HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Letter
Open Access

Real-world Experience of Approved Chimeric Antigen Receptor T-cell Therapies Compared to Clinical Trials Data

Jérôme Lambert[1,2,3], Roberta Di Blasi[4], Florence Rabian[3,5,6], Marie-Emilie Dourthe[7], André Baruchel[3,6,7], Catherine Thiéblemont[3,4,8], Nicolas Boissel[3,5,6], Vincent Levy[2,9], Marie-Quitterie Picat[1], Sylvie Chevret[1,2,3]

Correspondence: Sylvie Chevret (sylvie.chevret@u-paris.fr).

Advances in hemato-oncology have led to the development of chimeric antigen receptor (CAR) T cells therapies that obtained marketing authorization in Europe to treat hematological diseases in 2018 following the same 2017 decisions by the FDA: Kymriah (tisagenlecleucel, tisa-cel, Novartis Laboratory) and Yescarta (axicabtagene ciloleucel, axi-cel, Gilead). The FDA indication for tisa-cel is as follows: children and young adults up to 25 years of age, with refractory B-cell acute lymphoblastic leukemia (ALL) or relapse after transplant or after the second relapse, and adults with aggressive large B-cell lymphomas, relapsed or refractory after the second or more line of systemic therapy. Indications for axi-cel include adults with relapsed/refractory aggressive large B-cell lymphomas after a second or greater line of systemic therapy. These authorizations followed the report of favorable results across noncomparative phase II pivotal clinical trials with limited follow-up, namely, ZUMA-1 for axi-cel[1] and the ELIANA[2] and JULIET[3] trials for tisa-cel. Such noncomparative designs for marketing authorization are consistent with increasing approvals based on limited evidence.[4] Therefore, we hypothesized that population and CAR-T-cells effects based on real-world data (RWD) could differ from those observed in such single-arm clinical trials.

We thus aimed to compare the characteristics and outcomes of the patient population being treated in the commercial setting to those of published data from the pivotal trials.

[1]Biostatistic Department, Saint Louis Hospital (APHP), Paris, France
[2]ECSTRRA Team, UMR1153, Inserm, Université Paris Cité, Paris, France
[3]Paris Cité University, Paris, France
[4]Hemato-oncology Department, Saint Louis Hospital (APHP), Paris, France
[5]Unité d'Hématologie Adolescents et Jeunes Adultes, AP-HP, Hôpital Saint Louis, Paris, France
[6]URP-3518, Institut de Recherche Saint-Louis, Université Paris Cité, Paris, France
[7]Department of Pediatric Hematology and Immunology, AP-HP, Hôpital Universitaire Robert Debré, Paris, France
[8]Université Paris Cité, NF-kappaB, Différenciation et Cancer, Paris, France
[9]Centre d'investigations cliniques, Hôpital Avicenne, Bobigny, France

HemaSphere (2023) 7:6(e873).
http://dx.doi.org/10.1097/HS9.0000000000000873.
Received: September 22, 2022 / Accepted: March 8, 2023

In the present analysis, we used RWD from our centers collected in a national registry (DESCAR-T) approved by the French Health Authorities to collect detailed information for CAR-T cells in real life from July 2018, and supported by four academic cooperative groups on lymphoma, ALL and multiple myeloma.[5] In addition to data from the phase 2 uncontrolled trials that were the basis of the marketing authorizations, we also selected the experimental arm from one further RCT (BELINDA)[6] given that its target population was similar to that of the pivotal JULIET trial.

To compare the outcome of both the trial and RWD populations, we used a new approach, the matching-adjusted indirect comparison (MAIC)[7] to balance groups and thus reduce potential "confounding by indication" bias.[8] Its principle is to reweight the individual patient data (IPD) (in this case, patients from real life), such that their mean characteristics that may affect the outcome (prognostic variables) or treatment effect (effect modifiers) are balanced with those of the patients enrolled in the trials, as described in the published data.[9] Applying these weights allows the IPD to exactly match the mean of all the characteristics of the aggregated trial group. In this way, confounding biases are removed, and the patient outcomes can be roughly compared across the groups in the weighted sample. Thus, after weighting the DESCAR-T population, it has become close to the trial population, so the differences in outcomes can be attributed to the RWD versus the trial setting.

Two main outcomes were assessed, overall survival (OS) and event-free survival (EFS), both measured from the date of reinfusion of CAR-T cells. Events of interest were progression, relapse or death, whichever occurred first. Data were exported on October 13, 2021.

A search for potential confounders and effect modifiers was first performed using expert opinion (A.B., N.B., C.T.) and the literature,[10] with a standardized form derived to record information from published data and IPD. To assess the imbalances between treatment groups, the standardized mean difference was computed.[11] We computed weights for the RWD to match the trial means of all the predictors available for both datasets. The effective sample size (ESS) was computed as a measure of information provided by the weighted dataset. A small ESS, relative to the original sample size, is an indication that the weights are highly variable and that the estimate may be unstable. Survival trial data were obtained by digitizing reported overall survival Kaplan–Meier curves.[12] Then, on the pooled individual reconstructed survival data and weighted IPD, a weighted Cox model was fitted to compare the group outcomes. Analysis was performed in R 4.1.1 (https://www.R-project.org/).

On October 13, 2021, 239 patients from our sites were scheduled to receive CAR-T cells, among whom 222 were treated according to marketing authorization outside any research protocol and underwent leukapheresis. We selected 207 patients who received either tisa-cel or axi-cel. There were two main clinically relevant findings.

First, the real-life driving conditions differed from the trial conditions (Table 1). Interestingly, in adult patients with lymphoma being treated with tisa-cel in the commercial setting, the differences (regarding age, ECOG) between groups were erased from JULIET to BELINDA. Patients treated with axi-cel in real life compared to patients treated with axi-cel in ZUMA-1 mostly differed in terms of previous lines of therapy. In contrast, there were more differences across RWD and trial data regarding children with ALL who received tisa-cel (in age, previous treatment lines, and HSCT). As expected, the reweighted baseline characteristics for the intervention-treated patients matched those aggregate characteristics from the comparator trial. As expected, the ESS of the weighted RWD decreased, notably in the ALL population: this illustrates that the CAR-T cells for ALL have been administered mostly to young adults rather than children and that fewer patients had a history of HSCT, compared to the trial population.

The second main clinically relevant finding was the external validation of the trial results by comparing patient outcomes once differences across populations had been erased. Indeed, most of our comparisons suggested that outcomes from RWD, once the population had been balanced with that of the previous trial, were consistent with those published from the trial. No difference in outcomes was observed across the RWD and trial populations of patients with lymphoma treated with axi-cel. Unexpectedly, outcomes of patients with lymphoma treated with tisa-cel in real life appeared somewhat improved, even significantly when compared to the BELINDA trial, both for OS and EFS (Figure 1).

In this study, we aimed to assess whether the effects of CAR-T cells in real life coincide with those from clinical trials using a new approach, the MAIC. This approach is increasingly but generally employed to compare one drug to another. It was notably used to compare tisa-cel (JULIET) to axi-cel (ZUMA-1)[13] and, more recently, to liso-cel,[9] and it allows to erase baseline differences across populations to avoid biased findings.

Indeed, by matching the mean characteristics of the trial populations, unbiased estimates can be reached unless all factors that impact either the outcome or the treatment effect are not captured. Notably, we could not take into account the potential differences in the unreported information from either the registry or the trial publications. Similarly, differences in the definition of events for EFS in RWD and trial data cannot be handled by those methods. Additionally, we could not analyze the whole population screened for CAR-T-cells administration, given that the published survival curves from the trial only dealt with treated patients. All these points stress the need for detailed reporting of detailed information (potential confounders and treatment modifiers, EFS components,

Table 1

Aggressive Large B-cell Lymphoma and Acute Lymphoblastic Leukemia: Comparison of RWD and Trial Data Before Weighting

CAR-T Cells	Tisagenlecleucel								Axi-cel		
	Lymphoma					Acute Lymphoblastic Leukemia			Lymphoma		
Data Source	RWD	JULIET	SMD	BELINDA	SMD	RWD	ELIANA	SMD	RWD	ZUMA-1	SMD
	73 patients	111 patients		162 patients		57 patients	75 patients		77 patients	101 patients	
Mean age, y (range)	65 (21–77)	56 (22–76)	**0.66**	59.5 (19–79)	**0.37**	15 (1–27)	11 (3–23)	0.08	59 (23–75)	58 (23–76)	0.08
DLBCL	63%	79%	**0.36**	62%	0.02				76%	79%	0.07
ECOG 0	42%	55%	**0.26**						46%	42%	0.08
Ann Arbor III- IV	68%	76%	**0.18**	66%	0.04				60%	85%	**0.59**
IPI ≥ 2	90%			65%	**0.58**				82%		
≥ 3 lines	53%	52%	0.02			12%	50%	**1.89**	18%	69%	**1.18**
Allograft						49%	61%	**0.49**			
Blinatumomab						33%	0%	**2.27**			

Values above 0.1 indicating imbalances are bolded.

DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group Performance Scale; RWD = real-world data; SMD = standardized mean difference.

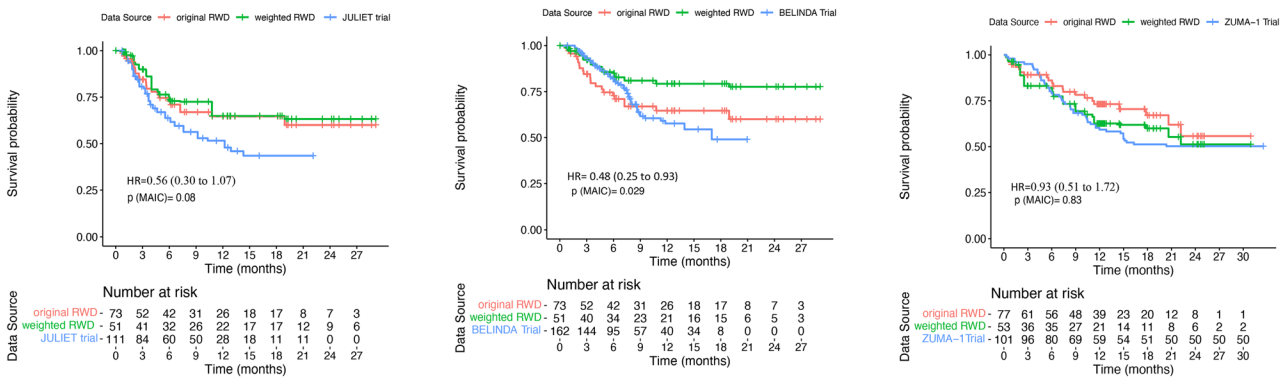

Figure 1. Comparison of survival data in patients with aggressive large B-cell lymphomas from real-life patients compared with the trial population, following Kymriah (JULIET and BELINDA) or Yescarta (ZUMA-1).

intent-to-treat population) when trial results are originally published.

In addition to the exploratory nature of our findings, one may wonder whether the improved outcomes of patients with lymphoma treated with tisa-cel in real life compared to the trial setting may rely on the source of the RWD data. Indeed, the RWD referred to well-known specialized centers compared to the multicentre BELINDA trial that included 65 centers from 18 countries.[14] This may point out the importance of center experience and specialization in the care of frail patients before and after CAR-T-cells treatment.

Finally, we believe that the secondary use of widely available health data, including trial data, should be promoted, which begins by encouraging secure and facilitated access to those data by researchers worldwide. To provide reliable evidence on the use, safety, and effectiveness of medicines for human use from RWD across the European Union, the creation of the "Data Analysis and Real-World Interrogation Network" (DARWIN EU) by the European Medicine Agency is promising.

ACKNOWLEDGMENTS

The authors thank Florence Broussais and all the DESCAR-T registry members for providing access to the registry data, and Ms. Hapsa Sall for technical support.

AUTHOR CONTRIBUTIONS

JL, M-QP, and SC designed the study. S.C. analyzed the results and made the figures; RDB, FR, MED, AB, CT, and NB, contributed to data collection. VL and JL contributed to study formulation/design and manuscript preparation; and all other authors made substantial contributions to all aspects of the preparation of this manuscript and approved the final version of the manuscript.

DISCLOSURES

RDB is an advisory board member and received honoraria from Gilead Sciences, Novartis; FR received honoraria from Gilead and Novartis; CT received honoraria from Roche, Amgen, Janssen, Celgene, Gilead Science/Kite; and Beigene; holds a consulting/advisory role in Roche, Gilead Sciences, Janssen, Celgene, Novartis, and Beigene; and received research funding and travel, accommodations, and funds from Roche, Novartis; NB is on the consultancy and advisory board for Amgen, Ariad-Incyte, Bristol-Myers Squibb, Celgene, Jazz Pharma, Novartis, Pfizer, Sanofi, Servier, and Shire, and received research funding from Amgen, Bristol-Myers Squibb, Novartis, and Jazz Pharma; AB is on the advisory role board and received funds for for symposia and travels from Novartis, Servier, Celgene, Jazz, Janssen, Sanofi, Amgen, and Astra-Zeneca, and research funding from Shire/Servier; VL received honoraria from Gilead, Janssen, Abbvie, and Astra.

SOURCES OF FUNDING

The authors declare no sources of funding.

REFERENCES

1. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol*. 2019;20:31–42.
2. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–448.
3. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2021;22:1403–1415.
4. Naci H, Davis C, Savović J, et al. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014-16: cross sectional analysis [Published online September 18, 2019]. *BMJ*. 2019;366:l5221.
5. Broussais F, Bay JO, Boissel N, et al. DESCAR-T, le registre national des patients traités par CAR-T Cells. *Bull Cancer (Paris)*. 2021;108:S143–S154.
6. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386:640–654.
7. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *PharmacoEcon*. 2010;28:935–945.
8. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
9. Cartron G, Fox CP, Liu FF, et al. Matching-adjusted indirect treatment comparison of chimeric antigen receptor T-cell therapies for third-line or later treatment of relapsed or refractory large B-cell lymphoma: lisocabtagene maraleucel versus tisagenlecleucel. *Exp Hematol Oncol*. 2022;11:17.
10. Zhang X, Lu X, Yang J, et al. Efficacy and safety of anti-CD19 CAR T-cell therapy in 110 patients with B-cell acute lymphoblastic leukemia with high-risk features. *Blood Adv*. 2020;4:2325–2338.
11. Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res*. 2011;46:399–424.
12. Guyot P, Ades A, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12:9.
13. Oluwole OO, Jansen JP, Lin VW, et al. Comparing efficacy, safety, and preinfusion period of axicabtagene ciloleucel versus tisagenlecleucel in relapsed/refractory large B cell lymphoma. *Biol Blood Marrow Transplant*. 2020;26:1581–1588.
14. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. *N Engl J Med*. 2022;386:629–639.