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Systematic Literature Review to Identify Influencing Factors of Efficacy and Safety Outcomes of Chimeric Antigen Receptor T-Cell Therapies in Large B-Cell Lymphoma

Jan-Michel Heger[1], Jonas Jost[2], Sybille Riou[3], Stefan Walzer[2,4,5], Joerg Mahlich[3,6], Peter Borchmann, MD[7]

[1] Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[2] MArS Market Access & Pricing Strategy GmbH, Weil am Rhein, Germany
[3] Miltenyi Biomedicine, Bergisch Gladbach, Germany
[4] State University Baden-Wuerttemberg, Loerrach, Germany
[5] University of Applied Sciences Weingarten-Ravensburg, Weingarten, Germany
[6] DICE; Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
[7] University of Cologne, Koeln, Germany

Background:
The interpretation of clinical data involving chimeric antigen receptor T-cell therapies (CAR-T's) in Large B-Cell Lymphoma (LBCL) requires a thorough understanding of factors that influence efficacy and safety outcomes.

Materials & Methods:
To identify relevant influencing factors of efficacy and safety outcomes, we conducted a systematic literature review for CAR-T cell therapies. Articles were searched on PubMed from 06.2018 till 06.2023. Data for progression free survival (PFS), overall survival (OS), complete response (CR), objective response rate (ORR), duration of response (DOR), and safety (i.e. Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS], and Cytokine Release Syndrome [CRS]) were extracted in accordance with the PRISMA guidelines.

Results:
A total of 236 articles were identified and narrowed to 44 publications for full text screening. 13 articles were included in the final analysis. The main reasons for exclusion were other indications, missing data, and lack of significance.

Factors affecting OS that were identified in more than one publication were Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) ≥ 2, presence of bulky disease, and high lactate dehydrogenase (LDH) values. For PFS it was presence of bridging therapy before CAR-T infusion, and LDH values as well. Table 1 presents the full list of identified variables. For DOR no influencing factor was observed.

Influencing factors for safety outcomes are summarized in table 2. Evidence is less compelling here because all identified variables were supported by one publication only.

Conclusion:
This review provides a set of factors that influences efficacy and safety outcomes of CAR-T therapies in LBCL. It can be used to assess comparability of different treatment arms in randomized controlled studies or to make careful adjustments when performing indirect treatment comparisons in order to better understand the true value of innovative treatments.

Table 1: Efficacy outcomes

Author	Variable	PFS	OS	CR	ORR
Alarcon 2023, Bhaskar 2022, Rabinovich 2021, Beyar Katz 2023, Locke 2020	LDH (Pre-CAR-T LDH >ULN; LDH >400IU; LDH at lymphodepletion)	↓↓	↓↓	↓↓	
Di Rocco 2021	ECOG PS 1 (vs 0)		↓		
Bourbon 2023, Di Rocco 2021	ECOG PS ≥ 2		↓↓		
Alarcon 2023, Bhaskar 2022	Bulky disease (presence of any mass with a single diameter >10 cm)		↓↓		
Locke 2020, Sang 2020, Zhang 2022	Peak level of CAR (-T) cells			↑	↑↑
Bourbon 2023, Locke 2020	CRP, mg/mL (CRP > 30 mg/L; Baseline CRP)		↓	↓	
Alarcon 2023	Ann Arbor stage II-IV (vs I), UVA		↓		
Di Rocco 2021	Ann Arbor stage III-IV		↓		
Alarcon 2023	Age, years > 65 (vs ≤ 65)		↓		
Di Rocco 2021	Sex (M)		↑		
Di Rocco 2021	receiving >3 lines of therapy		↓		
Beyar Katz 2023	extra-nodal disease at lymphodepletion > 2	↓	↓		
Bhaskar 2022, Alarcon 2023	Bridging therapy	↓↓			
Bhaskar 2022	Peak ferritin>5000	↓	↓		
Bourbon 2023	Ferritin, µg/L, >1 000 (vs <1 000), UVA		↓		
Bourbon 2023	mHLA-DR D−7, Ab/c <13 500, UVA [HLA-DR expression on monocytes at day minus 7 (D−7)]	↓	↓		
Bourbon 2023	CAR T-cell type, Tisa-cel (vs axi-cel)	↓			
Liu 2021	high MTV (MTV ≥ 291 cm3)	↓	↓		
Liu 2021	PD-L1 expression: H-score of ≥10		↑		
Neelapu 2017	CAR T-cell expansion				↑
Penack 2023	severe cytopenia	↓			
Sang 2020	lower maximum standard uptake value (SUV max, g/ml) of CD4/CD8 ratio before and after infusion				↑

↑positive statistically significant association of variable on endpoint was observed. ↓ negative statistically significant association of variable on endpoint was observed. ↑ or ↓ One publication reported data. ↑↑ or ↓↓ > 1 publications reported data.

Table 2: Safety outcomes

Author	Variable	CRS	ICANS
Bourbon 2023	low mHLA-DR D−7, Ab/c after CAR T-cell infusion (from D7 to D14)		↑
Neelapu 2017	IL-15	↑	
Neelapu 2017	IL-2Rα	↑	
Neelapu 2017	IFNγ	↑	
Neelapu 2017	IL-10	↑	
Neelapu 2017	Granzyme B	↑	
Zhang 2022	CAR T-cell expansion (All patients with robust CAR T cell expansion reaching >500 CAR T cells in 1mL of blood developed CRS)	↑	
Zhang 2022	dose of infusion (the stronger the CAR T amplification was, the greater the probability of CRS, all patients with robust CAR T cell expansion reaching >500 CAR T cells in 1mL of blood developed CRS)	↑	
Zhang 2022	tumor burden	↑	
Bourbon 2023	low mHLA-DR D−7, Ab/c after CAR T-cell infusion (from D7 to D14)	↑	

↑ "positive" means either (1) that a specific biomarker was significantly associated with CRS of grade 3 or higher, or (2) that the variable was associated with higher rates of ICANS, or (3) the proportion of patients who had CRS was positively associated with the variable.

Figure 1

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