Poster
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Axicabtagene Ciloleucel Vein-to-vein Time in Trial or Real-world Settings vs Other CAR T-cell Therapies for Relapsed/Refractory Large B-cell Lymphoma: a Systematic Literature Review and Meta-analysis

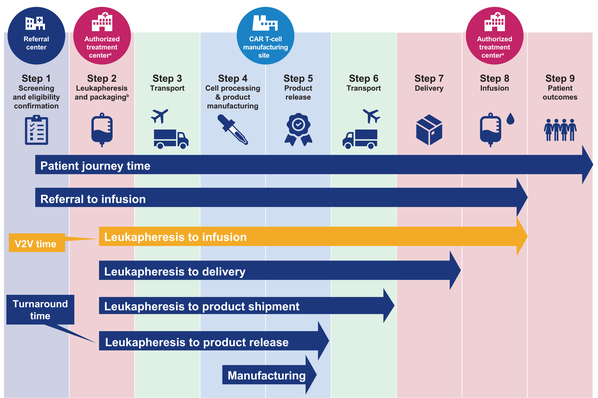
Frederick Locke, MD[1]; Michael T. Hemmer, MS[2]; Steve Kanters, PhD, MSc[3]; Michael J. Zoratti, PhD[3]; Zhen-Huan Hu, MPH[2]; Harry Miao, MD, PhD[2]; Shilpa Shahani, MD[2]; Clare Spooner, MBBS, BSc[2]; Christine Fu, PhD[2]; Anik Patel, PhD[2]; Hairong Xu, MD, PhD[2]; Marcelo C. Pasquini, MD, MS[4]

[1]Moffit Cancer Center, Tampa, FL, USA; [2]Kite, a Gilead Company, Santa Monica, CA, USA; [3]RainCity Analytics, Vancouver, BC, Canada; [4]Center for International Blood and Marrow Transplant Research (CIBMTR), Milwaukee, WI, USA

BACKGROUND

- Autologous chimeric antigen receptor (CAR) T-cell products are manufactured using cells from individual patients, leading to variable time between leukapheresis and infusion, or vein-to-vein time (V2Vt)[1–4]
  - V2Vt consists of subintervals, including time for transportation, manufacturing, and quality release (**Figure 1**)[4]
- An analysis of the JULIET trial estimated that reducing wait times from enrollment to infusion was associated with increased tisagenlecleucel (tisa-cel) efficacy in patients with diffuse large B-cell lymphoma (LBCL)[5]
- A retrospective, real-world study using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry found that shorter V2Vt was associated with improved overall survival (OS) in patients with relapsed or refractory (r/r) LBCL treated with axicabtagene ciloleucel (axi-cel)[4]
  - Patients with V2Vt ≥40 days had worse OS than patients with V2Vt <28 days (hazard ratio [HR]: 1.33; 95% confidence interval [CI]: 1.05–1.70; n=153 versus n=697) or patients with V2Vt ≥28 days to ≤40 days (HR: 1.36; 95% CI: 1.06–1.74; n=153 versus n=533)
- In recent studies that reported V2Vt in patients with r/r LBCL, axi-cel had a shorter median V2Vt compared with other CAR T-cell products[6–9]
  - Axi-cel: 28 days[6]
  - Tisa-cel: 45 days[6]
  - Lisocabtagene maraleucel (liso-cel): 36–37 days[7–9]

Figure 1. Overview of the Patient Journey With CAR T-cell Therapy[4]



[a]Authorized treatment centers are also referred to as qualified treatment centers. [b]Tisa-cel leukapheresis products are frozen prior to transport to the manufacturing facility.[10,11]
CAR, chimeric antigen receptor; tisa-cel, tisagenlecleucel; V2V, vein-to-vein.

OBJECTIVES

- To describe V2Vt and V2Vt subintervals and identify differences in patients with r/r LBCL treated with axi-cel, tisa-cel, or liso-cel
  - Including assessment of differences by geography and study design

METHODS

SCOPE OF SYSTEMATIC LITERATURE REVIEW (SLR)

- Systematic searches of MEDLINE, Embase, and CENTRAL conducted on October 5, 2022 (**Figure 2**)
  - MEDLINE searched up to October 4, 2022
  - Embase searched up to October 4, 2022
  - CENTRAL searched up to August 2022
- Search strategy was sensitive (included both specific and general terminology for diagnoses and interventions of interest)
- Supplemented with manual searches (including ASH 2022 abstracts) and cross-referencing of SLR materials

ASH, American Society of Hematology; CENTRAL, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica database; MEDLINE, Medical Literature Analysis and Retrieval System Online; SLR, systematic literature review.

METHODS *(Continued)*

Figure 2. Study Design

Study Eligibility	Screening/Statistical Analysis

• Described V2Vt and V2Vt subintervals in adult patients with r/r LBCL
  • ≥10 patients per study
  • ≥1 prior line of therapy before treatment with axi-cel, tisa-cel, or liso-cel
• Studies with pooled estimates for different interventions were excluded (analyses were run separately by axi-cel, tisa-cel, or liso-cel)
• Clinical trial or observational study designs (prospective and retrospective studies)
• Studies that presented clinical outcomes only, without at least V2Vt or 1 V2Vt subinterval, were not included
	• Screening (title/abstract and full-text level) and data extraction
	  • Independently and in duplicate by 2 reviewers
	• Study mapping was completed prior to data extraction
	• For each V2Vt subinterval in a study, the definition/description was collected along with the sample size, median, Q1/Q3, and range (as available)
	• Meta-analysis used noncomparative and treatment-specific median estimates for each V2Vt subinterval, which were pooled using a "median of medians" approach described by McGrath et al (2019)[12]
	  • Conducted in R (v4.2.1; r-project.org) using the metamedian package[13]

Primary outcome:
- V2Vt and V2Vt subintervals for axi-cel, tisa-cel, and liso-cel
  - Subintervals included leukapheresis-to-delivery, leukapheresis-to-product release, and leukapheresis-to-start of lymphodepleting chemotherapy

Axi-cel, axicabtagene ciloleucel; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; Q1, quartile 1; Q3, quartile 3; r/r, relapsed/refractory; tisa-cel, tisagenlecleucel; V2Vt, vein-to-vein time.

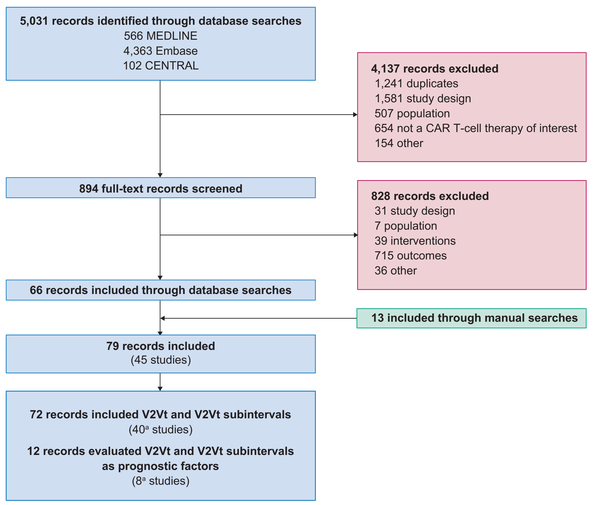
RESULTS

STUDY SELECTION

- SLR search identified 5,031 records, of which 894 were evaluated at full-text level and 66 met eligibility criteria (**Figure 3**)
  - Manual searches identified 13 additional publications
  - 79 publications were included, describing results from 45 studies
  - 40 studies reported V2Vt and V2Vt subintervals[a]
    - 29 observational (retrospective, n=20; prospective, n=9)
    - 11 clinical trials (single arm, n=8; randomized, n=3)
    - Included studies with patients treated with axi-cel (n=30),[b] tisa-cel (n=13),[b] and liso-cel (n=4)
  - 8 studies evaluated V2Vt and V2Vt subintervals as prognostic factors[a]

[a]3 studies reported V2Vt and V2Vt subintervals and evaluated V2Vt and V2Vt subintervals as prognostic factors. [b]7 studies reported on patients treated with axi-cel or tisa-cel.

Figure 3. Study Selection Process



[a]3 studies reported V2Vt and V2Vt subintervals and evaluated V2Vt and V2Vt subintervals as prognostic factors.
CAR, chimeric antigen receptor; CENTRAL, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica database; MEDLINE, Medical Literature Analysis and Retrieval System Online; V2Vt, vein-to-vein time.

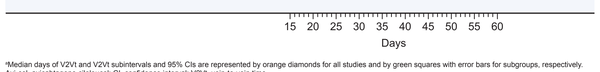
RESULTS *(Continued)*

META-ANALYSIS

- Overall, axi-cel had the shortest median V2Vt when compared with tisa-cel or liso-cel, irrespective of geography (United States versus Europe) or study design (clinical trials versus observational studies) (**Figures 4–6**)
  - **Overall median V2Vt:** 30.4 days (axi-cel) versus 48.4 days (tisa-cel) or 35.9 days (liso-cel)
  - **Clinical trials:** 25.5 days (axi-cel) versus 52.0 days (tisa-cel) or 35.9 days (liso-cel)
  - **Observational studies:** 30.9 days (axi-cel) versus 48.0 days (tisa-cel)
  - **United States only:** 27.0 days (axi-cel) versus 42.7 days (tisa-cel) or 35.8 days (liso-cel)
  - **Europe only:** 37.9 days (axi-cel) versus 50.5 days (tisa-cel)

Figure 4. Meta-analysis Results for V2Vt and V2Vt Subintervals for Axi-cel[a]

V2Vt and V2Vt subintervals and subgroups	Number of studies/ Number of patients	Median days (95% CI)	Median days (95% CI)
Leukapheresis-to-infusion (V2Vt)			
Overall	**22/3,293**		**30.4 (28.2–32.7)**
Study design			
Clinical trials	2/124		25.5 (19.7–31.4)
Observational studies	20/3,169		30.9 (28.6–33.2)
Geography			
United States only	12/2,479		27.0 (26.8–27.3)
Europe only	7/663		37.9 (36.1–39.6)
Leukapheresis-to-delivery			
Overall	**3/157**		**20.4 (14.6–26.2)**
Study design			
Clinical trials	3/157		20.4 (14.6–26.2)
Observational studies	–		–
Geography			
United States only	–		–
Europe only	–		–
Leukapheresis-to-start of lymphodepleting chemotherapy			
Overall	**3/314**		**21.3 (20.1–22.5)**
Study design			
Clinical trials	–		–
Observational studies	3/314		21.3 (20.1–22.5)
Geography			
United States only	3/314		21.3 (20.1–22.5)
Europe only	–		–

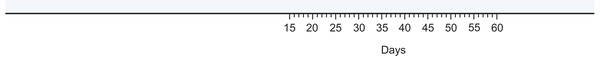


[a]Median days of V2Vt and V2Vt subintervals and 95% CIs are represented by orange diamonds for all studies and by green squares with error bars for subgroups, respectively.
Axi-cel, axicabtagene ciloleucel; CI, confidence interval; V2Vt, vein-to-vein time.

- 1 clinical trial in patients who received axi-cel reported a median of 13.0 days for the leukapheresis-to-product release interval (not presented here because the study did not report a 95% CI; **Figure 4**)

Figure 5. Meta-analysis Results for V2Vt for Tisa-cel[a]

V2Vt and subgroups	Number of studies/ Number of patients	Median days (95% CI)	Median days (95% CI)
Leukapheresis-to-infusion (V2Vt)			
Overall	**10/911**		**48.4 (42.9–52.9)**
Study design			
Clinical trials	1/155		52.0 (48.1–55.9)
Observational studies	9/756		48.0 (41.9–54.1)
Geography			
United States only	2/115		42.7 (37.8–47.6)
Europe only	4/429		50.5 (48.0–52.9)

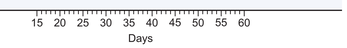


[a]Median days of V2Vt and 95% CIs are represented by orange diamonds for all studies and by green squares with error bars for subgroups, respectively.
CI, confidence interval; tisa-cel, tisagenlecleucel; V2Vt, vein-to-vein time.

- Patients who received liso-cel were only enrolled in clinical trials located at study sites in the United States (**Figure 6**)

Figure 6. Meta-analysis Results for V2Vt and V2Vt Subintervals for Liso-cel[a]

V2Vt and V2Vt subintervals and subgroups	Number of studies/ Number of patients	Median days (95% CI)	Median days (95% CI)
Leukapheresis-to-infusion (V2Vt)			
Overall	**3/419**		**35.9 (34.8–37.0)**
Study design			
Clinical trials	3/419		35.9 (34.8–37.0)
Observational studies	–		–
Geography			
United States only	2/330		35.8 (34.0–37.7)
Europe only	–		–
Leukapheresis-to-product release			
Overall	**4/443**		**24.4 (23.4–25.5)**
Study design			
Clinical trials	4/443		24.4 (23.4–25.5)
Observational studies	–		–
Geography			
United States only	3/399		23.7 (23.1–24.4)
Europe only	–		–



[a]Median days of V2Vt and V2Vt subintervals and 95% CIs are represented by orange diamonds for all studies and by green squares with error bars for subgroups, respectively.

EVALUATION OF V2Vt AS A PROGNOSTIC FACTOR

- Prognostic value of V2Vt for clinical outcomes with CAR T-cell therapy was evaluated in 8 studies, but parameterization of the data did not allow for meta-analyses
  - Most studies analyzed V2Vt and V2Vt subintervals as continuous variables instead of categorical variables
  - 1 of the 8 studies used an adjusted analysis method and treated V2Vt as a categorical variable[4]
    - This study found a statistically significant association between longer V2Vt and worse OS in patients treated with axi-cel

LIMITATIONS

- No real-world data from observational studies of patients treated with liso-cel were available at the time of review (meta-analysis of liso-cel V2Vt by study design was not performed)
- The scope of the SLR and meta-analysis did not address other potential factors impacting V2Vt, including bridging therapies and management of adverse events, or account for potential further improvements in V2Vt in the post-marketing setting
- Only a small number of eligible studies analyzed the association of V2Vt with efficacy and other clinical outcomes (did not allow for meta-analyses)
- While these results herein reflect consistently defined time intervals, V2Vt and V2Vt subintervals were not consistently defined across all studies initially evaluated

CONCLUSIONS

- Patients treated with axi-cel consistently had the shortest V2Vt compared with other products in clinical trial or real-world settings in patients with r/r LBCL
- V2Vt was shorter in the United States compared with Europe for patients treated with axi-cel or tisa-cel
- Further evaluation of the factors impacting V2Vt, and their association with efficacy/effectiveness and other clinical outcomes, is warranted

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DISCLOSURES

For author disclosures, please scan the QR code.

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FULL AUTHOR DISCLOSURES

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