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Real-World Bridging Therapy of Patients With Relapsed or Refractory Large B-Cell Lymphoma Treated With Chimeric Antigen Receptor T-Cell Therapy: A Systematic Literature Review and Meta-Analysis

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BACKGROUND

- Use of bridging therapy, defined as anticancer therapy given between leukapheresis and lymphodepletion, has varied in clinical studies of chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL)[1-3]
  - In the pivotal ZUMA-1 study of axicabtagene ciloleucel (axi-cel), use of bridging therapy was not allowed[1]
  - In the JULIET trial for tisagenlecleucel (tisa-cel), bridging therapy was allowed and given to 92% of the patients before infusion[2]
  - In the TRANSCEND trial for lisocabtagene maraleucel (liso-cel), systemic and/or radiation therapy as bridging therapy was allowed and given to 59% of the patients[3]
- Across all product types, bridging therapy is used in real-world settings among patients with R/R LBCL treated with CAR T-cell therapy
  - Use of bridging therapy is at the discretion of treating physicians

OBJECTIVE

- To conduct a systematic literature review to understand the patterns of bridging therapy use in real-world settings and to investigate its association with effectiveness and safety outcomes following CAR T-cell therapy among patients with R/R LBCL

METHODS

Figure 1. Study Design

Systematic Literature Review Study Design

- EMBASE, MEDLINE, and 14 conferences[a] through April 1, 2022, were searched for real-world observational studies

Assessments and Endpoints of Interest

- **Baseline**: patient demographics, disease characteristics, and bridging therapy use
- **Effectiveness**: ORR, PR, CR, PFS, and OS
- **Safety**: CRS and neurotoxicity (including ICANS)

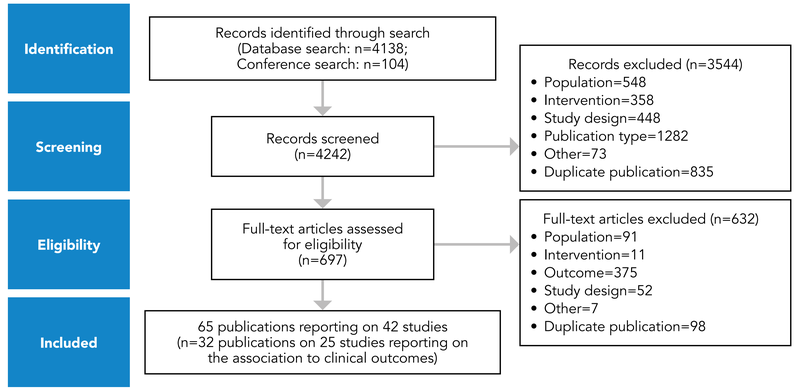
Meta-analysis

- Weighted means were calculated through both fixed- and random-effects meta-analyses
- Associations with outcomes were based on results available from the systematic literature review and were evaluated by adjusted and unadjusted treatment effects separately

[a] Included were conferences of the following organizations: American Society of Clinical Oncology (ASCO), American Society of Gene & Cell Therapy (ASGCT), American Society of Hematology (ASH), British Society for Haematology (BSH), European Society for Blood and Marrow Transplantation (EBMT), European Hematology Association (EHA), EBMT-EHA (CAR T-cell Meeting), European Organization for Research and Treatment of Cancer (EORTC), International Conference on Malignant Lymphoma (ICML), International Society for Pharmacoepidemiology (ISPE), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Society of Immunotherapy of Cancer (SITC), and Transplantation and Cellular Therapy (TCT).
CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

RESULTS

Figure 2. Systematic Literature Review Attrition Flow Diagram



- In total, the search identified 4242 citations (**Figure 2**)
- Of the 65 publications included within the evidence base, 32 publications on 25 studies reported on the associations between bridging therapy and clinical outcomes
  - No real-world study on liso-cel was found at the time of the search

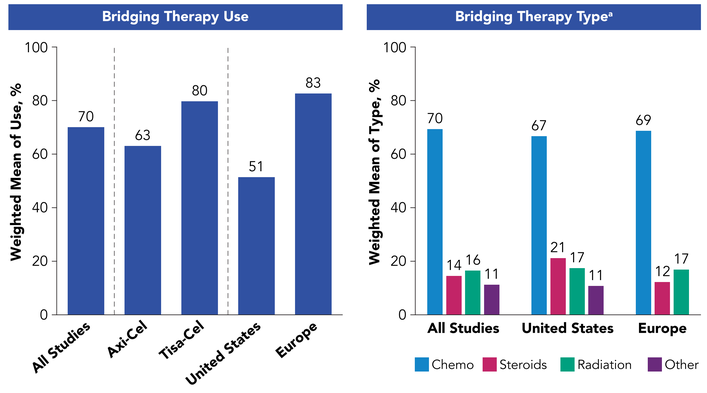
Table 1. Baseline Characteristics of Axi-Cel and Tisa-Cel Recipients

	Axi-Cel		Tisa-Cel		
	N Studies	Estimate (95% CI)	N Studies	Estimate (95% CI)	*P* Value[a]
Median age, y	**25**	**59.5 (58.3-60.6)**	**6**	**62.6 (60.6-64.6)**	**<.01**
Male sex	23	65% (62-67)	6	64% (60-67)	.61
DLBCL	19	73% (67-78)	6	78% (66-86)	.41
PMBCL	**16**	**6% (5-8)**	**4**	**1% (0-3)**	**<.01**
tFL	17	18% (14-22)	6	15% (10-22)	.42
Double-/triple-hit	11	18% (15-21)	2	15% (11-21)	.39
Stage III or IV	16	77% (73-80)	5	75% (71-78)	.43
IPI ≥3	**11**	**51% (47-54)**	**3**	**41% (33-49)**	**.03**
ECOG PS ≥2	17	10% (7-14)	7	11% (5-21)	.79
Bulky disease	**10**	**24% (21-27)**	**5**	**16% (13-21)**	**<.01**
Refractory disease	8	47% (31-64)	4	57% (31-80)	.50
Median prior lines	14	3.2 (2.8-3.7)	2	3.0 (2.0-5.0)	.80
No. of prior lines ≥4	13	66% (57-74)	4	66% (47-81)	1.00
Prior ASCT	16	29% (23-35)	5	27% (20-35)	.67
Mean vein-to-vein time, d	**8**	**31.1**	**3**	**47.8**	**N/A[b]**

[a] *P* values were calculated by two-sample Z test. [b] Comparison for vein-to-vein time was not conducted; results are descriptive only.
ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; d, day; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; N/A, not available; PMBCL, primary mediastinal large B-cell lymphoma; tFL, transformed follicular lymphoma; tisa-cel, tisagenlecleucel; y, year.

- Baseline characteristics among axi-cel and tisa-cel recipients were generally comparable (**Table 1**)
- Axi-cel recipients were younger compared with tisa-cel recipients and had significantly higher proportions of patients with International Prognostic Index score ≥3 and with bulky disease
- Mean reported vein-to-vein time (ie, time from leukapheresis to infusion) was 31 days for axi-cel versus 48 days for tisa-cel
  - The difference in average reported vein-to-vein times between axi-cel and tisa-cel was more pronounced in the United States (28 days vs 44 days, respectively) than in Europe (40 days vs 49 days, respectively)

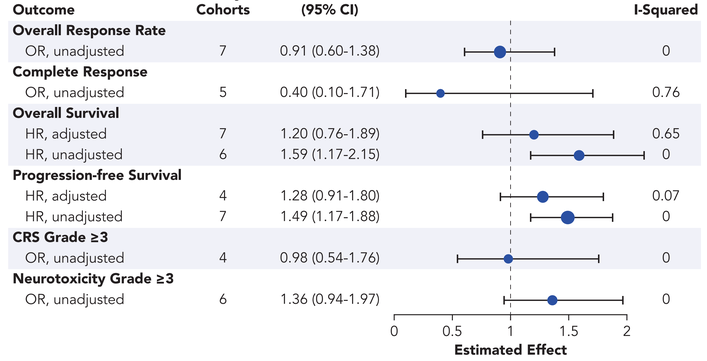
Figure 3. Patterns of Bridging Therapy Overall, by Products and by Regions



[a] Percentages are based on the proportion of patients receiving bridging therapy as the denominator.
Axi-Cel, axicabtagene ciloleucel; chemo, chemotherapy/chemoimmunotherapy; tisa-cel, tisagenlecleucel.

- On average, 63% of axi-cel patients received bridging therapy compared with 80% of tisa-cel patients (**Figure 3**)
- Use of bridging therapy was more common in Europe (83%) than in the United States (51%)
- Among patients who received bridging therapy, the most common type was chemotherapy/chemoimmunotherapy (70% overall; 62% for axi-cel; 88% for tisa-cel), followed by steroids in the United States (21%), or radiation therapy in Europe (17%)

Figure 4. Associations Between Use of Bridging Therapy and Clinical Outcomes[a]



[a] Associations were assessed through I^2 statistic.[4]
CRS, cytokine release syndrome; HR, hazard ratio; OR, odds ratio.

- Meta-analyses on adjusted results did not show sufficient evidence to indicate an association between use of bridging therapy and overall survival (hazard ratio [HR], 1.20; 95% CI, 0.76-1.89) or progression-free survival (HR, 1.28; 95% CI, 0.91-1.80; **Figure 4**)
- Limited to unadjusted results only, no significant associations were found between use of bridging therapy and overall response rate, complete response rate, Grade ≥3 cytokine release syndrome, or Grade ≥3 neurotoxicity

CONCLUSIONS AND LIMITATIONS

- These findings provide a comprehensive picture of patterns of bridging therapy use in real-world settings
- Notably, bridging therapy was more frequently used in Europe versus the US and among patients who received tisa-cel versus axi-cel
  - Despite the more frequent use of bridging therapy with tisa-cel, patients who received tisa-cel did not appear to have more severe disease
  - Vein-to-vein time for axi-cel recipients appeared to be shorter compared with tisa-cel recipients
- Though response to bridging therapy is a key consideration for treating physicians, it has not been well documented in real-world settings
- In this analysis, no associations between bridging therapy and effectiveness or safety outcomes following CAR T-cell therapy were observed
  - The lack of adjusted analyses limit the conclusions that can be drawn on the association between bridging therapy and clinical outcomes
- Prospective studies evaluating the value of integrating bridging therapy, including response to bridging, with CAR T-cell therapy are warranted

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DISCLOSURES

Full author disclosures are available through the Quick Response (QR) code.

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