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Axicabtagene Ciloleucel and Tisagenlecleucel for Diffuse Large B-cell Lymphoma

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Summary of Abstracts

CADTH

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Key Messages

- Twelve non-randomized studies were identified regarding the clinical effectiveness of axicabtagene ciloleucel in the treatment of adult patient with relapsed or refractory diffuse large B-cell lymphoma.
- Seven non-randomized studies were identified regarding the clinical effectiveness of tisagenlecleucel in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma.
- Two non-randomized studies were identified regarding the comparative effectiveness of axicabtagene ciloleucel versus tisagenlecleucel in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma.
- One economic evaluation was identified regarding the cost-effectiveness of axicabtagene ciloleucel versus tisagenlecleucel in the treatment of adult patient with relapsed or refractory diffuse large B-cell lymphoma.

Research Questions

1. What is the clinical effectiveness of axicabtagene ciloleucel (axicel) in the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)?
2. What is the clinical effectiveness of tisagenlecleucel (tisacel) in the treatment of adult patients with R/R DLBCL ?
3. What is the comparative clinical effectiveness of axicel versus tisacel in the treatment of adult patients with R/R DLBCL?
4. What is the cost-effectiveness of axicel versus tisacel in the treatment of adult patients with R/R DLBCL?

Research Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were axicabtagene ciloleucel, tisagenlecleucel, and B-cell lymphoma. No filters were applied to limit the retrieval by study type. Conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2017, and January 4, 2022. Internet links were provided, where available.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients (≥ 18 years) with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Intervention	Q1: Axicabtagene ciloleucel Q2: Tisagenlecleucel Q3 and Q4: Axicabtagene ciloleucel
Comparator	Q1 and Q2: Chemotherapy, targeted therapy, radiation therapy, stem cell transplant, usual or standard care, waitlist, placebo, no treatment Q3 and Q4: Tisagenlecleucel
Outcomes	Q1 to Q3: Clinical effectiveness (e.g., response or remission rate, survival, health-related quality of life, duration of response, relapse, need for subsequent treatments, hospitalization) and safety and harms (e.g., mortality, serious adverse events [i.e., grade 3 or 4], treatment-related adverse events, withdrawal due to adverse events, cytokine release syndrome, neurologic effects, prolonged cytopenia, infections and infestations, febrile neutropenia) Q4: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, cost per unit of health benefit)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations

DLBCL = diffused large B-cell lymphoma.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications.

Results

Twelve non-randomized studies (NRSs)[1,4-6,8,10-12,15,17,19,20] were identified regarding the clinical effectiveness of axicel in the treatment of adult patients with R/R DLBCL. Seven[7,9,13,14,16,18,21] NRSs were identified regarding the clinical effectiveness of tisacel in the treatment of adult patients with R/R DLBCL. Regarding the comparative effectiveness of axicel versus tisacel in the treatment of adult patients with R/R DLBCL, 2 NRSs were found.[2,3] Additionally, 1 economic evaluation[22] was identified regarding the cost-effectiveness of axicel versus tisacel in the treatment of adult patients with R/R DLBCL. No health technology assessments, systematic reviews, or randomized controlled trials were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

Twelve NRSs[1,4-6,8,10-12,15,17,19,20] were identified regarding the clinical effectiveness of axicel in the treatment of adult patients with R/R DLBCL. One of the 12 studies was phase I of the ZUMA-1 trial, which evaluated axicel in patients with refractory DLBCL, and showed that axicel induced durable remissions in participants and was safe for further study in phase II.[19] Two year follow-up of ZUMA-1 patients also concluded that treatment with axicel resulted in durable responses and a manageable long-term safety profile, in addition to a median overall survival of more than 2 years in patients with R/R large B-cell lymphoma.[17] Furthermore, a safety and efficacy profile similar to ZUMA-1 was produced in a retrospective cohort.[15] Another cohort study concluded that axicel led to significant efficacy in treating DLBCL in real-world settings, with a significant response of participants achieving complete remission at 3 months and treatment being generally well tolerated.[12] In a matching-adjusted indirect comparison analysis comparing data from 2 cohort studies, patients with refractory large B-cell lymphoma treated with axicel produced durable responses and a substantial survival benefit when compared to patients treated with salvage chemotherapy.[1]

Authors of 7 NRSs raised concerns on the adverse events observed in patients with R/R DLBCL treated with axicel.[4-6,8,10,11,20] Two cohort studies concluded that prolonged monitoring and prophylaxis is needed to improve the safety of axicel for R/R large B-cell lymphoma.[4,10] A retrospective cohort study found that although axicel was highly effective, infectious complications remain an important cause of morbidity and mortality.[11] Prolonged cytopenias that typically recovered over time were also commonly observed following axicel therapy in a prospective cohort study.[8] However, the same study found that patients experienced profound and prolonged immunosuppression without severe infection and reported no late deaths due to infection after 30 days.[8] In a multicentre phase II study of patients with refractory large B-cell lymphoma, patients treated with axicel had high levels of durable response, with a safety profile that included myelosuppression, cytokine release syndrome, and neurologic events.[20] Authors of retrospective cohort study observed that all but 1 participant experienced cytokine release syndrome and more than half experienced neurotoxicity.[5] Similarly, a prospective cohort study observed immune cell-associated neurotoxicity syndrome in about half of participants, the majority of which were considered high grade.[6]

Seven[7,9,13,14,16,18,21] NRSs were identified regarding the clinical effectiveness of tisacel in the treatment of adult patients with R/R DLBCL. Four publications[7,9,13,18] concluded that tisacel shows durable responses, and of those 4, 3 studies[7,9,13] suggested that tisacel has a manageable safety profile. One single-arm trial found that patients with R/R DLBCL who respond to tisacel had sustained clinically meaningful improvement in health-related quality of life.[14] One cohort study[16] provided preliminary evidence of tisacel's efficacy after bridging therapy in R/R DLBCL, while another study[21] found tisacel effective in treating R/R follicular lymphoma, in addition to R/R DLBCL. The latter study found high rates of durable remission in R/R follicular lymphoma or DLBCL, with recovery of B-cell and immunoglobulins in some patients.[21]

Two NRSs, 1 matching-adjusted indirect comparison[2] and 1 retrospective cohort,[3] were identified regarding the comparative clinical effectiveness of axicel versus tisacel in the treatment of patients with R/R DLBCL. Results of the matching-adjusted indirect analysis suggest that axicel may have superior efficacy but a greater risk of grade 1 to 2 cytokine release syndrome when compared to tisacel.[2] Alternatively, the retrospective cohort found no significant difference in the efficacy and safety between axicel and tisacel in patients

with R/R DLBCL.[3] Table 2 provides a detailed summary of the studies relevant to research questions 1 to 3.

One economic evaluation was identified regarding the cost-effectiveness of axicel versus tisacel in the treatment of adult patients with R/R DBCL.[22] The authors concluded that axicel was a superior treatment option in this simulation as it is predicted to achieve better outcomes at lower or minimal incremental costs versus tisacel.[22]

Table 2: Summary of Included Clinical Effectiveness Studies

Study citation	Study design, sample size	Intervention and comparator(s)	Relevant outcome(s)	Author's conclusions
Non-randomized studies				
Neelapu et al. (2021)[1]	**Study design:** Matching-adjusted indirect comparison **N = 101 (from ZUMA-1) and N = 434 (from SCHOLAR-1)**	**Intervention:** Axicel **Comparator:** Salvage chemotherapy	ORR, CRR, and 2-year survival rate, reduction in risk of death	Axicel produces durable responses and a substantial survival benefit when compared to non-CAR T-cell salvage regimens for patients with refractory LBCL.
Oluwole et al. (2020)[2]	**Study design:** Matching-adjusted indirect comparison **N = NR**	**Intervention:** Axicel **Comparator:** Tisacel	ORR, CRR, OS, and adverse events	The MAIC analysis suggests axicel may have superior efficacy but a greater risk of grade 1 to 2 cytokine release syndrome.
Sesques et al. (2020)[3]	**Study design:** Retrospective cohort study **N = 61**	**Intervention**: Axicel **Comparator**: Tisacel	ORR, CR, progression-free survival, OS, adverse events	No significant difference in efficacy and safety was found between axicel and tisacel.
Baird et al. (2021)[4]	**Study design:** Prospective cohort study **N = 41**	**Intervention:** Axicel **Comparator**: NA	Hematologic recovery, immune reconstitution, and infectious complications	Results support the use of supportive care, including long-term monitoring and anti-microbial prophylaxis beyond 12 months after axicel.
Grana et al. (2021)[5]	**Study design:** Retrospective cohort study **N = 37**	**Intervention:** Axicel **Comparator:** NA	Adverse events	All but one patient experienced cytokine release syndrome of any grade and 27 patients experienced neurotoxicity of any grade.
Holtzman et al. (2021)[6]	**Study design:** Prospective cohort study **N = 45**	**Intervention:** Axicel **Comparator:** NA	Adverse events	Immune cell-associated neurotoxicity syndrome after axicel was seen in half of patients, the majority of which were high grade.
Iacobani et al. (2021)[7]	**Study design:** Retrospective cohort study **N = 75**	**Intervention:** Tisacel **Comparator:** NA	OS, CR, progression-free survival, and adverse events	Tisacel showed a manageable safety profile and durable complete responses.

Study citation	Study design, sample size	Intervention and comparator(s)	Relevant outcome(s)	Author's conclusions
Logue et al. (2021)[8]	**Study design:** Retrospective cohort study **N = 85**	**Intervention:** Axicel **Comparator:** NA	Immune reconstitution and adverse events (infections)	Prolonged cytopenias are common following axicel therapy and typically recover with time. Most patients experience profound and prolonged immunosuppression without severe infection.
Schuster et al. (2021)[9]	**Study design:** Single-arm trial **N = 115**	**Intervention:** Tisacel **Comparator:** NA	ORR and safety	Tisacel shows durable activity and a manageable safety profile.
Strati et al. (2021)[10]	**Study design:** Posthoc analysis **N = 31**	**Intervention:** Axicel **Comparator:** NA	Immune reconstitution and infection	Prolonged monitoring and prophylaxis against opportunistic infections in these patients to improve the long-term safety of axicel.
Thakkar et al. (2021)[11]	**Study design:** Retrospective cohort study **N = 19**	**Intervention:** Axicel **Comparator:** NA	Immune reconstitution and infection	Although CAR T-cell therapy is highly affective, infectious complications remain an important cause of morbidity and mortality.
Abbasi et al. (2020)[12]	**Study design:** NR **N = 10**	**Intervention:** Axicel **Comparator:** NA	Response rate and adverse event	Axicel led to significant efficacy with manageable toxicity in a real-world setting.
Goto et al. (2020)[13]	**Study design:** Single-arm trial **N = 17**	**Intervention:** Tisacel **Comparator:** NA	Response rate (ORR and PR)	Tisacel showed a high best ORR with a manageable safety profile.
Marziarz et al. (2020)[14]	**Study design:** Single-arm trial **N = 99**	**Intervention:** Tisacel **Comparator:** NA	CR, PR, and HRQoL	Patients with refractory or relapsed DLBCL who responded to tisacel had sustained clinically meaningful improvement in HRQoL.
Nastoupil et al. (2020)[15]	**Study design:** Retrospective cohort study **N = 275**	**Intervention:** Axicel **Comparator:** NA	Adverse events, non-relapse mortality, ORR, CRR, progression-free survival	The safety and efficacy of axicel in the standard-of-care setting in patients was comparable to the registrational ZUMA-1 trial.
Bishop et al. (2019)[16]	**Study design:** Single-arm trial subset analysis **N = 7**	**Intervention:** Tisacel **Comparator:** NA	CR and adverse events	These results provide preliminary evidence of tisacel efficacy after bridging.
Locke et al. (2019)[17]	**Study design:** Single-arm trial **N = 119**	**Intervention:** Axicel **Comparator:** NA	ORR, OS, progression-free survival, duration of response, and adverse events	Axicel can induce durable responses and a median overall survival of greater than 2 years and had a manageable long-term safety profile.

Study citation	Study design, sample size	Intervention and comparator(s)	Relevant outcome(s)	Author's conclusions
Schuester et al. (2019)[18]	**Study design:** Single-arm trial **N = 93**	**Intervention:** Tisacel **Comparator:** NA	ORR, CR, PR, relapse-free survival, adverse events	In this study of CAR T-cell therapy, high rates of durable responses were produced with tisacel.
Locke et al. (2017)[19]	**Study design:** Single-arm trial **N = 7**	**Intervention:** Axicel **Comparator:** NA	ORR, adverse events	Axicel was safe for further study in phase II and induced durable remissions in patients.
Neelapu et al. (2017)[20]	**Study design:** Single-arm trial **N = 111**	**Intervention:** Axicel **Comparator:** NA	ORR (combined CR and PR), OS, and safety	Patients with refractory LBCL who received axicel had high levels of durable response, with a safety profile that included myelosuppression, cytokine release syndrome, and neurologic events.
Schuster et al. (2017)[21]	**Study design:** Single-arm trial **N = 28**	**Intervention:** Tisacel **Comparator:** NA	CR and adverse events	Tisacel can be effective in the treatment of R/R DLBCL or follicular lymphoma. High rates of durable remission were observed with recovery of B-cell and immunoglobulins in some patients.

axicel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; CR = complete response; CRR = complete response rate; DLBCL = diffuse large B-cell lymphoma; HRQoL = health-related quality of life; LBCL = large B-cell lymphoma; MAIC = matching-adjusted indirect comparison; NA = Not Applicable; NR = not reported; OS = overall survival; ORR = objective response rate; PR = partial response; R/R = refractory or relapsed; tisacel = tisagenlecleucel.

References

Health Technology Assessments

No literature identified.

Systematic Reviews

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

Comparative Studies

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Non-Comparative Studies

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Economic Evaluations

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Appendix 1: References of Potential Interest

Previous CADTH Reports

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Systematic Reviews

Unclear population: Not Specific to Diffuse Large B-cell Lymphoma

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Not Specific to Axicabtagene Ciloleucel and Tisagenlecleucel

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Randomized Controlled Trials

Alternative Population: Patients After 1 line of Systemic Therapy

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Non-Randomized Studies

Alternative Population: Patients in Partial Remission

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Unclear Population

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Unclear Intervention: Mixed Axicabtagene Ciloleucel and Tisagenlecleucel Findings

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Unclear Comparator

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Economic Evaluations

Alternative Comparator

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Note: This document details the appraisal of the clinical effectiveness of tisagenlecleucel within its marketing authorisation.