Healthcare Utilization and End-of-Life Outcomes in Patients Receiving CAR T-Cell Therapy

P. Connor Johnson, MD[1,*]; Caron Jacobson, MD, MMSc[2,*]; Alisha Yi[1]; Anna Saucier, MS[2]; Tejaswini M. Dhawale, MD[1]; Ashley Nelson, PhD[3]; Mitchell W. Lavoie, BS[3]; Mathew J. Reynolds, BA[3]; Carlisle E.W. Topping, BA[3]; Matthew J. Frigault, MD[1]; and Areej El-Jawahri, MD[1]

ABSTRACT

Background: CAR T-cell therapy has revolutionized the treatment of patients with hematologic malignancies, but it can result in prolonged hospitalizations and serious toxicities. However, data on the impact of CAR T-cell therapy on healthcare utilization and end-of-life (EoL) outcomes are lacking. **Methods:** We conducted a retrospective analysis of 236 patients who received CAR T-cell therapy at 2 tertiary care centers from February 2016 through December 2019. We abstracted healthcare utilization and EoL outcomes from the electronic health record, including hospitalizations, receipt of ICU care, hospitalization and receipt of systemic therapy in the last 30 days of life, palliative care, and hospice referrals. **Results:** Most patients (81.4%; n=192) received axicabtagene ciloleucel. Overall, 28.1% of patients experienced a hospital readmission and 15.5% required admission to the ICU within 3 months of CAR T-cell therapy. Among the deceased cohort, 58.3% (49/84) were hospitalized and 32.5% (26/80) received systemic therapy in the last 30 days of life. Rates of palliative care and hospice referrals were 47.6% and 30.9%, respectively. In multivariable logistic regression, receipt of bridging therapy (odds ratio [OR], 3.15; *P*=.041), index CAR-T hospitalization length of stay >14 days (OR, 4.76; *P*=.009), hospital admission within 3 months of CAR T-cell infusion (OR, 4.29; *P*=.013), and indolent lymphoma transformed to diffuse large B-cell lymphoma (OR, 9.83; *P*=.012) were associated with likelihood of hospitalization in the last 30 days of life. **Conclusions:** A substantial minority of patients receiving CAR T-cell therapy experienced hospital readmission or ICU utilization in the first 3 months after CAR T-cell therapy, and most deceased recipients of CAR T-cell therapy received intensive EoL care. These findings underscore the need for interventions to optimize healthcare delivery and EoL care for this population.

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[1]Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital Cancer Center & Harvard Medical School; [2]Department of Medical Oncology, Center for Lymphoma, Dana-Farber Cancer Institute & Harvard Medical School; and [3]Department of Psychiatry, Massachusetts General Hospital & Harvard Medical School, Boston, Massachusetts.

*These authors contributed equally as co-first authors.

Background

CAR T-cell therapy is a novel treatment that involves altering the patient's autologous T cells to target a cell surface antigen on the tumor.[1,2] CAR T-cell therapy has transformed the treatment of relapsed/refractory large B-cell lymphomas.[3–5] However, patients receiving this treatment are often hospitalized and experience unique toxicities, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). These toxicities can result in high rates of ICU admissions and prolonged lengths of stay (LoS) in the hospital.[4–10]

Despite the revolutionary nature of CAR T-cell therapy and its treatment-related toxicity, we lack a basic understanding of healthcare utilization in this population. Given the potential for remission despite their rapidly progressive disease, patients undergoing cellular therapy are at risk for intensive healthcare utilization and face immense prognostic uncertainty. It remains unclear to which population cellular therapy may offer a curative potential, leaving patients unsure about their future health. Unfortunately, approximately 50% of patients experience disease progression and die within 6 months of CAR T-cell therapy.[4,5,11] However, data describing healthcare utilization and end-of-life (EoL) outcomes in this population are lacking.

In the present study, we sought to describe the healthcare utilization and EoL outcomes among patients treated with CAR T-cell therapy. We also aimed to examine associations among patient and clinical characteristics and important EoL outcomes. Data depicting patients' healthcare utilization and EoL care could allow clinicians to communicate important information about the ramifications of treatment and provide patients with critical information to plan for the future. Understanding factors associated with intensive EoL care can be instrumental in identifying a high-risk population that may benefit from interventions to optimize their EoL care.

Methods

Study Design

We conducted a retrospective analysis of adult patients treated with CAR T-cell therapy at Dana-Farber Cancer Institute (DFCI) or Massachusetts General Hospital (MGH) between February 2016 and December 2019. We excluded patients who were seen for consultation but did not receive CAR T-cell therapy at either institution. We identified the eligible cohort through the MGH and DFCI CAR-T therapy database, which includes all patients receiving CAR T-cell therapy at our institutions. The Dana-Farber/Harvard Cancer Center Institutional Review Board approved this study.

Clinical Information

We abstracted information from the electronic health record (EHR) through a comprehensive chart review about patients' demographics; ECOG performance status (determined within 2 weeks of CAR T-cell infusion); diagnosis; dates of relapse and CAR T-cell infusion; therapies received; CAR T-cell product; presence and grade of toxicities, including CRS and ICANS; receipt of tocilizumab and/or corticosteroids; response to treatment; and duration of follow-up. For patients with ≥1 year of follow-up, we determined the rate of survival at 1 year after CAR T-cell therapy infusion.

Healthcare Utilization and EoL Care

We obtained information regarding LoS, frequency and dates of hospital readmission, and ICU admissions from the EHR. We calculated the rates of ICU admission during CAR T-cell therapy treatment and the rates of ICU admission and hospital readmission within 3 months of CAR T-cell therapy infusion. We reviewed the discharge summaries of hospital readmissions to determine the primary reason for each hospital readmission. We adapted a coding schema previously developed in patients with leukemia to determine reasons for hospital readmissions.[12] In the schema for our study, these reasons included symptoms, fever without a source, febrile neutropenia, confirmed infection, dehydration/electrolyte abnormalities, planned hospitalization, hospitalization due to a noncancer medical condition, cancer progression, and hospitalization due to CAR T-cell toxicities (CRS and ICANS).[12,13] We used symptoms as the reason for hospital admission when the admission was for symptom management; all other causes of admission were excluded or no primary etiology of the admission was defined.

We determined patients' place of death, cause of death, palliative care utilization, hospice utilization, and LoS in hospice using the EHR and the Social Security Death Index. We also determined whether patients were hospitalized (yes vs no), received systemic therapy (yes vs no), or were admitted to the ICU (yes vs no) within 30 days of death. For most patients receiving CAR-T therapy, the healthcare utilization and EoL care occurred within our system. Additionally, the clinical team maintaining the CAR-T database obtains information on healthcare utilization and EoL outcomes at other institutions and these are scanned into the EHR to maintain high data quality.

Statistical Analysis

We used descriptive statistics to summarize patients' sociodemographic and clinical characteristics, rates of toxicities and response, and rates of survival at 1 year after CAR T-cell therapy infusion. We used descriptive statistics to describe healthcare utilization for all patients in this cohort and to characterize EoL outcomes for patients who died in the cohort.

We used multivariable logistic regression to examine the association between patient demographics and clinical factors and binary outcomes of interest (hospitalization within 30 days of death and hospice referral). We examined factors associated with these outcomes given they are important outcomes in EoL care.[14] We first conducted univariate analyses to assess the association between patient demographic (eg, marital status) and clinical factors (ECOG performance status, index hospitalization LoS >14 days, prior therapies received, prior autologous stem cell transplant, CAR T-cell product, ICU admission within 3 months after CAR T-cell infusion, hospital admission within 3 months after CAR T-cell infusion, CRS, ICANS, receipt of tocilizumab and/or steroids, disease response, and palliative care consultation) with the binary outcomes of interest. Variables with a P value <.10 in the univariate analyses were included in the multivariable models.[15,16] In the multivariate model of hospitalization within 30 days of death, we forced age, sex, receipt of bridging therapy, and disease subtype into the model a priori because these variables have been associated with EoL outcomes. In the multivariate model of hospice referral, we included age, sex, and disease subtype a priori because of their known association with hospice utilization.[17–19] All reported P values are 2-sided with a value of <.05 considered statistically significant. We performed statistical analyses using STATA, version 14.2 (StataCorp LP).

Results

Study Participants

Table 1 describes the sociodemographic and clinical characteristics of the study cohort (n=236). Median age was 62.5 years, and most patients were male (n=145; 61.4%), White (n=218; 92.4%), and married/had a life

Table 1. Patient Characteristics

Characteristic	n (%)
Total, n	236
Age, median (range), y	62.5 (19–82)
Female sex	91 (38.6)
White race[a]	218 (92.4)
Relationship status	
Married/Life partner	163 (69.1)
Single	40 (17.0)
Divorced/Legally separated	13 (5.5)
Widowed	13 (5.5)
Unknown	7 (3.0)
CAR T-cell product	
Axicabtagene ciloleucel	183 (77.5)
Tisagenlecleucel	36 (15.3)
Axicabtagene ciloleucel combined with immunotherapy	9 (3.8)
KTE-X19	7 (3.0)
Lisocabtagene maraleucel	1 (0.4)
Lymphoma subtype	
DLBCL/Grade 3B follicular lymphoma	107 (45.3)
Indolent lymphoma transformed to DLBCL[b]	40 (17.0)
HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements	40 (17.0)
Follicular lymphoma	22 (9.3)
Primary mediastinal large B-cell lymphoma	12 (5.1)
Other	15 (6.4)
ECOG performance status	
0–1	194 (82.2)
2–4	38 (16.1)
Unknown	4 (1.7)
Received bridging therapy	93 (39.4)
Prior lines of therapy, median (range)	3 (0–10)
Prior autologous stem cell transplant	65 (27.5)
Days from relapse to CAR T-cell therapy, median (range)[c]	58 (11–391)
Toxicity and response	
Cytokine release syndrome (any grade)	183 (77.5)
ICANS (any grade)	126 (53.4)
Received tocilizumab	120 (50.9)
Received corticosteroids	107 (45.3)
Overall response	201 (85.2)
Complete response	152 (64.4)
Survival	184
Alive 1 year after CAR T-cell therapy[d]	116 (63.0)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome.
[a]3 patients either had missing data or declined to report for race.
[b]Richter transformation was classified under other.
[c]5 patients had missing data.
[d]Including only evaluable patients.

partner (n=163; 69.1%). Most patients (n=194; 82.2%) had an ECOG performance status of 0 or 1. The most common lymphoma subtype was diffuse large B-cell lymphoma (DLBCL) or grade 3B follicular lymphoma (n=107; 45.3%), and the median prior lines of therapy was 3. Overall, 81.4% of patients (n=192) received axicabtagene ciloleucel, 39.4% (n=93) received bridging therapy, and 27.5% (n=65) had a prior autologous stem cell transplant.

In terms of toxicities, 77.5% of patients (n=183) had CRS, with 5.9% (n=14) having grade ≥3 CRS. In addition, 53.4% of patients (n=126) had ICANS, with 22.0% (n=52) having grade ≥3 ICANS. Approximately one-half of patients (n=120; 50.9%) received tocilizumab, and 45.3% (n=107) received corticosteroids. The overall response rate was 85.2% (n=201), the complete response rate was 64.4% (n=152), and 63.0% (116/184) of evaluable patients were alive 1 year after CAR T-cell therapy. Overall, 60.6% of patients experienced a complete or partial response and did not experience disease progression, 24.6% had an initial response followed by subsequent progression, and 14.8% had stable disease or experienced progression despite receipt of CAR T-cell therapy. Among patients with a complete or partial response and no subsequent relapse, 6.3% (9/143) had grade ≥3 CRS, 25.2% (36/143) had grade ≥3 ICANS, and 86.9% (86/99) of evaluable patients were alive 1 year after CAR T-cell therapy.

Healthcare Utilization

Table 2 describes the healthcare utilization of patients receiving CAR T-cell therapy in our cohort. Median LoS for CAR T-cell therapy hospitalization was 15 days, and 12.7% of patients (30/236) required an ICU admission during the hospitalization. Overall, 15.5% of patients (36/232) had an ICU admission within 3 months of CAR T-cell infusion, and 28.1% (65/231) had at least one hospital readmission within 3 months of CAR T-cell infusion. The median time from discharge to first hospital readmission was 18 days. Among patients with a complete or partial response and no subsequent relapse, 15.0% (21/140) had an ICU admission within 3 months of CAR T-cell infusion, and 23.7% (33/139) had at least one hospital readmission within 3 months of CAR T-cell infusion.

Table 2. Healthcare Utilization Among CAR T-Cell Therapy Patients (n=236)

Outcome	n (%)
Length of stay for CAR T-cell hospitalization, median (range), d	15 (7–91)
ICU admission during admission for CAR T-cell therapy	30 (12.7)
Any ICU admission within 3 mo of CAR T-cell infusion[a]	36 (15.5)
Any hospital readmission within 3 mo of CAR T-cell infusion[b]	65 (28.1)
Number of hospital readmissions within 3 mo of CAR T-cell infusion among those rehospitalized, median (range)	1 (1–4)
Days from discharge to first readmission, median (range) (n=65 readmissions)	18 (1–91)
Reason for first hospital readmission (n=64 readmissions)	
Symptoms	22 (34.4)
Noncancer medical condition	10 (15.6)
Cancer progression	8 (12.5)
Infections	6 (9.4)
Febrile neutropenia	5 (7.8)
Neurotoxicity	5 (7.8)
Cytokine release syndrome	2 (3.1)
Other	6 (9.4)

[a]4 patients had missing data.
[b]5 patients had missing data.

Table 3. End-of Life Outcomes Among Deceased Patients After CAR T-Cell Therapy (n=84)

End-of-Life Outcome	n (%)
Hospitalization within 30 d of death	49 (58.3)
Chemotherapy within 30 d of death[a]	26 (32.5)
ICU admission within 30 d of death	10 (11.9)
Receipt of a palliative care consultation	40 (47.6)
Receipt of palliative care >30 d before death[b]	18 (22.0)
Receipt of hospice services[c]	25 (30.9)
Hospice length of stay >7 d[a]	18 (22.5)
Place of death	
Home	17 (20.2)
Hospital, rehabilitation facility, or nursing home	31 (36.9)
Inpatient hospice	6 (7.1)
Unknown	30 (35.7)
Cause of death	
Cancer progression	58 (69.1)
CAR T-cell therapy complication	4 (4.8)
Other causes	6 (7.1)
Unknown	16 (19.1)

[a]4 patients with missing data.
[b]2 patients with missing data.
[c]3 patients with missing data.

The most common reason for first hospital readmission was patient symptoms (22/64; 34.4%; Table 2). Among those admitted for symptoms, the most common were pain (27.3%), fatigue/weakness (18.2%), and confusion (13.6%). For those admitted for noncancer medical conditions, among the most common causes were transient ischemic attack (10%), hematoma (10%), and incarcerated hernia (10%).

EoL Outcomes

Table 3 provides the EoL outcomes among the cohort of deceased patients (n=84). Within 30 days of death, 58.3% (49/84) were hospitalized, 32.5% (26/80) received systemic therapy, and 11.9% (10/84) were admitted to the ICU. Among the deceased cohort, 47.6% (40/84) had a palliative care consultation, and a minority (18/82; 22.0%) received palliative care >30 days before death. Only 30.9% (25/81) received hospice services, and most (62/80; 77.5%) had a hospice LoS ≤7 days. Among all deceased patients, 36.9% (n=31) died in a hospital, rehabilitation facility, or nursing home; 20.2% (n=17) died at home; 7.1% (n=6) died in inpatient hospice; and 35.7% (n=30) had an unknown place of death. The most common cause of death was cancer progression (58/84; 69.1%). Within 30 days of death among 19 evaluable patients with a complete or partial response and no subsequent relapse, 42.1% (n=8) were hospitalized, 10.5% (n=2) received systemic therapy, and 21.1% (n=4) were admitted to the ICU. Among evaluable patients in this group, 12.5% (2/16) received hospice services, 21.1% (4/19) had a palliative care consultation, and 25% (3/12) died at home.

In multivariable analysis, receipt of bridging therapy (odds ratio [OR], 3.15; 95% CI, 1.05–9.52; P=.041), index hospitalization LoS >14 days (OR, 4.76; 95% CI, 1.47–15.37; P=.009), hospital admission within 3 months of CAR T-cell therapy (OR, 4.29; 95% CI, 1.36–13.49; P=.013), and a diagnosis of indolent lymphoma transformed to DLBCL (OR, 9.83; 95% CI, 1.66–58.24; P=.012) were all associated with a higher likelihood of hospitalization within 30 days of death (Table 4).

Additionally, we identified factors associated with likelihood of hospice referral utilizing multivariable logistic regression (Table 5). Controlling for age, sex, ECOG performance status, response, and lymphoma subtype, we found that palliative care consultation was associated with a greater likelihood of hospice referral (OR, 3.18; 95% CI, 1.03–9.78; P=.044).

Discussion

In this study, we demonstrate that patients receiving CAR T-cell therapy experience substantial healthcare utilization, especially at EoL. More than one-quarter of CAR T-cell recipients had one hospital readmission within

Table 4. Factors Associated With Hospitalization Within 30 Days of Death

Variable	OR (95% CI)	SE	*P* Value
Age	0.98 (0.94–1.03)	0.02	.446
Female sex	0.61 (0.19–1.95)	0.36	.406
Received bridging therapy	3.15 (1.05–9.52)	1.78	**.041**
Complete response	0.21 (0.06–0.66)	0.12	**.008**
Length of stay >14 d	4.76 (1.47–15.37)	2.85	**.009**
Hospital admission within 3 mo of CAR T-cell infusion	4.29 (1.36–13.49)	2.51	**.013**
Indolent lymphoma transformed to DLBCL	9.83 (1.66–58.24)	8.92	**.012**

Bold indicates statistically significant *P* value.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; OR, odds ratio.

Table 5. Factors Associated With Hospice Referral

Variable	OR (95% CI)	SE	*P* Value
Age	1.02 (0.98–1.07)	0.02	.349
Female sex	0.36 (0.10–1.30)	0.24	.119
Response	0.25 (0.08–0.78)	0.14	**.017**
Palliative care consultation	3.18 (1.03–9.78)	1.82	**.044**
ECOG performance status	1.40 (0.78–2.50)	0.41	.261
HGBCL with *MYC* and *BCL2* and/or *BCL6* translocations	1.80 (0.50–6.51)	1.18	.372

Bold indicates statistically significant *P* value.
Abbreviations: HGBLC, high-grade B-cell lymphoma; OR, odds ratio.

3 months of CAR T-cell therapy and 15.5% required ICU level of care. Notably, among deceased patients, 58.3% were hospitalized within 30 days of death, and most died in the hospital or healthcare facility. Unfortunately, most patients did not receive palliative care or hospice services. These findings underscore the intensity of EoL care for patients receiving CAR T-cell therapy and the need to optimize EoL care delivery in this population.

Healthcare utilization during the index hospitalization for CAR T-cell infusion was significant, with a median LoS exceeding 2 weeks and an ICU admission rate of nearly 13%. Approximately one-quarter of patients experienced a rehospitalization within 3 months of CAR T-cell infusion; however, multiple rehospitalizations were uncommon, occurring in <10% of patients. Moreover, most first rehospitalizations occurred within 30 days of the index CAR T-cell hospitalization and were most commonly due to uncontrolled symptoms. In our cohort, 5.9% of patients experienced grade ≥3 CRS and 22.0% experienced grade ≥3 ICANS, which was lower than the toxicity rates demonstrated with axicabtagene ciloleucel in the non-trial setting.[20] This could be secondary to differences in the patient populations or due to the use of other CAR T-cell products with lower toxicity rates by some patients in our cohort. Our cohort had similar rates of response and 1-year survival to those reported in the published literature.[4,5,20–24] These findings suggest that early rehospitalization after CAR T-cell therapy is an important contributor to healthcare utilization in this population, and suggest that care transitions and symptom monitoring interventions at the time of discharge may be useful targets for future research.

We also demonstrate that patients receiving CAR T-cell therapy experience substantial healthcare utilization at EoL. Despite established evidence that most patients with cancer prefer to die at home and minimize time in the hospital at EoL,[25,26] most patients receiving CAR T-cell therapy were hospitalized within the last 30 days of life, and most died in a hospital or healthcare facility. Palliative care and hospice services were infrequently used in this population, despite the demonstrated benefits of these services for improving quality of life and care for patients with cancer.[27–34] The immense prognostic uncertainty along with the absence of a clear transition between the curative and palliative phase treatment in many patients receiving CAR T-cell therapy likely impacts EoL decision-making and contributes to high healthcare utilization at the EoL in this population.[35] Prior studies have also shown high healthcare utilization at EoL and low rates of hospice and palliative care referrals in patients with hematologic malignancies.[17,36,37] Interestingly, in our cohort, palliative care utilization was the only factor associated with hospice utilization, which may serve to optimize EoL care in this population. Given the demonstrated benefits of early palliative care integration for improving the quality of life and care for patients with solid tumors and hematologic malignancies, early referral to palliative care while pursuing curative-intent CAR T-cell therapy is a potentially helpful strategy to address the EoL care needs of this population.

We also determined that there are several clinical factors associated with the risk of hospitalization in the last 30 days of life. Factors such as the need for bridging therapy, a hospital readmission within 3 months of CAR T-cell infusion, and an index hospitalization >14 days are important clinical markers that identify a subset of patients at high-risk for acute clinical decompensation and worse EoL outcomes. These clinical factors can be used as triggers for additional interventions to optimize EoL care in this population. Importantly, these findings can help better inform both patients' and clinicians' expectations regarding the possible illness trajectory.

Our study has several limitations worth considering. First, this study is a retrospective study of patients at 2 large academic sites, which lacked racial diversity, and thus our findings may not generalize to other populations. Second, we were limited to information about patients' healthcare utilization and EoL outcomes that were available in the EHR, and therefore our data may not have fully captured all healthcare utilization and EoL outcomes. Finally, our sample size limited the number of covariates we could analyze in multivariable logistic regression for EoL outcomes; thus, our model may not fully account for all possible confounders. Future research studies should assess healthcare utilization and EoL outcomes in a diverse population of patients undergoing CAR T-cell therapy to ensure the generalizability of these findings. Future efforts should also explore costs of care at EoL in this population.

Conclusions

We demonstrated that approximately one-quarter of patients receiving CAR T-cell therapy experience a hospitalization within 3 months of their CAR T-cell infusion, and most experience high healthcare utilization at EoL. We also identified salient factors associated with the risk for hospitalization within 30 days of death. Our findings underscore the need to develop transitional care and EoL care interventions to improve the quality of care for patients receiving CAR T-cell therapy.

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Correspondence: P. Connor Johnson, MD, Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey 7B, Boston, MA 02114.
Email: pcjohnson@mgh.harvard.edu

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