Economic Burden of Neurologic Toxicities Associated with Treating Relapsed or Refractory Diffuse Large B-Cell Lymphoma in the United States

Michael S. Broder, MD, MSHS[1]; Qiufei Ma, PhD[2]; Tingjian Yan, PhD[1]; Eunice Chang, PhD[1]; Lamis Eldjerou, MD[2]; Yanni Hao, PhD[2]; David Kuzan, MD[2]; Jie Zhang, PhD[2]

[1] Partnership for Health Analytic Research, LLC, Beverly Hills, CA, United States; [2] Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Introduction

- Chimeric antigen receptor T (CAR-T) cell therapies targeting CD19 antigen can yield durable remissions, and have expanded treatment options for relapsed refractory diffuse large B-cell lymphoma (r/r DLBCL).[1,2]
- Yet CAR-T use can involve potentially severe toxicities, such as cytokine release syndrome and neurologic toxicities.[3]
- Management of neurologic toxicities requires vigilant monitoring and intensive supportive care.[4,5]
- We found no studies reporting healthcare costs associated with treatment-related neurotoxic events (NEs) in patients with r/r DLBCL.

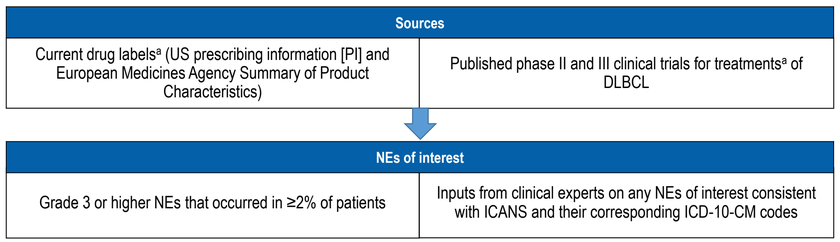
Objective

- To develop an evidence-based list of r/r DLBCL treatment-related NEs, including the most recently approved CAR-Ts, and to estimate the healthcare costs associated with the NEs in a real-world setting

Methods

- **Identification of NEs (Figure 1)**

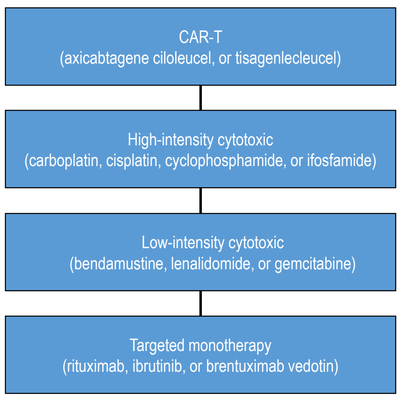
Figure 1. Identification of NEs of interest in DLBCL



DLBCL: diffuse large b-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; ICD-10-CM: International Classification of Disease, 10th Revision, Clinical Modification; NEs: neurotoxic events. [a] CAR-T therapies: tisagenlecleucel and axicabtagene ciloleucel; chemotherapies: dose-adjusted EPOCH-rituximab, dose-dense CHOP 14 +/- rituximab, bendamustine +/- rituximab, brentuximab vedotin, DHAP +/- rituximab, GDP +/- rituximab, GemOX +/- rituximab, ICE +/- rituximab, lenalidomide +/- rituximab, oxaliplatin w/ROAD, rituximab.

- **Identification of r/r DLBCL**
  - Retrospective analysis of 3 large nationally representative administrative claims databases
  - Patients included if: 1) received treatment beyond first-line (2L+) during identification (ID) period; and 2) had ≥1 inpatient or ≥2 outpatient claims for DLBCL during study period with ≥1 having occurred before or on date of 2L+ treatment (see **Figure 2** for details)
    - 2L+ treatments selected based on National Comprehensive Cancer Network Clinical Practice Guidelines and clinical expert input
    - To maximize CAR-T sample, treatments categorized hierarchically into 4 therapy groups **(Figure 3)**

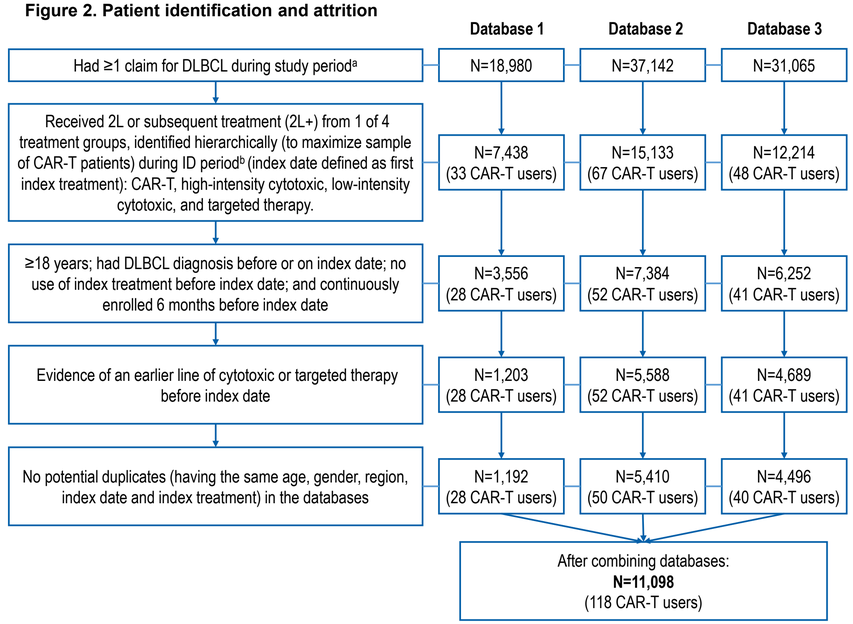
Figure 3. Treatment hierarchy



- **Outcomes of Interest** (during 30-day post-index period)
  - Rates of NEs
  - Differences in total healthcare costs for patients with and without NEs
- **Statistical Analysis** (performed using SAS© version 9.4)
  - Descriptive statistics reported with costs inflated to 2019 Q1 US dollars

Methods (continued)

Figure 2. Patient identification and attrition



CAR-T: Chimeric antigen receptor T; ID: identification. [a] From 1/1/2007 to 12/31/2018, 1/15/2019, and 3/31/2019 for database 1, 2, and 3 respectively. [b] From 7/1/2007 to 12/31/2018, 1/15/2019, and 3/31/2019 for database 1, 2, and 3 respectively.

Results

- 16 NEs were identified based on drug PI, clinical trials, and ICANS
  - 13 from CAR-T, 5 from conventional immuno-chemotherapy, and 2 from both
  - 11 included in the claims analysis based on availability of ICD-9/10-CM diagnosis: encephalopathy, somnolence, mental status changes/disorientation, disturbances in attention, seizure, cerebral edema, speech disorder, aphasia, delirium, agitation/restlessness, abnormal motor activity
- 11,098 patients with r/r DLBCL were identified from claims data **(Table 1)**

Table 1. Patient demographics and Charlson comorbidity index score

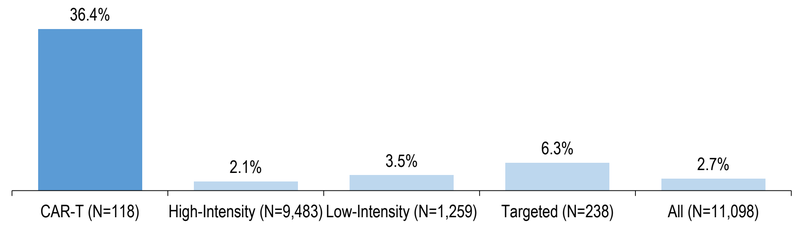
	CAR-T N=118; 1.1%	High-Intensity N=9,483; 85.4%	Low-Intensity N=1,259; 11.3%	Targeted N=238; 2.1%	All 11,098; 100%
Age, year, mean (SD) [median]	58.5 (10.5) [60]	61.2 (13.7) [62]	66.0 (13.3) [65]	60.2 (14.2) [60]	61.7 (13.7) [62]
18-54, n (%)	34 (28.8)	2,535 (26.7)	224 (17.8)	68 (28.6)	2,861 (25.8)
55-64	52 (44.1)	3,318 (35.0)	378 (30.0)	91 (38.2)	3,839 (34.6)
65+	32 (27.1)	3,630 (38.3)	657 (52.2)	79 (33.2)	4,398 (39.6)
Female, n (%)	35 (29.7)	4,207 (44.4)	570 (45.3)	111 (46.6)	4,923 (44.4)
Charlson comorbidity index, mean (SD) [median]	3.6 (2.3) [3]	4.5 (3.0) [3]	4.6 (3.1) [3]	4.7 (2.9) [4]	4.5 (3.0) [3]

CAR-T: Chimeric antigen receptor T; SD: standard deviation.

- 299 (2.7%) of patients had ≥1 NE during the 30-day post-index period **(Figure 4)**
  - Of the 118 CAR-T users, 36.4% had ≥1 NE; 28.0% had encephalopathy
  - Rates of other NEs were low and occurred in <10% of patients from each therapy group
- CAR-T patients had the greatest cost differences between patients with and without any NEs **(Figure 5)**
  - Among the 13 NEs from CAR-T, encephalopathy was not only the most prevalent one, but also incurred higher incremental costs

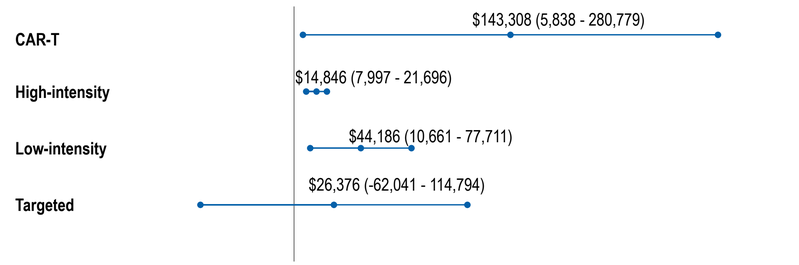
Results (continued)

Figure 4. CAR-T users had the highest rate of NEs



CAR-T: Chimeric antigen receptor T; NE: neurotoxic event.

Figure 5. Patients with CAR-T therapy had the greatest difference in mean total healthcare costs (95% confidence interval) between those with vs. without any NEs



CAR-T: Chimeric antigen receptor T; NE: neurotoxic event.

Conclusions

- **This is the first study of the economic burden of neurotoxic events (NEs) associated with treating relapsed or refractory diffuse B-cell lymphoma (r/r DLBCL) in a real-world setting with data that reflects the current range of treatment options.**
- **For patients treated with chimeric antigen receptor T (CAR-T) therapy, those with severe/life-threatening NEs incur substantially higher costs than those without such events. Effective CAR-T therapy with a better neurological safety profile may help to reduce these costs.**

Limitations

- The sample size of CAR-T patients is relatively small.
- We are unable to separate out the two CAR-Ts (axicabtagene ciloleucel, tisagenlecleucel) in the claims due to the shared coding.
- ICD-9-CM and ICD-10-CM codes were used to identify NEs, and these codes are not the same as those used in clinical trials. Thus, the specific events that are evaluated may not directly correspond to those in trials.

References

1. Schuster S, et al. *N Engl J Med.* 2019;380(1):45-56. 2. Locke FL, et al. *Lancet Oncol.* 2019;20(1):31-42. 3. Rubin D, et al. *Brain.* 2019;142(5):1334-1348. 4. Brudno J, et al. *Blood.* 2016;127(26):3321-3330. 5. Neelapu SS, et al. *Nat Rev Clin Oncol.* 2017;15:47.

Disclosures

Poster presented at ASH Annual Meeting and Exposition, Orlando, FL, December 7-10, 2019.

This study was sponsored by Novartis Pharmaceuticals Corporation. M.S. Broder, T. Yan, E. Chang, are employees of Partnership for Health Analytic Research, LLC, a health services research company, paid by Novartis to conduct this research. Q. Ma, L. Eldjerou, Y. Hao, D. Kuzan, J. Zhang are employees of Novartis.