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FEATURE ARTICLE

Six-Year Trends in ICU Admission, Management, and Outcomes of Chimeric Antigen Receptor T-Cell Patients in the ICU

Prabalini Rajendram, MD[1]
R. Scott Stephens, MD[2]
Anne Rain T. Brown, PharmD, BCCCP, FCCM[3]
Heather P. May, PharmD[4]
Joseph L. Nates, MD[5]
Stephen M. Pastores, MD[1,6]
Ananda Dharshan, MD[7]
Alice Gallo de Moraes, MD[8]
Matthew K. Hensley, MD[9]
Lei Feng, MD[10]
Colleen McEvoy, MD[11]
Sikemi Ibikunle, MD[9]
Melissa Beasley[11]
Elena Mead, MD[6]
Jason Westin, MD[12]
Natalie T. Kostelecky, RN[1]
Simon Mucha, MD[13]
Agrima Mian, MD[14]
Sairah Ahmed, MD[12]
Arsal Tharwani, MD[15]
Brian T. Hill, MD[14]
Megan M. Herr, PhD[16]
Yi Lin, MD[17]
Cristina Gutierrez, MD[18]
and the Chimeric Antigen Receptor for the ICU (CAR-ICU) Initiative

OBJECTIVES: To evaluate evolving management, ICU admission, and outcomes for critically ill chimeric antigen receptor (CAR) T-cell patients over a 6-year period.

DESIGN: Multicenter retrospective cohort study from January 2018 to September 2023.

SETTING: Eight U.S. centers.

PATIENTS: Adult CAR T-cell patients requiring ICU admission.

INTERVENTIONS: None.

METHODS: Summary statistics included mean, SD, median, and interquartile range (IQR). Fisher exact test or chi-square test were used to evaluate association between year treated and other categorical variables. Cochran-Armitage test was performed to assess significance of trends across years. Multivariable logistic regression was performed to assess covariates associated with mortality.

MEASUREMENTS AND MAIN RESULTS: Demographics, toxicity management, ICU admission, support modalities, toxicity severity, and survival (ICU, hospital, and 3-mo) were compared year-to-year. From 2018 to 2023, 2238 patients received CAR T cells, with increasing number of patients treated yearly; 398 (17.8%) required ICU care. Of those admitted to the ICU, 66.1% were male, 89.2% had lymphoma, and median age was 64 years (53–71 yr). ICU admission rates declined from 38.5% (95% CI, 31.6–45.8%) in 2018 to 16.4% in 2023 (95% CI, 13.5–19.7%; $p < 0.0001$). Cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome was the reason for ICU admission in 87.9%. In 2023 vs. 2018, ICU patients were older (median, 65 yr [IQR, 55–73 yr] vs. 58 yr [48–67 yr]; $p = 0.003$) with higher comorbidity indices (4 [4–6] vs. 3 [2–4]; $p = 0.005$) and more severe toxicities (≥ grade 3: 90.1% vs. 69.9%; $p = 0.004$). Corticosteroid use for less severe toxicities (≤ grade 2 toxicity: 73.8% vs. 40.6%; $p = 0.0001$) and anakinra use (56% vs. 5.5%; $p < 0.0001$) increased throughout the years. Mortality from cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome remained low (5.5%). Age, Sequential Organ Failure Assessment greater than or equal to 10 at ICU admission, and ICU admission for noncytokine release/neurotoxicity syndrome reasons were associated with hospital mortality (odds ratios, 1.02 [95% CI, 1–1.04; $p = 0.046$], 4.69 [2.44–9.01; $p < 0.0001$], and 3.74 [1.91–7.3; $p = 0.0001$], respectively).

CONCLUSIONS: ICU admission rates after CAR T-cell treatment are declining. Although ICU patients are older with higher severity of illness and toxicity grades, ICU mortality after CAR T-cell therapy remains low.

KEYWORDS: chimeric antigen receptor T cell; intensive care unit admission; intensive care unit resources; outcomes; toxicities

This article has an accompanying editorial.

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KEY POINTS

Question: How has the evolving management of hematological malignancies with different U.S. Food and Drug Administration approved chimeric antigen receptor (CAR) T-cell products, impacted ICU admission, and outcomes of critically ill patients receiving this therapy?

Finding: This retrospective multicenter cohort study between 2018 and 2023, found that despite more patients receiving CAR T cells yearly, ICU admission rates after this treatment are declining. While throughout the years ICU patients have become older with higher severity of illness and toxicity grades, ICU mortality after CAR T-cell therapy remains low.

Meaning: CAR T-cell therapy is increasingly safe and is leading to reduced reliance on ICU resources.

Chimeric antigen receptor (CAR) T-cell therapies lead to sustained remission in patients with hematologic malignancies (1). Their toxicities, such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and sepsis, have led to ICU admission in 35% of patients (2–4). Despite this significant rate of ICU admission, ICU mortality has been low (< 9%) encouraging intensivists to offer aggressive support to these patients (2, 3).

In recent years, changes related to these therapies have likely impacted ICU utilization. First, recently approved CAR T-cell products have a lower prevalence of grade 3 or higher CRS and ICANS (5–7). Second, guidelines published in 2021 streamlined toxicity grading, management, and antimicrobial prophylaxis (8, 9). These recommend earlier interventions (corticosteroids for grade 1–2 toxicities) and highlighted additional therapies such as anakinra (interleukin-1 receptor antagonist) and ruxolitinib (Janus kinase inhibitor) (8, 9). Third, some CAR T-cell products are now recommended for earlier disease stages, which could impact the prevalence of CRS/ICANS and sepsis (10, 11). Collectively, these factors likely reduce ICU utilization.

Because studies of CAR T-cell patients requiring ICU were published before all these changes, new analyses are needed to understand how ICU admission and patient outcomes may be evolving. The aim of this study was to describe changes in ICU admission, management, and outcomes of CAR T-cell recipients requiring ICU from 2018 to 2023 and assess covariates associated with mortality and survival.

METHODS

Study Design

Retrospective cohort study of adult patients (≥ 18 yr) requiring ICU admission post-U.S. Food and Drug Administration-approved CAR T-cell therapy, between January 2018 and September 2023, at 11 U.S. centers. Details of methods and centers are previously reported (2). Local Institutional Review Boards approved the protocol and waived informed consent (**Supplement 1**, https://links.lww.com/CCM/H857). Procedures followed Strengthening the Reporting of Observational Studies in Epidemiology and Helsinki Declaration 1975 (12). De-identified data were examined by two authors (C.G., A.R.T.B.) and discrepancies resolved with each center. Patients admitted to the ICU within 30 days after CAR T-cell infusion (time period when toxicities occur) were identified using internal registries (8, 9). Only the first ICU admission was included; ICU readmissions, ICU length of stay (LOS), and ICU admission rate were collected. A Research Electronic Data Capture (Vanderbilt University, Nashville, TN) (13) tool captured demographics, Charlson Comorbidity Index (CCI), malignancy, ICU admission reason, toxicities, Sequential Organ Failure Assessment (SOFA) scores, and organ support (vasopressors, mechanical ventilation, and renal replacement therapy). Presence and severity of CRS, ICANS, and immune effector cell-associated hemophagocytic lymphohistiocytosis (IEC-HS) were defined according to the American Society for Transplantation and Cellular Therapy criteria (9, 14) (**Supplement 2**, https://links.lww.com/CCM/H857). Reported toxicities, features, and cause of death were compared with institutional databases. For toxicity-specific treatments, we recorded the indication (toxicity grade) for the first dose administered. To analyze if practices reflected changes in guidelines, the indication for each medication was grouped according to the following recommendations: anakinra used for grade greater than or equal to 3 CRS/ICANS, tocilizumab

and corticosteroids used for grade 1 CRS, and corticosteroids for grade 2 ICANS. Patients were grouped according to ICU admission year. ICU, hospital, and 3-month survival post-infusion were recorded.

Statistical Analysis

Summary statistics (median [interquartile range (IQR)]) were used for continuous variables (e.g., age, SOFA score, LOS), and frequency counts and percentages for categorical variables (e.g., year treated, CAR T-cell product, CRS/ICANS grades treatment). Associations between year treated and categorical variables were evaluated with Fisher exact test or chi-square test, and trends over time evaluated with Cochran-Armitage test. Wilcoxon rank-sum test was used to evaluate the difference in time from infusion to ICU admission between patients who died in ICU/hospital and those who did not. Differences in continuous variables were evaluated with Kruskal-Wallis tests. We calculated hospital/ICU LOS as the interval from hospital/ICU admission to ICU/hospital discharge or death. Multivariate logistic regression models were fitted to estimate associations between covariates and ICU/hospital mortality. Covariates with univariate p value of less than 0.10 were included in the full model; backward selection was used to reach a final model including covariates with p values of less than 0.05. ICU admission year was forced in the model. No collinearity was identified. Overall survival (OS) was calculated from ICU admission to death; surviving patients were censored at 3 months. We estimated OS with Kaplan-Meier methods and evaluated OS difference among ICU admission years with log-rank test. SAS (Version 9.4; SAS Institute, Cary, NC) and S-Plus 8.2 (TIBCO Software, Palo Alto, CA) statistical software were used.

RESULTS

During the study period, 2317 patients received CAR T-cell therapy at 11 centers. Three centers could not provide data after 2019, and their patients (n = 79) were excluded. Among the eight centers included in the final analysis, 2238 patients received CAR T-cell therapy from 2018 to 2023, and 398 patients (17.8%) were admitted to the ICU (**Fig. 1**). Of those, 27 patients had received CAR T cells in the outpatient setting and 11 in the ICU (admitted before for stabilization/close monitoring). Most patients admitted to the ICU had lymphoma (89.2%) and received axicabtagene ciloleucel (axi-cel; 67.8%; **Table S10**, https://links.lww.com/CCM/H857). The median (IQR) age was 64 years (53–71 yr), and CCI was 4 (3–5). Most patients were admitted to the ICU for CRS and/or ICANS (87.9%): 45.4% admitted for ICANS, 28.6% for CRS, and 26% for both. At the time of ICU admission, grade 3 or higher toxicities were observed in 62.6% of all admitted patients and median SOFA score was 5 (4–8). Infections during ICU stay were documented in 95 patients (24%). prevalence of IEC-HS was 3.8% with 88.2% mortality. ICU and hospital mortality were 17.8% and 22.4%, respectively, with only 5.5% of patients dying from CRS or ICANS (Table S10, https://links.lww.com/CCM/H857).

ICU Admission Trends 2018–2023

The number of patients treated with CAR T-cell therapy increased over the years except for 2020 (**Fig. 2**). The annual ICU admission rate was highest in 2018 (38.5%; 95% CI, 31.6–45.8%) and was lowest in 2022 (9.5%; 95% CI, 7.3–12.2%); this decreasing trend of ICU admission rates among the years was significant ($p < 0.0001$; Fig. 2). ICU admission rates and low-grade toxicities at admission varied across centers ($p < 0.0001$; **Table S1a** and **b**, https://links.lww.com/CCM/H857). While axi-cel was the most common product, the use of other products increased significantly in 2020 (**Table 1**). The lowest median age and median CCIs were observed in 2018; CAR T-cells were administered earlier in the disease course beginning in 2020 ($p < 0.005$; Table 1). At admission, SOFA scores varied over the years ($p = 0.01$) while grade 3 or higher toxicities were similar (52.4–68.8%; $p = 0.4$; and Table 1). Variations in organ support were not significant (Table 1).

Changes in Management of Patients With CAR T-Cell–Related Toxicities

Among the 398 patients admitted to the ICU, 350 patients had CRS and ICANS at the time of ICU admission. However, 382 patients (96%) experienced CRS or ICANS at some point during their ICU stay; 17.3% had CRS, 21.4% ICANS, and 57.3% both toxicities (**Table S11**, https://links.lww.com/CCM/H857). Overall, 80.9% of these patients developed grade 3 or higher toxicities, with an increasing trend in severe

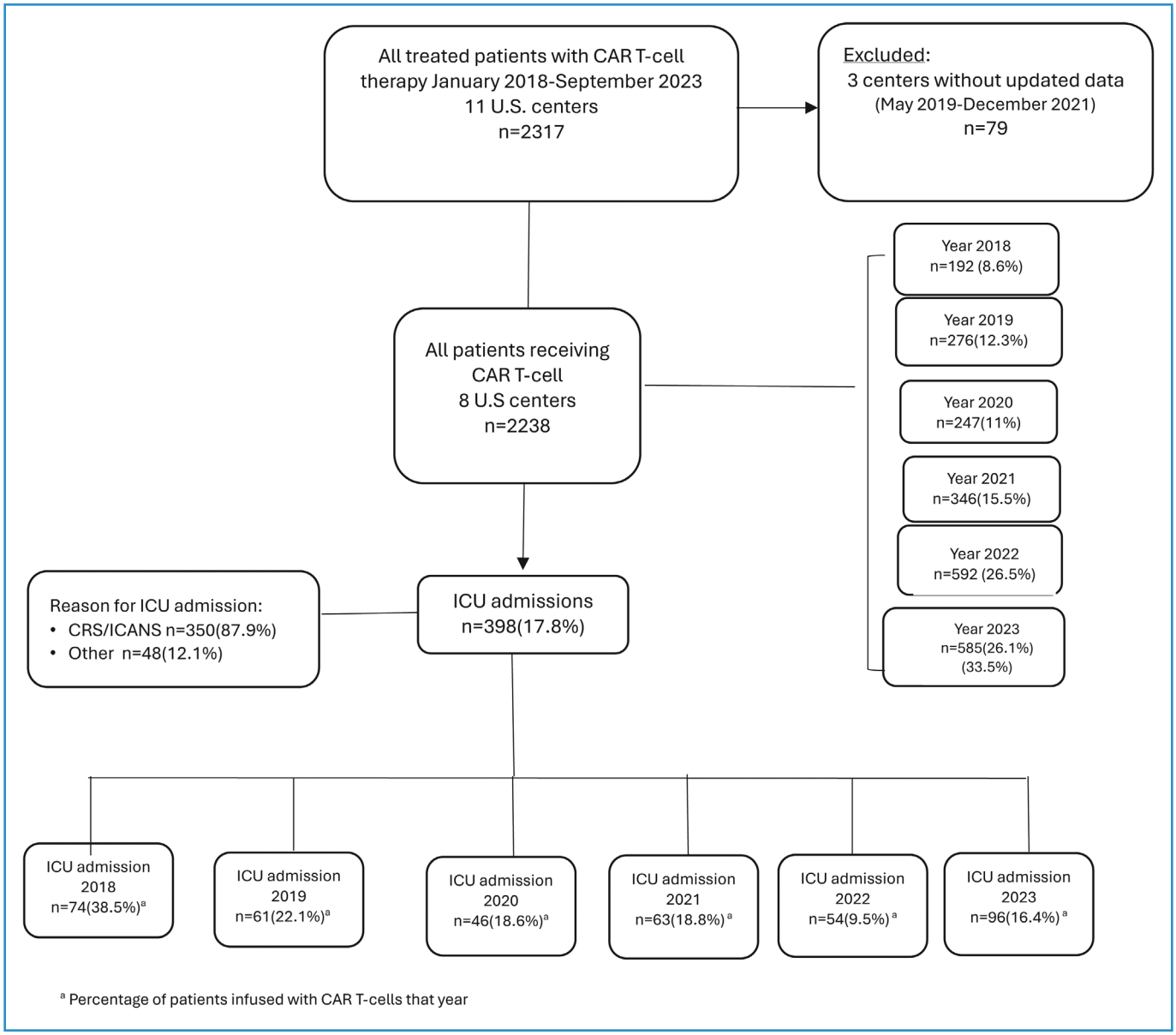
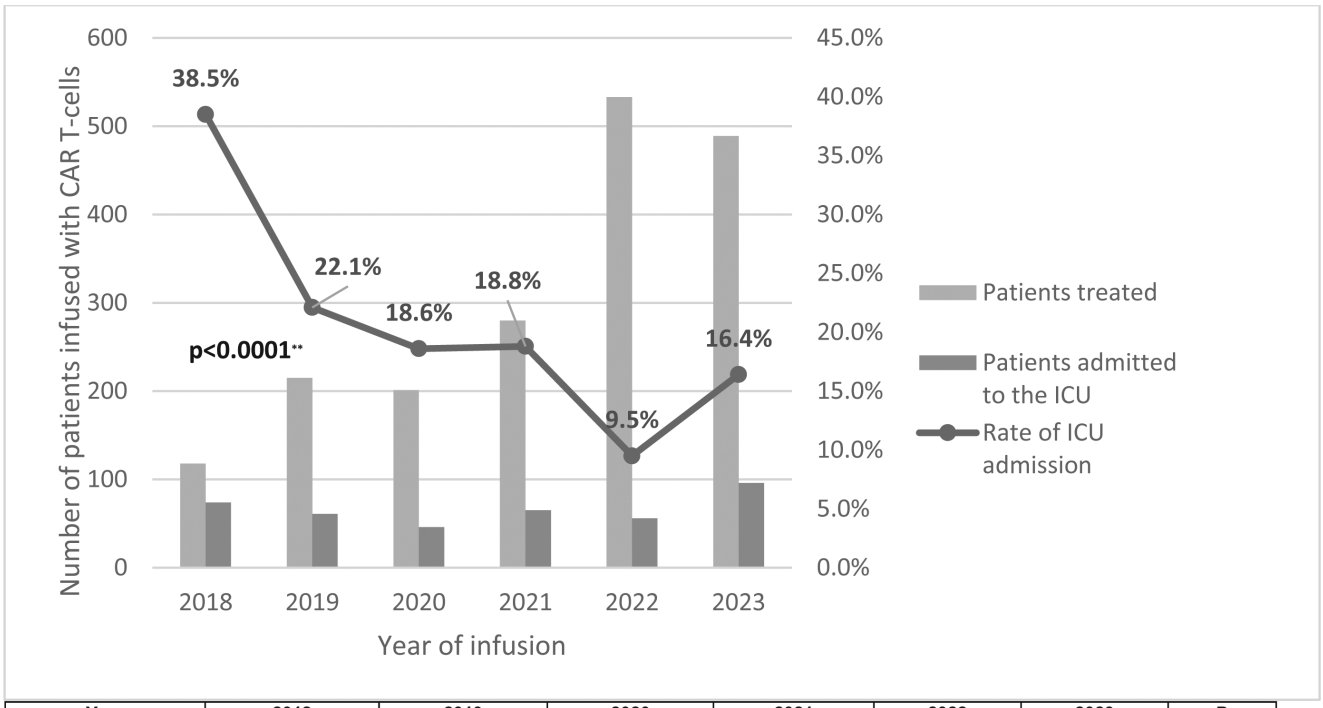


Figure 1. Patients treated with chimeric antigen receptor (CAR) T-cell therapy and admitted to the ICU during the study period 2018–2023. CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome.

toxicities throughout the years (p = 0.004; **Table S2**, https://links.lww.com/CCM/H857). Associated organ toxicities such as cardiomyopathy, renal failure, coagulopathy, and liver dysfunction were uncommon (**Table 2**). The rate of arrhythmias varied significantly throughout the years and was lowest in 2018 (20.4%) and highest in 2022 (65.2%; p = 0.0008). Need for vasopressor support increased over time (p = 0.05; Table 2). The rate of grade 3 or higher ICANS did not differ significantly among the years, and the rates of cerebral edema and seizures, were consistently low (Table 2).

Tocilizumab (88%) and corticosteroids (94.8%) remained the most common treatments for CRS and ICANS over the course of the study. While the rate of patients receiving tocilizumab or siltuximab did not vary significantly (p > 0.5; Table 2), there was an increasing trend in use of anakinra over time (lowest in 2018; 5.5%) and highest in 2023 (56%; p < 0.0001; Table S2, https://links.lww.com/CCM/H857). Corticosteroid use for ICU patients with nonsevere toxicities (grade 1–2) differed significantly among years (Table 2), with an increasing trend of earlier administration throughout the study period (40.6% in 2018 and 68.5% in 2023 for grade 1–2 toxicities; p = 0.0001; Table S2, https://links.lww.com/CCM/H857). The median cumulative dose of corticosteroids did not



Year	2018	2019	2020	2021	2022	2023	P value**
95% CI: ICU admission rate (range)	38.5% (31.6~45.8%)	22.1% (17.3~27.5%)	18.6% (14.0~24.0%)	18.8% (14.9~23.4%)	9.5% (7.3~12.2%)	16.4% (13.5~19.7%)	**p<0.0001**

**Cochran-Armitage trend

Figure 2. Rate of ICU admission post-chimeric antigen receptor (CAR) T-cell therapy: 2018–2023.

vary significantly. The use of alternative treatments for refractory toxicities was consistently low (6.8%) and varied across centers.

Outcomes of Critically Ill CAR T-Cell Patients

ICU LOS remained similar throughout the study period; however, hospital LOS shortened from a median of 24–29 days in 2018–2019 to 22 days in 2023 (p = 0.01; Table 1). ICU readmission rates differed significantly, with a higher rate in 2018 and 2019 (20.3–23%) and lower in 2021–2023 (5.4–10.4%; p = 0.03; and Table 1). Overall ICU (8.1–21.7%) and hospital (16.2–30.4%) mortality did not vary significantly ($p > 0.05$; Table 1). Deaths from CRS and ICANS were 1.8–6.5% but peaked in 2021 (16.9%). Sepsis remained the most common cause of death in this patient population (34% of all deaths) followed by malignancy progression (18%).

In univariate analysis, patients who died in the ICU were more likely to have a reason for ICU admission other than CRS/ICANS, have grade 3 or higher CRS, positive cultures during their ICU stay, higher SOFA scores, require organ support, receive siltuximab, anakinra, higher doses of cumulative corticosteroids, and be admitted in the year 2020 (**Table S3**, https://links.lww.com/CCM/H857). Patients who died were admitted later post-infusion to the ICU than those who were alive (median [IQR], 13 d [8–23 d] and 9 d [6–14 d]; p = 0.001). In multivariate logistic regression analysis, the following covariates were associated with ICU mortality: ICU admission for reasons other than CRS/ICANS (odds ratio [OR], 4.56; 95% CI, 2.29–9.09; $p < 0.0001$) and having a SOFA score on ICU admission greater than or equal to 10 (OR, 4.12; 95% CI, 2.13–8.29; $p < 0.0001$; **Table S4**, https://links.lww.com/CCM/H857). For hospital mortality, in multivariate logistic regression model, age (OR, 1.02; 95% CI, 1.00–1.04; p = 0.046), ICU admission for reasons other than CRS/ICANS (OR, 3.74; 95% CI, 1.91–7.3; p = 0.0001), having a SOFA score on ICU admission greater than or equal to 10 (OR, 4.69; 95% CI, 2.44–9.01; $p < 0.0001$) were significantly associated with hospital mortality (**Fig. 3*A***). Sepsis as a reason for ICU admission, year

of ICU admission, or type of CAR T-cell product were not associated with hospital mortality on multivariate analysis (Fig. 3*A*; and **Table S5**, https://links.lww.com/CCM/H857).

Among all 398 patients admitted to ICU, 66% were alive at 3 months post-ICU admission. The difference in OS among years was significant ($p = 0.03$; **Fig. 3*B***). However, when excluding year 2020 (OS rate: 48%) the difference was not significant (OS rate: 60–75%; $p = 0.42$; **Fig. 3*C***). The patients with cumulative doses of corticosteroids greater than or equal to 1621 mg had lower OS rate at 3 months (53%; 95 CI, 46–60%; **Fig. S1**,

TABLE 1.
Yearly Differences 2018 to 2023: Characteristics and Outcomes of Chimeric Antigen Receptor T-Cell Patients Admitted to the ICU (*n* = 398)

Characteristics	2018, *n* = 74 (18.6%)	2019, *n* = 61 (15.3%)	2020, *n* = 46 (11.6%)	2021, *n* = 65 (16.3%)	2022, *n* = 56 (14.1%)	2023, *n* = 96 (24.1%)	*p*[a]
Male sex	51 (68.9%)	34 (55.7%)	23 (50%)	43 (66.2%)	39 (69.6%)	73 (76.0%)	**0.02**
Age, yr, median (IQR)	58 (48–67)	65 (54–71)	64 (55–69)	68 (55–75)	63 (52–72)	65 (55–73)	**0.003**
Comorbidity index[e],median (IQR)	3 (2–4)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (4–6)	**0.005**
Type of malignancy							
Lymphoma	73 (98.6%)	61 (100%)	46 (100%)	61 (93.8%)	44 (78.6%)	70 (72.9%)	**< 0.0001**
Multiple myeloma	(0)	(0)	(0)	2 (3.1%)	8 (14.3%)	15 (15.6%)	
Leukemia	1 (1.4%)	(0)	(0)	2 (3.1%)	3 (5.4%)	9 (9.4%)	
Other[b]	(0)	(0)	(0)	(0)	1 (1.9%)	1 (1%)	
Lines treatment[f], median (IQR)	4 (3–5)	4 (3–5)	3 (3–4)	3 (2–4)	3 (2–4)	3 (2–4.5)	**0.0003**
Chimeric antigen receptor T-cell products[c]							**< 0.0001**
Axicabtagene ciloleucel	69 (93.2%)	54 (88.5%)	38 (82.6%)	36 (55.4%)	32 (57.1%)	41 (42.7%)	
Tisagenlecleucel	5 (6.8%)	7 (11.5%)	6 (13%)	7 (10.8%)	1 (1.8%)	3 (3.1%)	
Brexucabtagene autoleucel	(0)	(0)	2 (4.3%)	13 (20%)	12 (21.4%)	28 (29.2%)	
Lisocabtagene vicleucel	(0)	(0)	(0)	7 (10.8%)	1 (1.8%)	8 (8.3%)	
Idecabtagene vicleucel	(0)	(0)	(0)	2 (3.1%)	5 (8.9%)	6 (6.3%)	
Ciltacabtagene autoleucel	(0)	(0)	(0)	(0)	5 (8.9%)	10 (10.4%)	
Variables in ICU							
Reason ICU admission							0.16
CRS and/or ICANS	70 (94.6%)	52 (85.2%)	37 (80.4%)	60 (92.3%)	47 (83.9%)	84 (87.5%)	
Other[d]	4 (5.4%)	9 (14.8%)	9 (19.6%)	5 (7.7%)	9 (15.3%)	12 (12.5%)	
SOFA ICU admission, median (IQR)	4 (3–6)	5 (3–7)	5 (3–7)	5 (3–8)	6 (4–9)	6 (4–8)	**0.01**
Maximum SOFA, median (IQR)	6 (4–8)	6 (5–8)	7 (4–10)	6 (4–10)	7 (5–11)	7 (5–10)	0.21
Vasopressors	12 (16.2%)	16 (26.2%)	15 (32.6%)	23 (35.4%)	21 (37.5%)	33 (34.4%)	0.06
Mechanical ventilation	8 (10.8%)	11 (18.0%)	15 (32.6%)	13 (20%)	15 (26.8%)	17 (17.7%)	0.06
Renal replacement	5 (6.8%)	4 (6.6%)	5 (10.9%)	9 (13.9%)	6 (10.7%)	10 (10.4%)	0.71

(*Continued*)

TABLE 1. (*Continued*)
Yearly Differences 2018 to 2023: Characteristics and Outcomes of Chimeric Antigen Receptor T-Cell Patients Admitted to the ICU (n = 398)

Characteristics	2018, *n* = 74 (18.6%)	2019, *n* = 61 (15.3%)	2020, *n* = 46 (11.6%)	2021, *n* = 65 (16.3%)	2022, *n* = 56 (14.1%)	2023, *n* = 96 (24.1%)	*p*[a]
Resources and outcomes							
ICU LOS, d, median (IQR)	4 (2–7)	3 (2–6)	3 (1–6)	3 (1–7)	3 (2–6)	3 (2–7)	0.65
Hospital LOS, d, median (IQR)	24 (16–34)	29 (18–42)	27 (16–49)	19 (13–26)	23 (15–43)	22 (15–34.5)	**0.01**
ICU readmission	15 (20.3%)	14 (23%)	7 (15.2%)	6 (9.2%)	3 (5.4%)	10 (10.4%)	**0.03**
ICU mortality	6 (8.1%)	10 (16.4%)	10 (21.7%)	13 (20%)	11 (19.6%)	17 (17.7%)	0.34
Hospital mortality	12 (16.2%)	13 (21.3%)	14 (30.4%)	18 (27.7%)	12 (21.4%)	20 (20.8%)	0.47
CRS/ICANS related	2 (2.7%)	2 (3.3%)	3 (6.5%)	11 (16.9%)	1 (1.8%)	3 (3.1%)	**0.005**
Other	10 (13.5%)	11 (18%)	11 (23.9%)	7 (10.8%)	11 (19.6%)	17 (17.7%)	

CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome, IQR = interquartile range, LOS = length of stay, SOFA = Sequential Organ Failure Assessment.
[a]*p* value reflects the comparison of data within years.
[b]Two patients with diagnosis of Waldenstrom macroglobulinemia.
[c]Products were approved by the U.S. Food and Drug Administration in the following years: axicabtagene ciloleucel-2017; tisagenlecleucel-2017, brexucabtagene autoleucel-2020; lisocabtagene vicleucel-2021; idecabtagene vicleucel-2021; and ciltacabtagene autoleucel-2022.
[d]Other reasons for ICU admission include: sepsis (27.1%), respiratory failure (22.9%), cardiac complications (16.7%), optimization before therapy (8.3%), and other (25%).
[e]Charlson Comorbidity Index.
[f]Lines of chemotherapy before chimeric antigen receptor T cells.
Data are expressed as *n* (%), unless otherwise indicated. Boldface values are significant.

https://links.lww.com/CCM/H857). There was no significant difference in survival among types of malignancy (**Fig. S2**, https://links.lww.com/CCM/H857).

DISCUSSION

To our knowledge, this is the most comprehensive study to report changes in ICU admission rates, characteristics of CAR T-cell toxicities, their management, and outcomes of CAR T-cell patients admitted to intensive care from 2018 to 2023. Less than 20% of patients who received CAR T-cell therapy required ICU admission and nearly 90% of ICU admissions were for CRS/ICANS, in line with previous studies (2, 3). Our findings show that while there is an increasing availability of CAR T-cell products for different malignancies and a yearly increase in number of patients treated with CAR T cells at our institutions, rates of ICU admission have decreased significantly. Throughout the years, patients admitted to the ICU were older, with higher comorbidities, increasing SOFA scores on ICU admission, and grade 3 or higher toxicities during their ICU stay. Despite this, hospital mortality (16.2–30.4%) did not vary significantly across the years and mortality due to CRS and ICANS remained low (5.5%). Older age, ICU admission for reasons other than CRS/ICANS, and having a SOFA score on ICU admission greater than or equal to 10 were associated with hospital mortality.

Despite more patients being treated yearly with CAR T-cell therapy at our institutions, rates of ICU admission more than halved, from 38.5% in 2018 to 16.4% in 2023, in our study. This is lower than the 27–35% rates in previous multicenter studies (3, 4, 15). This decrease in ICU admission rates could potentially be explained by the increasing use of recently approved CAR T-cell products with lower rates of grade 3 or higher CRS and ICANS, and perhaps to the expertise and resources available at our highly specialized centers (6, 7, 16). As new products with improved toxicity profiles are

TABLE 2.
Toxicities and Treatments of Patients Who Experienced Cytokine Release Syndrome and Immune Effector Cell-Associated Neurotoxicity Syndrome During ICU Stay (*n* = 382)

Toxicities and Treatments	2018, *n* = 73 (19.1%)	2019, *n* = 58 (15.2%)	2020, *n* = 43 (11.3%)	2021, *n* = 63 (16.5%)	2022, *n* = 54 (14.1%)	2023, *n* = 91 (23.8%)	*p*[a]
CRS/ICANS toxicities							
Grade ≥ 3 CRS/ICANS at ICU admission	43 (59.7%)	38 (67.9%)	27 (67.5%)	33 (54.1%)	37 (68.5%)	66 (72.5%)	0.22
Grade ≥ 3 CRS/ICANS during ICU stay[b]	51 (69.9%)	47 (81%)	32 (74.4%)	53 (82.8%)	48 (84.2%)	82 (90.1%)	**0.03**
Grade ≥ 3 CRS	16 (21%)	15 (25.9%)	9 (20.9%)	25 (39.1%)	19 (33.3%)	35 (38.5%)	0.07
Grade ≥ 3 ICANS	44 (60.3%)	39 (67.2%)	29 (67.4%)	46 (71.9%)	40 (70.2%)	61 (67%)	0.78
Vasopressor support	11 (15.1%)	15 (25.9%)	12 (27.9%)	22 (34.9%)	20 (37%)	31 (34.2%)	**0.05**
Arrhythmias[f]	11 (20.4%)	15 (36.6%)	7 (23.3%)	19 (38.0%)	15 (65.2%)	22 (52.4%)	**0.0008**
Cardiomyopathy[f]	2 (3.7%)	3 (7.5%)	4 (13.8%)	2 (4.7%)	2 (4.7%)	2 (8.7%)	0.56
Acute renal failure[f]	9 (16.7%)	10 (25%)	5 (16.7%)	8 (18.6%)	8 (34.8%)	12 (28.6%)	0.41
Liver dysfunction[f]	15 (27.8%)	12 (30%)	4 (13.3%)	6 (14%)	2 (8.7%)	7 (16.7%)	0.13
Disseminated intravascular coagulation[f]	3 (5.6%)	2 (5.1%)	2 (6.7%)	2 (5.4%)	1 (4.3%)	4 (9.5%)	0.95
Immune effector cell-associated hemophagocytic lymphohistiocytosis	2 (3.6%)	1 (2.6%)	4 (13.3%)	4 (10.8%)	2 (8.7%)	2 (4.8%)	0.36
Seizures[g]	11 (18.6%)	11 (22.0%)	8 (21.6%)	13 (25%)	8 (18.6%)	14 (19.4%)	0.96
Cerebral edema[g]	2 (3.4%)	1 (2.0%)	2 (5.4%)	3 (5.8%)	(0)	(0)	0.25
Treatments for toxicities							
Tocilizumab	61 (83.6%)	50 (86.2%)	36 (83.7%)	55 (87.3%)	49 (90.7%)	85 (93.4%)	0.39
First dose grade 1[c]	20 (32.8%)	25 (50%)	18 (50.0%)	25 (45.5%)	26 (53.1%)	46 (54.1%)	0.17
Siltuximab	7 (9.6%)	8 (13.8%)	6 (14.0%)	11 (17.5%)	7 (13%)	12 (13.2%)	0.87
Anakinra	4 (5.5%)	9 (15.5%)	13 (30.2%)	25 (39.7%)	27 (50%)	51 (56%)	**< 0.0001**
First dose grade ≥ 3[c]	4 (100%)	6 (66.7%)	6 (46.2%)	15 (60.0%)	15 (55.6%)	31 (60.8%)	0.54
Corticosteroids	64 (87.7%)	57 (98.3%)	42 (97.7%)	56 (88.9%)	54 (100%)	89 (97.8%)	**0.002**
First dose grades 1–2[c]	26 (40.6%)	25 (43.9%)	31 (73.8%)	34 (60.7%)	33 (61.1%)	61 (68.5%)	**0.0007**
Cumulative corticosteroid dose[d], mg, median (interquartile range)	1428.5 (251.5–3820)	1386.7 (640–3387)	2586.4 (1150–4795)	1920 (906–4930)	1693 (821–3585)	1440 (533–3136)	0.06
Other therapies[e]	4 (5.5%)	3 (5.2%)	3 (7.0%)	4 (6.3%)	3 (5.6%)	9 (9.9%)	0.85

CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome.

[a]*p* value reflects the comparison of data within years.

[b]Maximum grade toxicity during ICU stay as per to American Society for Transplantation and Cellular Therapy (ASTCT) grading consensus. Grades 3 and 4 includes hypoxemia requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, hypotension requiring vasopressors, seizures (any type including status epilepticus), CAR-T-cell-therapy-associated TOXicity /Immune Effector Cell Encephalopathy score < 3, cerebral edema, motor deficits, and obtundation. Grade 5 = death.

[c]Indications according to ASTCT guidelines for treatment of toxicities.

[d]Corticosteroid equivalent of methylprednisolone and throughout all hospital stay.

[e]Other therapies include: intrathecal corticosteroids, ruxolitinib, antithymocyte globulin, dasatinib, infliximab, etoposide, IV immunoglobulin, and methotrexate.

[f]Among those with CRS.

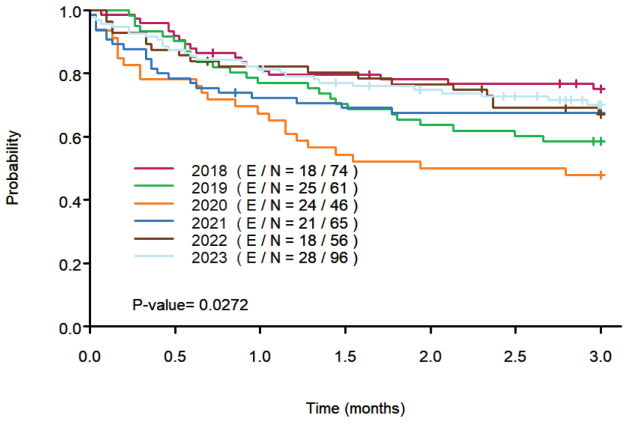
[g]Among those with ICANS.

Trend analysis with Cochran-Armitage test was significant for ≥ grade 3 toxicities during ICU stay anakinra and corticosteroid use across the years. Boldface values are significant.

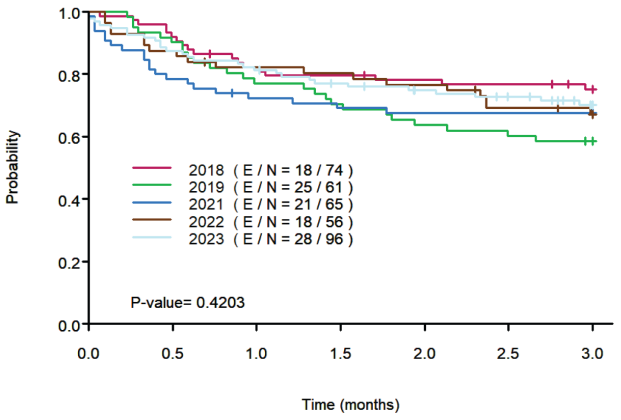
A *Multivariate logistic regression for hospital mortality of all patients admitted to the ICU*

	Hospital Mortality			
	Univariate analysis		Multivariate analysis	
Covariates	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Age	1.02 (1.00-1.04)	0.04	1.02 (1-1.04)	0.046
Other reason for ICU admission (non-CRS/ICANS)	3.57 (1.91-6.69)	<0.0001	3.74 (1.91-7.3)	0.0001
Admission SOFA score ≥10	4.44 (2.39-8.23)	<0.0001	4.69 (2.44-9.01)	<0.0001
Year of ICU admission				
2019 vs 2018	1.4 (0.59-3.34)	0.45	0.98 (0.39-2.48)	0.97
2020 vs 2018	2.26 (0.94-5.46)	0.07	1.48 (0.58-3.79)	0.41
2021 vs 2018	1.98 (0.87-4.51)	0.1	1.51 (0.63-3.64)	0.35
2022 vs 2018	1.41 (0.58-3.43)	0.45	0.82 (0.31-2.16)	0.69
2023 vs 2018	1.36 (0.62-2.99)	0.44	0.98 (0.43-2.26)	0.96

B *Overall survival Including all years (2018-2023)*



C *Overall survival excluding year 2020*



Variable	Level	N	Event	OS rate at 1 month (95%CI)	OS rate at 2 months (95%CI)	OS rate at 3 months (95%CI)	p-value
	All patients	398	134	0.78 (0.74-0.82)	0.7 (0.65-0.75)	0.66 (0.61-0.71)	
Time Period	2018	74	18	0.82 (0.74-0.92)	0.78 (0.69-0.88)	0.75 (0.66- 0.86)	**0.03**[b]
	2019	61	25	0.77 (0.67-0.88)	0.64 (0.53-0.77)	0.59 (0.47 -0.72)	
	2020	46	24	0.67 (0.55-0.82)	0.5 (0.37-0.67)	0.48 (0.35-0.65)	
	2021	65	21	0.72 (0.62-0.84)	0.68 (0.57-0.8)	0.68 (0.57-0.8)	
	2022	56	18	0.82 (0.73-0.93)	0.77 (0.66-0.89)	0.67 (0.56-0.81)	
	2023	96	28	0.81 (0.74-0.89)	0.75 (0.67-0.84)	0.7 (0.61-0.8)	

Median overall survival on our prior reports is 10.2 months and was not reached for the last cohort of patients in this study (data set of patients admitted after 2022) therefore median OS was not reported. [b] p=0.42 when excluding the year of 2020

Figure 3. chimeric antigen receptor (CAR) **A**, Variables associated with hospital mortality in multivariate logistic regression. Year of ICU admission was not associated to hospital mortality. **B**, Overall 3-mo survival curves of patients treated with CAR T-cell therapy admitted to the ICU in each year; year 2020 had a significant shorter 3-mo survival when compared with other years. **C**, Year 2020 was excluded to assess differences in 3-mo overall survival (OS) among all other years. No significant difference was observed among 2018, 2019, 2021, 2022, and 2023. CRS = cytokine release syndrome, E = number of events, ICANS = immune effector cell-associated neurotoxicity syndrome, N = number of all patients, SOFA = Sequential Organ Failure Assessment.

approved and used, along with advances in interventions to prevent progression to severe toxicities, ICU admission rates could decrease further. While this decrease in ICU admission rate was observed in half of the centers included in this study, none of our centers reported any change in their ICU admission criteria.

However, request for ICU admission by the treating oncologist was part of ICU admission criteria at all centers, which could explain the differences in rate of ICU admission and severity of toxicities at the time of ICU admission among centers. While there were no changes in ICU LOS, ICU readmission rates, and hospital LOS decreased throughout the years.

While corticosteroids and tocilizumab remained the cornerstones of therapy for toxicities, corticosteroids were used earlier for less severe toxicity (grade 1–2) in our ICU patients throughout the years. In addition, anakinra was used more and for severe toxicities (grade 3 or higher), and a variety of other therapies for refractory toxicity in a relatively center-specific fashion. Some of these changes reflect recommendations from recently published guidelines, which suggest earlier use of corticosteroids and tocilizumab, as well as anakinra for greater than or equal to grade 3 CRS/ICANS and IEC-HS, interventions designed to halter further progression of these toxicities (9, 11, 16–18). Despite data suggesting an association between higher corticosteroid doses and decreased survival after CAR T-cell therapy, cumulative corticosteroid doses in critically ill CAR T cell patients did not decrease during the study period and cumulative doses of greater than or equal to 1621 mg were associated to lower 3-month OS (2, 19). The rates of corticosteroid use were higher than previously reported in smaller studies, which could be due to increasing rates of corticosteroid administration for less severe toxicities (grade 1–2) (15, 20). Therefore, trials evaluating corticosteroid-sparing treatments in patients with severe toxicities could impact patient outcomes. Some of our centers participated in trials evaluating prophylactic anakinra to reduce CRS and ICANS, and while only 16 of our ICU patients (12.4%) were included in those trials, data suggest that prophylactic anakinra significantly reduced the rate of severe toxicities (21, 22). It is possible that all these therapeutic changes could be reducing the prevalence of severe toxicities, leading to our observed reduction in ICU admission rates (8, 16, 21–24). However, an evaluation of treatment changes among both ICU and non-ICU patients is needed to further elucidate the impact of these therapeutic changes on the reduction of severe toxicities.

CAR T-cell patients admitted to the ICU during the study period had increasing age, CCIs, severity of illness (SOFA scores), and rates of grade 3 or more toxicities. Despite our patients being older, with more comorbidities and being sicker than those reported in earlier studies, mortality remained low (4, 25–27). Prior data of studies in the United States have shown that patients with increasing comorbidities and age have similar outcomes post-CAR T-cell therapy (4). These findings are likely related to the reversibility of both ICANS and CRS when recognized and treated early, toxicities that in our study were present in more than 92% of patients. It is important to note that patients who died were admitted to the ICU later following CAR T-cell infusion. Therefore, ICU admission should not be delayed in these patients. Close collaboration and communication with the ICU team to facilitate timely ICU admission may improve outcomes in this patient population.

Documented positive cultures during ICU stay were present in 24% of all patients, including 18% of survivors and 54% of nonsurvivors. This is in stark contrast to the reported 5% rates of severe infections in CAR T-cell patients (3, 28). These findings complement prior documentation of the impact of sepsis on morbidity and mortality in this population, specifically those with severe toxicities, and emphasizes the importance of empiric antibiotics and a high index of suspicion for infection in critically ill CAR T-cell patients (3, 11, 29). We observed an increase in arrhythmias and vasopressor support with time. Furthermore, ICU patients who died in the ICU or hospital were those with ICU admission for reasons other than CRS/ICANS and with higher SOFA scores. It is possible that in some instances critical illness was wrongly attributed to CRS, and instead reflected another process such as unrecognized sepsis, which has a 40% prevalence in the first 30 days post-CAR T-cell infusion (28-30). Differentiation of CRS from sepsis remains challenging, and predictive patterns of cytokine profiles are less informative in severe illness, whether from CRS or sepsis (31, 32). Further investigations in our cohort evaluating infections in the ICU after CAR T-cell therapy, risk factors, antibiotic prophylaxis, concomitant immunosuppressive therapies, and timing of onset in relation to CRS, represent key opportunities for future studies.

Last, our 3-month survival is lower than reported in previous studies and was entirely due to a significantly lower 3-month survival in 2020 (2, 3). After excluding 2020, there was no significant difference in 3-month survival among the years. Notably, there was no

difference in ICU or hospital mortality throughout the years; thus, the difference in 3-month survival could reflect changes in post-hospital care. It is possible that indirect effects of the COVID-19 pandemic, such as decreased hospital bed capacity or patient unwillingness to engage with the healthcare system affected long-term outcomes for that year. Regardless, the effect was transient, and 3-month outcomes in 2021, 2022, and 2023 were indistinguishable from those in 2018 and 2019.

Our study, while being the largest multicenter study of life-threatening complications after CAR T-cell therapy, has limitations. First, all study sites were academic centers in the United States with significant experience in both inpatient and intensive care management of patients receiving cellular therapy since the approval of these therapies in 2018. As we observed, significant decreases in rates of admission can be center-specific, especially if there's variation in ICU admission criteria. Therefore, our findings may not be generalizable to all centers. Second, while the latter years of our study period saw the advent of new cellular therapies, most of our patients received either axi-cel or tisagenlecleucel for lymphoma, and applicability to other agents may be limited. Third, while objective criteria for ICU admission did not change at our centers during the study period, centers did report admitting patients when it was requested by the oncologist. This subjective variable, difficult to assess retrospectively, could have impacted rates of ICU admission across centers and years, and severity of illness at the time of ICU admission. Furthermore, differences in practices among centers could have an impact on our findings; however, this is the nature (and strength) of a multicenter study. Finally, our study focuses only on critically ill patients, and we did not assess changes in practice of non-ICU patients. Future studies looking at outcomes and interventions in all CAR T-cell recipients may be beneficial and could help understand if any specific interventions have led to a decrease in severe toxicities and therefore ICU utilization.

CONCLUSIONS

Despite an increasing number of patients treated among our centers, ICU admission rates of patients receiving this therapy are decreasing. Despite CAR T-cell patients admitted to the ICU being older and sicker, with higher severity of illness and toxicity grades, hospital mortality, including that related to CRS and ICANS, has remained low.

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1 *Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY.*

2 *Bone Marrow Transplant Intensive Care Unit, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD.*

3 *Clinical Pharmacy Specialist in Critical Care, Division of Pharmacy, The University of Texas M.D. Anderson Cancer Center, Houston, TX.*

4 *Department of Pharmacy, Mayo Clinic, Rochester, MN.*

5 *Division of Anesthesiology and Critical Care, Department of Critical Care, The University of Texas M.D. Anderson Cancer Center, Houston, TX.*

6 *Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY.*

7 *Roswell Park Comprehensive Cancer Center and Department of Anesthesiology, Jacobs School of Medicine & Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY.*

8 *Department of Medicine, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, MN.*

9 *Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Pittsburgh, Pittsburg, PA.*

10 *Department of Statistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.*

11 *Department of Medicine, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO.*

12 *Department of Lymphoma and Myeloma, The University of Texas M.D. Anderson Cancer Center, Houston, TX.*

13 *Department of Critical Care Medicine, Integrated Hospital Care Institute, Cleveland Clinic, Cleveland, OH.*

14 *Department of Critical Care, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH.*

15 *Department of Pulmonary and Critical Care, Integrated Hospital Care Institute, Cleveland Clinic, Cleveland, OH.*

16 *Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY.*

17 *Department of Medicine, Division of Hematology, Division of Experimental Pathology, Mayo Clinic, Rochester, MN.*

18 *Division of Anesthesiology and Critical Care, Department of Critical Care, The University of Texas M.D. Anderson Cancer Center, Houston, TX.*

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For information regarding this article, E-mail: CGutierrez4@mdanderson.org

REFERENCES

1. Cappell KM, Kochenderfer JN: Long-term outcomes following CAR T cell therapy: What we know so far. *Nat Rev Clin Oncol* 2023; 20:359–371
2. Gutierrez C, Brown ART, May HP, et al: Critically ill patients treated for chimeric antigen receptor-related toxicity: A multicenter study. *Crit Care Med* 2022; 50:81–92
3. Azoulay E, Castro P, Maamar A, et al; Nine-I investigators: Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): An international, multicentre, observational cohort study. *Lancet Haematol* 2021; 8:e355–e364
4. 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; 38:3119–3128
5. Yamshon S, Gribbin C, Alhomoud M, et al: Safety and toxicity profiles of CAR T cell therapy in non-Hodgkin lymphoma: A systematic review and meta-analysis. *Clin Lymphoma Myeloma Leuk* 2024; 24:e235–e256.e2
6. Munshi NC, Anderson LD, Shah N, et al: Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med* 2021; 384:705–716
7. Berdeja JG, Madduri D, Usmani SZ, et al: Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): A phase 1b/2 open-label study. *Lancet* 2021; 398:314–324
8. Santomasso BD, Nastoupil LJ, Adkins S, et al: Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. *J Clin Oncol* 2021; 39:3978–3992
9. Hines MR, Knight TE, McNerney KO, et al: Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. *Transplant Cell Ther* 2023; 29:438.e1–438.e16
10. Lutfi F, Patel A, Mehta J, et al: Second-line treatment with CAR T-cell therapy for large B-cell lymphoma. *Clin Adv Hematol Oncol* 2023; 21:170–178
11. Brudno JN, Kochenderfer JN: Current understanding and management of CAR T cell-associated toxicities. *Nat Rev Clin Oncol* 2024; 21:501–521
12. von Elm E, Altman DG, Egger M, et al; STROBE Initiative: The Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Lancet* 2007; 370:1453–1457

13. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–381
14. 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; 25:625–638
15. Le Cacheux C, Couturier A, Sortais C, et al: Features and outcomes of patients admitted to the ICU for chimeric antigen receptor T cell-related toxicity: A French multicentre cohort. *Ann Intensive Care* 2024; 14:20
16. Topp MS, van Meerten T, Houot R, et al: Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. *Br J Haematol* 2021; 195:388–398
17. Oluwole OO, Bouabdallah K, Muñoz J, et al: Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. *Br J Haematol* 2021; 194:690–700
18. Gaffney KJ, Davis JA, McGann M, et al: Early versus standard management of chimeric antigen receptor therapy toxicities and management's impact on safety and efficacy. *J Oncol Pharm Pract* 2024; 30:151–158
19. 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; 137:3272–3276
20. Constantinescu C, Moisoiu V, Tigu B, et al: Outcomes of CAR-T cell therapy recipients admitted to the ICU: In search for a standard of care—a brief overview and meta-analysis of proportions. *J Clin Med* 2023; 12:6098
21. Park JH, Nath K, Devlin SM, et al: CD19 CAR T-cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: Phase 2 trial interim results. *Nat Med* 2023; 29:1710–1717
22. Strati P, Jallouk A, Deng Q, et al: A phase 1 study of prophylactic anakinra to mitigate ICANS in patients with large B-cell lymphoma. *Blood Adv* 2023; 7:6785–6789
23. Gazeau N, Liang EC, Wu QV, et al: Anakinra for refractory cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome after chimeric antigen receptor T cell therapy. *Transplant Cell Ther* 2023; 29:430–437
24. Wehrli M, Gallagher K, Chen Y-B, et al: Single-center experience using anakinra for steroid-refractory immune effector cell-associated neurotoxicity syndrome (ICANS). *J ImmunoTher Cancer* 2022; 10:e003847
25. Jacobson CA, Munoz J, Sun F, et al: Real-world outcomes with chimeric antigen receptor T cell therapies in large B cell lymphoma: A systematic review and meta-analysis. *Transplant Cell Ther* 2024; 30:77.e1–77.e15
26. Berning P, Shumilov E, Maulhardt M, et al: Chimeric antigen receptor-T cell therapy shows similar efficacy and toxicity in patients with diffuse large B-cell lymphoma aged 70 and older compared to younger patients: A multicenter cohort study. *Hemasphere* 2024; 8:e54
27. Bishop MR: The benefit of CAR T cells in older patients. *Blood* 2020; 135:2020–2021
28. Hill JA, Li D, Hay KA, et al: Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood* 2018; 131:121–130
29. Haidar G, Garner W, Hill JA: Infections after anti-CD19 chimeric antigen receptor T-cell therapy for hematologic malignancies: Timeline, prevention, and uncertainties. *Curr Opin Infect Dis* 2020; 33:449–457
30. Wudhikarn K, Perales M-A: Infectious complications, immune reconstitution, and infection prophylaxis after CD19 chimeric antigen receptor T-cell therapy. *Bone Marrow Transplant* 2022; 57:1477–1488
31. Diorio C, Shaw PA, Pequignot E, et al: Diagnostic biomarkers to differentiate sepsis from cytokine release syndrome in critically ill children. *Blood Adv* 2020; 4:5174–5183
32. Wang L, Lv Y, Zhou L, et al: Cytokine-based models for efficient differentiation between infection and cytokine release syndrome in patients with hematological malignancies. *Exp Hematol Oncol* 2024; 13:28