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Efficacy and Safety of Experimental versus Approved CAR T-cell Therapies in Large B-cell Lymphoma Using Matching Adjusted Indirect Comparisons: A Systematic Review and Meta-Analysis Protocol

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Abstract:

Background: *Relapsed and refractory large B cell lymphomas (RR-LBCL) have a poor prognosis. Chimeric antigen receptor (CAR) T-cell therapies have shown considerably high response rates even in RR-LBCL patients who fail to achieve remission after multiple chemotherapy lines. Currently, three CAR T-cell treatments - axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), and lisocabtagene maraleucel (Breyanzi) - have been approved for adults with RR-LBCL by regulatory agencies. Non-pivotal clinical trials have independently examined different types of CAR T-cells and have demonstrated remarkable clinical benefit and safety. Yet, no comparison of the experimental and approved CAR T-cells has been conducted.*

Objectives: *To address this limitation, we aim to: (1) Identify comparative efficacy and safety of experimental CAR T-cells to the approved CAR T-cells, and (2) Identify how observed differences vary by different CAR T-cell types and regimens differences in CAR T-cell administration.*

Methodology: *This protocol proposes a matching-adjusted indirect comparison (MAIC) of experimental CAR T-cell trials based on individual patient data (IPD) vs. three existing pivotal trials (comparator trials). The MAIC approach is appropriate given that CAR T-cells have solely been assessed in single-arm trials consisting of heterogeneous patient populations and the lack of IPD for the existing pivotal trials (active comparator trials), which hampers the traditional network meta-analysis approach.*

Conclusion: *Knowledge of the relative value of experimental CAR T-cell products compared to the currently approved ones may provide insights for patients, clinicians, and CAR T-cell developers to advance and optimize the balance of potency and toxicity of these targeted immunotherapies.*

Keywords: *large B-cell lymphoma, chimeric antigen receptor T-cell therapy, matching adjusted indirect comparison, individual patient-based meta-analysis.*

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INTRODUCTION

Relapsed and refractory large B cell lymphomas (RR-LBCL) have a poor prognosis (Epperla et al., 2019). Chimeric antigen receptor (CAR) T-cells are genetically engineered T-cells derived from two different sources: autologous (self-derived) or allogeneic (healthy donors). These transplanted cells activate the patient's immune system, leading to the recognition and destruction of tumor cells (Sadelain et al., 2013). The National Comprehensive Cancer Network (NCCN) 2021 guideline has included CAR T-cell therapies as a salvage treatment for RR-LBCL (National Comprehensive Cancer Network, 2021).

Currently, three CAR T-cell treatments have been approved by regulatory agencies worldwide (e.g., FDA, EMA), which include axicabtagene ciloleucel, with a 54% complete response rate (CRR) (Neelapu et al., 2017), tisagenlecleucel, with a 40% CRR (Schuster et al., 2019), and lisocabtagene maraleucel, with a 53% CRR (Abramson et al., 2020). These therapies have been approved for RR-LBCL treatment after ≥ 2 chemotherapy lines in adult populations. Several clinical trials have independently examined CAR T-cells varying by their target antigens (CD-19, CD20, bispecific, or concurrent administration of anti-CD20 and anti-CD19 CAR T-cells), co-stimulatory domains (CD28, 4-1BB, or CD28 and 4-1BB), and combination or not with stem cell transplantation (SCT). Some of these CAR T-cells have shown remarkable clinical benefit and desirable safety (Brudno et al., 2020; Huang et al., 2020; Kebriaei et al., 2016; Kochenderfer et al., 2017; Shah et al., 2020; Tong et al., 2020; Z. Ying et al., 2019; Zhitao Ying et al., 2019; Zhang et al., 2016).

However, no comparison of the experimental and approved CAR T-cells has yet been conducted.
Knowledge of the relative advantages of experimental CAR T-cell products compared to the currently approved ones may provide insights for patients and clinicians and guide clinical decision-making to select appropriate CAR T-cell treatment options (among various available CAR T-cell products). It may also inform CAR T-cell manufacturers and clinical trialists to identify the most appropriate type of CAR T-cells with a view toward higher efficacy and lower toxicity in relation to the current gold-standard, FDA-approved CAR T-cells. Additionally, the possibility of in-house production of CAR T-cells has been anticipated to reduce manufacturing costs and waiting time until infusion.

To date, CAR T-cells have solely been assessed in single-arm trials comprised of heterogeneous patient populations. When this study design couples with other factors (e.g., heterogeneity in the study population, CAR T-cell dose, and CAR T-cell target), it contributes to between-trial differences and potentially leads to erroneous or biased estimates when a traditional network meta-analysis is used. The matching-adjusted indirect comparisons (MAICs) approach intends to address this methodological gap by reducing the bias derived from trial differences. Several studies have used this approach to evaluate the comparative efficacy and safety of treatments for various diseases, including multiple myeloma (Van Sanden et al., 2018) and mantle cell lymphoma (Telford et al., 2019), when IPD is unavailable in both the intervention and comparator arms. This method, for instance, was used in the ZUMA-1 trial, a recent pivotal study comparing the efficacy and safety of axicabtagene ciloleucel versus tisagenlecleucel in RR-LBCL (Oluwole et al., 2020). As we acknowledge the substantial heterogeneity across small experimental CAR T-cell trials, we propose MAICs to assess the comparative efficacy and safety of experimental CAR T-cell products in comparison to the three currently approved CAR T-cell therapies.
The PICO for this study is as follows:

- Population: Individuals with refractory or relapsed LBCL treated with CAR T-cells regardless of gender, race, or ethnicity.
- Interventions: This study's intervention encompasses existing experimental CAR T-cell therapies that have been assessed in clinical trials irrespective of their molecular structures. Characteristics of CAR T-cells and management-related data (CAR T-cell generation, CAR T-cell origin [autologous/allogeneic], target antigens, vector systems, the molecular structure of antibodies, and co-stimulatory domains of CAR T-cells defining the specific generations) will be identified from eligible trials to assess how these factors potentially impact the efficacy and toxicity of CAR T-cell therapy. We will collect therapeutic strategy-related data, including dosage and conditioning regimen.
- Comparator: Experimental CAR T-cells' clinical efficacy and safety will be compared to the FDA-approved CAR T-cell therapies, based on aggregated data, from the pivotal ZUMA-1, JULIET, and TRANSCEND trials.
- Primary outcomes: Clinical efficacy (Progression-Free Survival) and safety of CAR-T-cell therapy (Cytokine Release Syndrome and Neurotoxicity) in LBCL.

METHODS

Eligibility criteria

Patients with RR-LBCL after two or more systemic therapies who have received CAR T-cell therapy regardless of the type of CAR T-cells, geography, health care setting (inpatient and outpatient), and demographic characteristics (age, gender, race, or ethnicity). We will carefully review the published data from 2010 through 2021 to determine whether to include or exclude patients based on the following inclusion and exclusion criteria:

Inclusion criteria: Patients with RR-LBCL after ≥ 2 lines of systemic therapy who have been treated with any CAR T-cell therapy regardless of:

- Type of CAR T-cells;
- Regulatory status (approved/experimental);
- The geographical location of clinical trials;
- Healthcare setting (inpatient/outpatient);
- Demographic characteristics (age, gender, race/ethnicity, presence of comorbidities).

Exclusion criteria: Patients who have received other concomitant drug therapies (e.g., CAR T-cell therapy + PD-1 inhibitors) during the clinical trial (except for bridging or lymphodepleting chemotherapy).

Information sources

Literature search terms will be developed based on medical subject headings (MeSH) and text words related to CAR T-cells and Lymphoma. Electronic databases will be searched to identify either published or grey/white papers as listed following. To capture comprehensive literature, we will review the cited documents in the included studies to identify the relevant literature. The study team and topic expertise will review and verify the final list of eligible studies.

Electronic databases:

- Cochrane Central, Medline via Ovid, Embase via Ovid, Scopus Elsevier, Web of Science, Education Resources Center (ERIC)

Conference proceedings of the most relevant societies:

- American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association

International trial registries:

- International: ClinicalTrials.gov, International Standard Randomised Controlled Trial Number (ISRCTN registry), World Health Organization International Clinical Trials Registry Platform (ICTRP), Deutsches Register Klinischer Studien (DRKS)
- Asian: Chinese Clinical Trial Registry (ChiCTR)
- European Clinical Trials Register (www.clinicaltrialsregister.eu)
- Latin American and Caribbean Health Science Information Database (LILACS)
- Australian and New Zealand Clinical Trials Registry

Search for unpublished trials among the grey literature:

- Google engine, Grey Literature Report (greylit.org), OpenGrey (opengrey.eu), and hand searching.
- Data obtained from the eligible trial authors.

Search strategy

We will search for systematic reviews with meta-analysis on the topic in PubMed, Google Scholar, and PROSPERO to identify the research and knowledge gap. Our search will include both published and unpublished trials using comprehensive algorithms without restriction to study design, geography, language, or date, as follows:

A draft Embase / MEDLINE search query is ('chimeric antigen receptor':ti OR 'car t-cell':ti OR 'large cell lymphoma':ti) AND 'diffuse large b cell lymphoma':ab,ti OR 'high grade b cell lymphoma':ab,ti OR 'transformed follicular lymphoma':ab,ti OR 'primary mediastinal b cell lymphoma':ab,ti.

This draft query will be adapted to the other electronic databases. The search will be updated every month during the study period to ensure the inclusiveness of recently published eligible studies.

Study records

Data management: We will use Mendeley and Google SpreadSheet for data collection and real-time collaborations. Rayyan QCRI web application (accessible at https://rayyan.qcri.org/welcome) will be used for citation sharing, blinding reviewers on the other reviewers' exclusion/inclusion decisions of the articles, and comparison of final decisions. All IPD and aggregate data will be managed according to PRISMA guidelines (Moher et al., 2016; Shamseer et al., 2015).

Selection process: Authors (BW, SS, and GH) will independently assess and select eligible studies using the Rayyan QCIR web application (accessible at https://rayyan.qcri.org/welcome). Authors will be blinded to each other's decision and will resolve the disagreement by discussion or consultation with the clinical expert of the study's therapeutic area (AVM).

Data collection process: Review authors (BW, SS, YL, YA) will collect individual patient-level data from each

selected study, including administrative information of each trial (trial center, clinical trial identifiers, author-date of published articles, etc.), follow-up period, study design, methodology, participant demographics/baseline characteristics, each reviewed study's definitions, and measured results of the primary and secondary outcomes and any of the additional outcomes. Review authors will cross-check data collected by other authors for verification. Data collectors will ensure the contents of IPD include (1) patients diagnosed with RR-LBCL; (2) patients treated with CAR T-cell therapies; (3) clinical trials with single or more arms regardless of study design; (4) no restrictions regarding recruitment date; (5) published and unpublished articles with or without IPD. We will contact experts and authors of the eligible trials to obtain the necessary unreported information in the published articles, should this be the case.

Data items

We will aim to retrieve comprehensive baseline characteristics, including the clinically essential variables: disease status, history of autologous stem cell transplantation (ASCT), age, history of transformed LBCL or de novo LBCL, and history of previous systemic therapies (chemo-, immune-, cellular, and/or radiation therapy) at the time of CAR T-cell administration. CAR T-cell and treatment regimen-related covariates that have been reported by previous studies with various associations with survival and safety outcomes will be collected as follows.

- CAR T-cell antigens, viral vectors, and dose-levels, and T-cell origin (autologous vs. allogeneic);
- Treatment strategies: CAR T-cells combined vs. non-combined with SCT and/or other drugs.

Outcomes and prioritization

The primary outcomes we recommend in this study are as follows:

- Progression-free survival (PFS): defined as the time interval from the date of first CAR T-cell administration to the first confirmed event (disease progression, death, last follow-up / data-cut for data censoring).
- Grade 3 and 4 cytokine release syndrome (CRS) and neurotoxicity (NT) rate and/or immune effector cell-associated neurotoxicity syndrome (ICANS).

Additional outcomes:

We will assess the overall survival (OS) rate, treatment-related adverse events (TRAEs), objective response rates (ORR), and serious adverse events (SAEs) for additional outcomes:

- Overall survival (OS): defined as the time interval from CAR T-cell administration to death, last follow-up, or data-cut.
- Other treatment-related adverse events (TRAEs), including intervention-related mortality and excluding CRS and NT.
- Objective response rate (ORR), complete response rate (CRR), and partial response rate (PRR) at equivalent predefined time points.

Risk of bias in individual studies

The extent of the overall and trial-specific risk of bias will be assessed using the ROBINS-I tool and categorized into low, moderate, serious, and critical levels. The first four authors will assess each published and independent IPD trial to determine the potential source of bias across seven domains: confounding, selection bias, measurement of classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Clinical trials identified to have a serious or critical bias will be excluded from the final analysis. The decisions to exclude studies or contact trial authors to request pending information will be made independently by two review authors following the relevant Cochrane guideline (Higgins 2020) and then by consulting with a topic expertise author as necessary.

Data Synthesis

IPD collected from the eligible independent trials and aggregate data collected from three published pivotal trials will be used for quantitative analysis. All trials will be described by descriptive summary measures of key baseline covariates. We will conduct unanchored MAICs following the NICE DSU Technical Support Document 18 on Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE (Phillippo et al., 2016) to compare the safety and efficacy of experimental CAR T-cell therapies, based on IPD, with the FDA-approved CAR T-cell therapies, based on aggregated data, from the pivotal ZUMA-1, JULIET and TRANSCEND trials. Given that the existing clinical trials on CAR T-cells are mostly single-arm trials, an indirect treatment comparison using unanchored MAIC is mandated. In consultation with our topic expertise and literature review, we will identify clinically meaningful baseline variables available across eligible trials to adjust for between-trial heterogeneity. Once baseline variables are identified for the adjustment, summary

statistics of these variables in the IPD trials will be compared to the reported summary statistics of the same variables in the ZUMA-1, JULIET, and TRANSCEND trials (Abramson et al., 2020; Neelapu et al., 2017; Schuster et al., 2019). Using the MAIC framework, the method of moments will estimate the weights to balance the mean covariate values between the weighted IPD population and the aggregate data population based on the key baseline variables. Subsequently, treatment outcomes will be reweighted. Then, the reweighted outcomes will be compared using odds ratios (OR) for response outcomes, hazard ratios (HR) for time-to-event outcomes, and their corresponding 95% confidence intervals (CIs) for comparing the efficacy of experimental CAR T-cells vs. approved CAR T-cells by intervention and regimen-related factors. Statistical significance of comparative treatment efficacy will be decided based on the inclusion or exclusion of a null value 1 in the 95% CI of the ORs and HRs.

- As unanchored MAIC requires, we will use IPD from experimental trials on CAR T-cells and aggregate data from the three pivotal trials mentioned above. Then, all eligible trials will be matched on their selected baseline characteristics to reduce between-trial differences.
- After matching, the resulting treatment outcomes will be compared across balanced trial populations.
- If a quantitative synthesis is inappropriate, a descriptive analysis using informative tables will be performed.

Subgroup analyses will be conducted by key treatment factors, assuming adequate sample size, as follows:

- CAR T-cell antigens, viral vectors, and dose-levels, and T-cell origin (autologous vs. allogeneic);
- Treatment strategies: CAR T-cells combined vs. non-combined with SCT.

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Conflict of Interest

All listed authors have completed the International Committee or Journal of Medical Journals Editors (ICMJE) form to address potential conflicts of interest. There are no personal or financial conflicts of interest disclosed by the authors concerning this study. Additionally, all authors have read and approved the content of this manuscript.

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