Real-World Outcomes Following Chimeric Antigen Receptor (CAR) T-Cell Therapy for Large B-Cell Lymphoma

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BACKGROUND

- Chimeric antigen receptor (CAR) T-cell therapy is engineered from patients' own immune cells whereby T-cells are removed and genetically modified to produce CARs to treat their cancer.[1]
- Clinical trials have demonstrated CD19 directed CAR T-cell therapy efficacy for relapsed/refractory (R/R) B-cell malignancies.[2]
- These therapies have revolutionized treatment for B-cell malignancies. Currently, anti-CD19 CAR T-cell therapy is now considered standard of care for patients with R/R aggressive diffuse large B-cell lymphoma (LBCL) non-Hodgkin lymphoma (NHL) after two or more lines of therapy.[2,3]
- Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are two common CAR T-cell associated toxicities.[3,4] Both CRS and ICANS range from fever in mild cases to severe, life-threatening cases requiring intensive medical management. Real-world prevalence of severe CRS and ICANS ranges from 5.3% to 9.1% and 2.9% to 24.0%, respectively.[5,6] Moderate to severe CRS is frequently treated with antipyretics, tocilizumab and/or corticosteroids. ICANS is often managed with corticosteroids, anticonvulsant therapy and other supportive therapies.[7]
- Current treatment pattern data following CAR T-cell therapy is limited. At 6-month post CAR T-cell infusion, reports indicate one-third of patients are at risk of initiating additional treatment.[8] A median time to subsequent treatment between 98 to 107 days is reported in the real-world.[9]
- Real-world data are needed to better understand clinical outcomes following CAR T-cell infusion outside the clinical trial setting.

OBJECTIVES

- To identify real-world CAR T-cell treated members for LBCL and describe clinical outcomes following CAR T-cell therapy administration.

METHODS

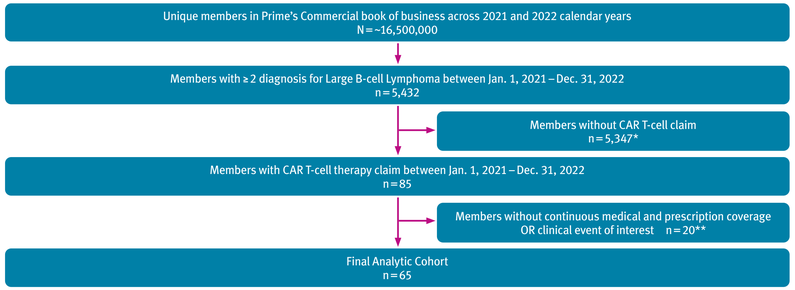
- This was a retrospective, observational cohort study using a 6-month post index follow-up design.
- Study index date was defined as the first date of a medical claim for CAR T-cell therapy infusion between January 1, 2021 and December 31, 2022.
- Integrated pharmacy and medical claims data were queried among 16.5 million commercially insured members per month from July 1, 2020 to July 1, 2023.
- Data obtained for this study included medical claims (date of service, diagnoses received, procedures performed, place of service, and drugs received), pharmacy claims (fill dates and National Drug Code [NDC] numbers), and eligibility information (patient demographics and health insurance enrollment history).
- Study inclusion was limited to members with 2 or more claims containing an LBCL diagnosis on different dates of service, a CAR T-cell drug claim drug claim, identified by health care common procedure coding system (HCPCS) or NDC, between January 1, 2021 and December 31, 2022, less than 65 years of age at index date, and continuously enrolled 1 month prior to CAR T-cell administration date as well as 6 months following or until earliest claim indicating initiation of subsequent treatment, death at discharge or hospice care, whichever occurred first.
- Baseline member characteristics such as average age, gender, and Charlson Comorbidity Score (CCI) are reported.[10]
- The primary CAR T-cell adverse outcomes were ICANS and CRS within 6 months following CAR T-cell therapy infusion.
- Other study clinical outcome measures within 6 months following CAR T-cell therapy infusion were initiation of subsequent systemic cancer therapy, death or hospice defined as:
  - Systemic cancer therapy included chemotherapy, targeted therapy and radiation therapy.
  - All hospice outcomes were determined using place of service codes.
  - Death was captured using discharge status codes.
- All study endpoints were calculated separately across the 6-month follow-up period.
- Results were summarized using descriptive statistics, and Kaplan-Meier methods were used for time-to-event analysis.

LIMITATIONS

- This study was retrospective in nature and data were sourced from administrative health care claims data. Claims data are subject to coding error and incompleteness, which could impact LBCL diagnosis assignment resulting in misclassification bias, as well as, mortality due to lack of death identification comprehensively in claims.
- Due to delays in claims submission and adjudication, at the time of data extraction members receiving CAR T-cell therapy during the study index period may have may been omitted.
- This study used a 6-month follow-up which may be too short to observe subsequent treatment or other clinical outcomes used to measure clinical effectiveness of therapy.
- Findings are limited to commercially insured members and may not be representative of members insured under government programs.
- CAR T-cell utilizers were identified by product-specific identification logic in HCPCS and/or NDC claim fields. CAR T-cell therapy billing requirements do not require specific HCPCS or NDC and can be non-specific; therefore, CAR T-cell therapy identification via billing is likely incomplete and under represents total CAR T-cell therapy cases and, frequently, a specific CAR T-cell product could not be determined,[11] resulting in excluding the case from this analysis.

FIGURE 1

Member Attrition



CAR = chimeric antigen receptor. n = number of members.

Note: Members were followed until hospice, death, subsequent cancer therapy initiation, or end of 6-month study follow-up from CAR T-cell therapy index date, whichever occurred first.

* Some members may have received CAR T-cell therapy during the index date period but excluded from our analysis due to nonspecific CAR T-cell therapy coding at time of claim adjudication OR service was not fully adjudicated at time of database access and claims extraction.

** Due to reliance on claims data for clinical outcomes, some members may have been erroneously excluded from the final analytic cohort. For example, member was not continuous enrolled or composite outcome was not observed, these members may have been misclassified.

TABLE 1

Characteristics of 65 Large B-Cell Lymphoma Members Treated with Chimeric Antigen Receptor (CAR) T-Cell Therapy

Characteristics	CAR T-cell Utilizers N = 65
Age at time of CAR T-cell initiation, mean years (SD)	**53.6 (10.0)**
Age categories (n, %)	
<40 years	8 (12.3%)
40 to <50 years	5 (7.7%)
50 to <60 years	33 (50.8%)
≥60 years	19 (29.2%)
Female gender (n, %)	**26 (40.0%)**
Charlson Comorbidity Score[10], mean (SD)	**4.3 (2.8)**

CAR = chimeric antigen receptor. n = number of members. SD = standard deviation.

CAR T-cell therapy utilizers and clinical events were identified between 1/1/2021 to 12/31/2022 among 16.5 million commercial insured members. Members were followed until hospice, death, subsequent cancer therapy initiation, or end of 6-month study follow-up from index date, whichever occurred first.

TABLE 2

Cytokine Release Syndrome (CRS) and Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) Following Chimeric Antigen Receptor (CAR) T-Cell Therapy Treatment for Large B-Cell Lymphoma

CAR T-cell-associated toxicity	CAR T-cell Utilizers N=65
Number of members with CRS or ICANS during study follow-up (n, %)	**29 (44.6%)**
Number of members with CRS during study follow-up (n, %)	**27 (41.5%)**
Grade 3 or Higher	1
Grade Unspecified	12
Tocilizumab use	**5**
Number of members with ICANS during study follow-up (n, %)	**4 (6.2%)**
Grade 3 or Higher	4
Grade Unspecified	0

CRS = Cytokine Release Syndrome. ICANS = Immune effector Cell-associated Neurotoxicity Syndrome. N = number of utilizers. SD = standard deviation.

CAR T-cell therapy utilizers and clinical events were identified between 1/1/2021 to 12/31/2022 among 16.5 million commercial insured members. Members were followed until hospice, death, subsequent cancer therapy initiation, or end of 6-month study follow-up from index date, whichever occurred first.

TABLE 3

Clinical Outcomes Occurring within 6 Months Following Chimeric Antigen Receptor (CAR) T-Cell Therapy Among Members with Large B-Cell Lymphoma

Clinical Outcome	CAR T-cell Utilizers N=65
Number of members initiating systemic cancer treatment (n, %)	**24 (36.9%)**
Radiation, n	7
Time to radiation, mean days (SD)	59.6 (36.8)
Chemotherapy, n	17
Time to chemotherapy, mean days (SD)	72.4 (38.4)
Number of members with death, (n, %)	**6 (6.2%)**
Time to death, mean days (SD)	92.7 (61.1)

CAR = chimeric antigen receptor. N=number of members.

CAR T-cell therapy utilizers and clinical events were identified between 1/1/2021 to 12/31/2022 among 16.5 million commercial insured members. Members were followed until hospice, death, subsequent cancer therapy initiation, or end of 6-month study follow-up from index date, whichever occurred first.

TABLE 4

Time-to-Event Analysis (Event = Systemic cancer therapy initiation, hospice or death) Among 65 Large B-Cell Lymphoma Members Treated with Chimeric Antigen Receptor (CAR) T-Cell Therapy

Time-to-Event	CAR T-cell Utilizers N=65
CAR T-cell members with an event during study follow-up (i.e., 6 months)	**27 (41.5%)**
CAR T-cell members with no event during study follow-up (i.e., 6 months)	**38 (58.5%)**
Median time-to-event, days (95% CI)	**NR (127 – NR)**

CAR = chimeric antigen receptor. CI = confidence interval. N = number of utilizers. NR = not reached.

Time-to-event calculated using Kaplan-Meier method. Event defined as the first occurrence initiation of cancer systemic therapy, hospice, or death, whichever occurred first. CAR T-cell therapy utilizers and clinical events were identified between 1/1/2021 to 12/31/2022 among 16.5 million commercial insured members. Members were followed until hospice, death, subsequent cancer therapy initiation, or end of 6-month study follow-up from index date, whichever occurred first.

RESULTS

- Among 85 CAR T-cell therapy utilizers during the study index period, 65 (76.5%) met full study inclusion criteria. **(Figure 1)**
- A majority of utilizers were male (60.0%), and the average age was 53.6 years (standard deviation [SD] = 10 years) at time of CAR T-cell therapy administration. **(Table 1)**
- Mean Charlson Comorbidity score was 4.3 (SD = 2.8).
- 29 (44.6%) of 65 members had 1 or more claims for any grade CRS or any grade ICANS during follow-up. **(Table 2)**
  - 27 (41.5%) members had a claim indicating CRS. Among members with CRS, 12 were unspecified grade and one was grade 3 or higher. Five members received tociluzumab.
  - Four (6.2%) members had a claim indicating ICANS; all four members had grade 3 or higher ICANS.
- 24 (36.9%) of 65 members initiated subsequent systemic treatment prior to disenrollment or end of follow-up. **(Table 3)**
  - Chemotherapy was most frequently initiated (n = 17, 26.2%) followed by radiation (n = 7, 10.8%).
    - Among members initiating chemotherapy, average time to chemotherapy was 72.4 days (SD = 38.4).
    - Among members initiating radiation, average time to radiation was 59.6 days (SD = 36.8).
- Six (9.2%) of 65 members died within six months follow-up. Average time to death was 92.7 days (SD = 61.1).
- Using Kaplan-Meier statistical methods, median time to event (event defined as first occurrence of systemic therapy initiation or death) was not reached (95% confidence interval: 127 days to not reached). **(Table 4)**
  - 27 (41.5%) members had an event (i.e., death or systemic cancer therapy initiation).
  - 38 (58.5%) members were censored at the end of the 6-month follow-up.

CONCLUSION

- Using CAR T-cell specific drug identification logic, we observed a small proportion (1.5%) of members diagnosed with LBCL receiving CAR T-cell therapy.
- This real-world cohort study found 4 out of every 10 CAR T-cell treated members for LBCL experienced CRS. Less than 1 out of every 10 CAR T-cell treated members experienced ICANS, a similar rate previously reported in the real-world setting.[5,6]
- Additionally, we described subsequent clinical outcomes following CAR T-cell administration. Despite median time-to-event not reached, over 40% of members met the event definition of first occurrence for systemic therapy initiation or death within 6 months of CAR T-cell infusion.
- Real-world clinical outcomes associated with CAR T-cell therapies are fundamental for value assessments and supporting value-based contracting with pharmaceutical manufacturers. This real-world study found 4 in 10 members with LBCL failing to achieve positive CAR T-cell therapy outcomes; at 40% treatment failure, pharmaceutical manufacturers should be offering value-based purchase agreements.
- Further research should assess the relationship between CAR T-cell therapy outcomes and total cost of care.

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