11.5%, $p = 0.01$), higher baseline ferritin (625 vs. 211 ng/dL, $p = 0.02$) and C-reactive protein (CRP) levels (0.8 vs. 0.3 mg/dL, $p = 0.01$). There was no difference in other oncologic characteristics between CVAE and no CVAE group (Supplementary Table 2). Baseline BNP levels were higher in the CVAE group (194.6 vs. 91.5 pg/mL, $p = 0.049$). There were no differences in baseline cardiac comorbidities, baseline troponin levels or other baseline electrocardiogram/echocardiogram characteristics between CVAE and no CVAE group.

The clinical events during CAR-T index hospitalization are summarized in Table 1. Overall, 3.7% developed CRS grade ≥ 3 in our cohort. Patients who developed CVAE had a higher incidence of grade ≥ 3 CRS compared to no CVAE group (25% vs. 0.7%, $p < 0.001$). The incidence of grade ≥ 3 immune cell-associated neurologic syndrome (ICANS) was higher in the CVAE group (35% vs. 7.6%; $p = 0.001$). Tocilizumab (95% vs. 66%, $p = 0.02$), steroids (70% vs. 33.3%, $p = 0.003$), and anakinra (20% vs. 0.7%, $p < 0.001$) were prescribed more frequently in CVAE compared to no CVAE group.

The median follow-up was 12 months for the entire cohort (interquartile range: 8.8–16.0 months). The estimated median OS was not reached. The overall response rate (ORR) was similar between CVAE and no CVAE group (Table 1). The presence of CVAE was associated with inferior OS in univariate Kaplan-Meier analysis (Fig. 1A; $p = 0.006$), with an early and steep decrease in survival within the first month of infusion. On univariate Cox-proportional analysis, the presence of CVAE (HR:2.51; 95% CI:1.27–4.96, $p = 0.008$) was associated with inferior OS. After adjusting for R-ISS III and CRS grade ≥ 3, CVAE was no longer associated with inferior survival (HR:1.18; 95% CI:0.46-3.01; $p = 0.73$; Supplementary Table 4). We additionally investigated a joint variable of CRS grade ≥ 3 and CVAE with OS and observed that patients with CRS grade ≥ 3, irrespective of CVAE, had inferior OS compared to all other groups, particularly early in the post-infusion period (Supplemental Fig. 1). Moreover, patients with CVAE without CRS had similar outcomes to patients without CVAE.

Lastly, to further characterize patients with early deaths after CAR-T, we performed a competing risks analysis by CVAE status. Irrespective of CVAE status, the probability of a non-myeloma-related death was higher early (within first month) in the follow-up period while the probability of a myeloma-related death was higher later in the follow-up period. The presence of CVAE did not affect the cumulative incidence of myeloma-related deaths

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Table 1. Clinical characteristics.

	Total	No cardiac events	Cardiac events	*P*-value
		(*N* = 144)	(*N* = 20)	
Age	63.4 ± 9.3	63.1 ± 9.2	65.8 ± 9.6	0.21
Sex (Male)	93 (56.7%)	86 (59.7%)	7 (35.0%)	0.06
Baseline ECOG				0.94
0	82 (50.6%)	73 (51.0%)	9 (47.4%)	
1	73 (45.1%)	64 (44.8%)	9 (47.4%)	
2	7 (4.3%)	6 (4.2%)	1 (5.3%)	
High BM Burden	51 (32.7%)	41 (30.1%)	10 (50.0%)	0.13
R-ISS				**<0.001**
I	28 (21.5%)	26 (23.0%)	2 (11.8%)	
II	80 (61.5%)	74 (65.5%)	6 (35.3%)	
III	22 (16.9%)	13 (11.5%)	9 (52.9%)	
Baseline Ferritin (ng/dL)	229.0 [62.0;719.0]	211.0 [60.5;650.5]	625.0 [143.0;2561.0]	**0.02**
Baseline CRP (mg/dL)	0.4 [0.2;0.9]	0.3 [0.2; 0.8]	0.8 [0.5; 2.5]	**0.01**
CRS Grade				**<0.001**
0	28 (17.1%)	28 (19.4%)	0 (0.0%)	
1	100 (61.0%)	92 (63.9%)	8 (40.0%)	
2	30 (18.3%)	23 (16.0%)	7 (35.0%)	
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4	3 (1.8%)	1 (0.7%)	2 (10.0%)	
5	3 (1.8%)	0 (0%)	3 (15.0%)	
Maximum CRS Grade 3 or above	6 (3.7%)	1 (0.7%)	5 (25.0%)	**<0.001**
Duration of CRS	2.8 ± 1.7	2.8 ± 1.6	3.2 ± 2.4	0.44
Maximum ICANS				<0.001
0	139 (84.8%)	126 (87.5%)	13 (65.0%)	
1	7 (4.3%)	7 (4.9%)	0 (0.0%)	
2	7 (4.3%)	4 (2.8%)	3 (15.0%)	
3	7 (4.3%)	6 (4.2%)	1 (5.0%)	
4	4 (2.4%)	1 (0.7%)	3 (15.0%)	
Maximum ICANS Grade 3 or above	18 (11.0%)	11 (7.6%)	7 (35.0%)	**0.001**
Length of Stay (days)	10.1 ± 10.2	9.0 ± 7.2	17.8 ± 20.7	0.08
ICU stay	10 (6.1%)	4 (2.8%)	6 (30.0%)	**<0.001**
Tocilizumab Use	114 (69.5%)	95 (66.0%)	19 (95.0%)	**0.02**
Steroid Use	62 (37.8%)	48 (33.3%)	14 (70.0%)	**0.01**
Anakinra Use	5 (3.0%)	1 (0.7%)	4 (20.0%)	**<0.001**
Maximum Ferritin (ng/dL)	6827.7 ± 20753.9	4769.2 ± 12488.4	21648.5 ± 47518.8	0.13
Maximum CRP(mg/dL)	10.4 ± 7.8	10.4 ± 7.9	10.5 ± 7.2	0.96
ORR 1 Month	61.6%	61.1%	65.0%	0.928
ORR 3 Month	73.4%	75.4%	60.0%	0.237

Data are presented as mean ± Standard deviation, median [interquartile range] or number (percentage), depending on type of data. *P*-value <0.05 are bolded. *ECOG* Eastern Cooperative Oncology Group performance status, *BM* bone marrow, *R-ISS* Revised International Staging System, *CRP* C-reactive protein, *CRS* cytokine release syndrome, *ICANS* immune cell-associated neurologic syndrome, *hsCRP* high-sensitivity C-reactive protein, *ORR* overall response rate. Reference values: Ferritin (<400 ng/dL); hsCRP (<0.5 mg/dL).

($p = 0.06$) or the cumulative incidence of non-myeloma-related deaths ($p = 0.29$), as shown in Fig. 1B.

In the current study involving two BCMA-targeting CAR-Ts, we found that CVAE occurs relatively frequently at 12.2%. The most common CVAE observed in our cohort was atrial arrhythmias, followed by CTRCD. This incidence of CVAE is consistent with previously established studies for anti-CD19 CAR-T [6–8, 12] and ide-cel [10].

Baseline oncologic characteristics associated with CVAE observed in our study were advanced R-ISS III, elevated baseline ferritin, and CRP levels. More advanced myeloma stages develop more inflammatory process and place additional stress on the body, potentially leading to more CVAE. Baseline cardiovascular comorbidities and risk factors were not associated with CVAE in our cohort, consistent with our prior findings in anti-CD19 CAR-T and ide-cel specific cohorts.

A consistent risk factor of CVAE in the literature and in current study is high-grade CRS. Mechanistically, an increased pro-inflammatory state from CAR-T may cause temporary cardiac manifestations, including cardiac dysfunction and atrial arrhythmias.

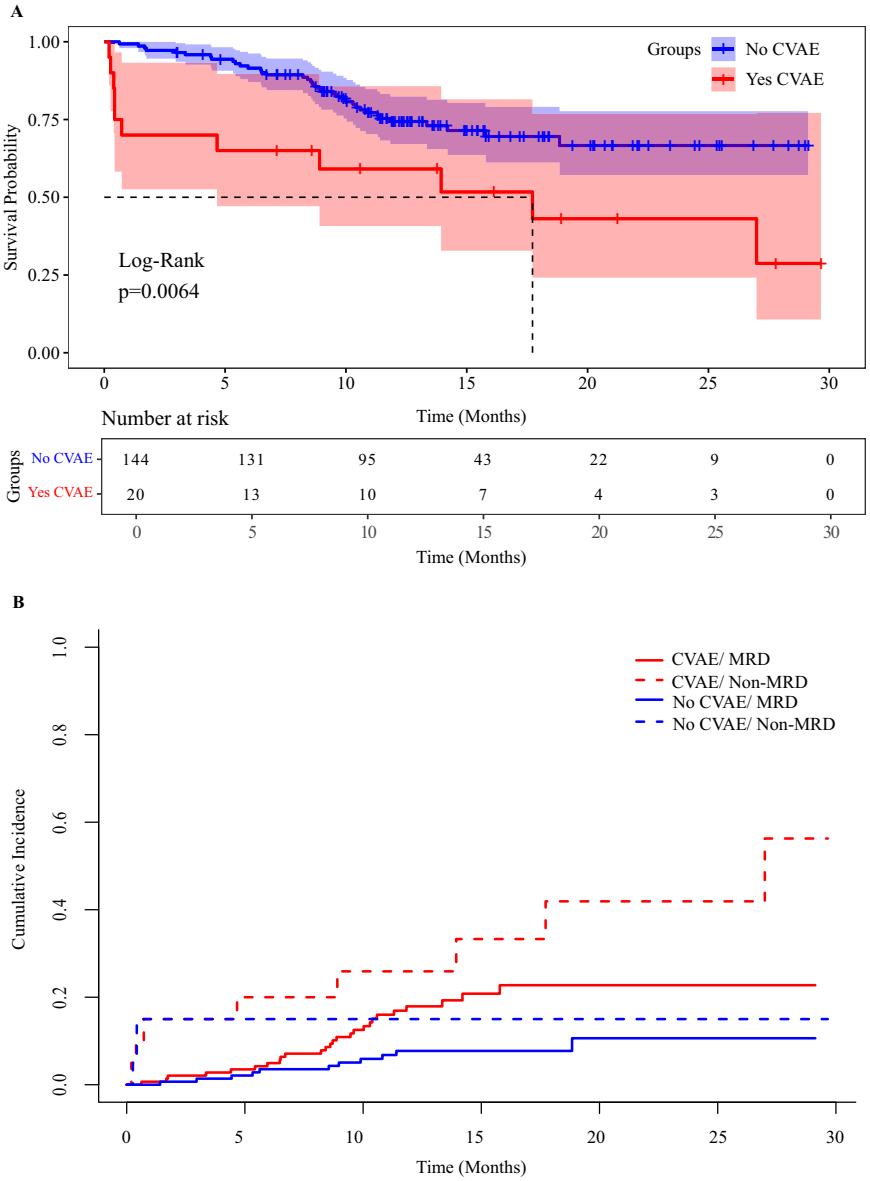

Fig. 1 Clinical Outcomes by CVAE. Overall survival (OS) based on the presence of cardiovascular adverse events (CVAE) after anti-BCMA CAR-T is shown in (**A**). Univariate Kaplan-Meier survival curve of OS estimates are shown. The lines depict survival curve of patients who did not develop CVAE (Blue line) and of patients who did develop CVAE (Red line). The highlighted area depicts the 95% confidence interval of each group. The *X*-axis depicts survival time in months. Cumulative incidence of death between four different groups (With or without CVAE and myeloma-related deaths or non-myeloma-related deaths) are shown in (**B**). The blue lines depict patients who did not develop CVAE. The red lines depict patients who developed CVAE. The solid lines depict myeloma-related deaths. The dotted line depicts non-myeloma-related deaths. CVAE cardiovascular adverse events. MRD Myeloma-related deaths, Non-MRD non-myeloma-related deaths.

In fact, pro-inflammatory cytokine levels are increased in CVAE [12, 13], suggesting a pathophysiological link. In contrast to the early CAR-T period when tocilizumab was selectively used only for CRS grade ≥ 2, it is now common practice to use tocilizumab in select CRS grade ≥ 1 with elevated inflammatory levels (ferritin/CRP) and/or high tumor burden. Similarly, the incidence of severe CVAE, including new onset heart failure, is lower in recent studies [8]. It is possible that a more aggressive supportive treatment of CRS led to a decrease in severe CVAE, but additional research is warranted.

The survival curve exhibited a notable steep decline early in the post-infusion time-period (<1 month) among patients with CVAE. However, over half of CVAEs were characterized by hemodynamically stable atrial fibrillation, a condition commonly observed in the context of systemic illness, such as CRS and infection [14]. Also, the early mortality was mostly from non-myeloma-related deaths, including high-grade CRS, systemic infection, and cardiovascular death. While CVAE was associated with inferior OS in univariate analysis, we found that CVAE was not associated with inferior OS after adjustment with covariates, including high-grade CRS. Further, in the competing risks analysis, the incidence of death occurred early in non-myeloma-related deaths, irrespective of presence or absence of CVAE. Therefore, our data suggests that acute systemic illness (such as infection and CRS) are the driver of early mortality after CAR-T, and that CVAE is a byproduct of these systemic illnesses, rather than a driver of inferior survival. While recent advancements in CRS management have led to a reduction of severe CVAE, continued efforts are essential to further minimize the occurrence of high-grade CRS to prevent early mortality.

This study has several limitations. First, this was a retrospective observational single-center study. As such, it is possible that CVAE

and other clinical covariates could have been missed or under-reported, or even over-reported [15]. However, there are no published data on prospective observational studies of cardiovascular outcomes after anti-BCMA CAR-T and a multi-center collaborative effort with longer follow up is warranted. Second, the sample size is relatively small, and the CVAE rate was relatively low, limiting our power to detect associations and to perform a more comprehensive multivariable analysis. However, this is the largest comprehensive study investigating CVAE in anti-BCMA CAR-T. Further, we limit our covariates of the multivariable analysis to three clinically important variables (CVAE, CRS, and R-ISS) on OS to prevent overfitting.

In conclusion, CVAEs are common after anti-BCMA CAR-T with risk factors including advanced RRMM stage with subsequently increased incidence of high-grade CRS. Importantly, while CVAEs can contribute to early mortality, our findings suggest that CRS and infections, rather than CVAEs themselves, are the primary drivers of early death following CAR-T. These insights emphasize the need for effective CRS management strategies, as well as vigilant cardiovascular monitoring, to improve outcomes in this patient population. Additionally, this study underscores the importance of personalized treatment approaches based on baseline characteristics and the potential for reducing the incidence of severe CVAEs with tailored interventions.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceived and designed of study: SP, MJ, FLL, MA, DKH, DHL Acquired data: SP, HK, MA, RCB, SC, GDA, CF, AGC, KH, OACP, SS, ABS, EW, DKH, DHL Interpretation of the results: SP, LCP, MA, DKH, DHL Drafted or revised the manuscript: SP, LCP, HK, MA, RCB, BJB, SC, GDA, CF, RG, AGC, KH, KDH, TN, GHO, LBO, OACP, SS, ABS, EW, KHS, MJ, FLL, MA, DKH, DHL Approved the final version: SP, LCP, HK, MA, RCB, BJB, SC, GDA, CF, RG, AGC, KH, KDH, TN, GHO, LBO, OACP, SS, ABS, EW, KHS, MJ, FLL, MA, DKH, DHL.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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