Systematic Review of Prognostic Factors for Efficacy and Safety Outcomes in CAR-T Cell Therapy for Diffuse Large B-Cell Lymphoma

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Authors: J. Jost[2], J. K. Schleifenbaum[1], J. M. Heger[1], U. Rosato[3], S. Riou[3], P. Borchmann[1], S. Walzer[2,4,5], J. Mahlich[3,6]

[1]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Medical Faculty and University Hospital Cologne, Cologne, Germany. [2]MArS Market Access & Pricing Strategy GmbH, Geffelbachstraße 6, 79576 Weil am Rhein. [3]Miltenyi Biomedicine, Friedrich-Ebert-Straße 68, 51429 Bergisch Gladbach, Germany. [4]State University Baden-Wuerttemberg, Hangstraße 46-50, 79539 Lörrach. [5]University of Applied Sciences Weingarten-Ravensburg, Doggenriedstraße 70, 88250 Weingarten, Germany. [6]DICE; Heinrich-Heine-University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany.

INTRODUCTION

Diffuse Large B-cell Lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype. While chemo-immunotherapy is the standard first-line treatment, CAR T-cell therapy has become an established option for relapsed or refractory patients.

Despite CAR-T therapy's effectiveness, over 50% of patients relapse. The factors predicting relapse are not well understood, necessitating novel prognostic models. Understanding these factors is crucial for optimizing treatment strategies, patient counseling, and improving clinical trial design in this rapidly evolving field.

OBJECTIVE

To systematically identify and evaluate prognostic factors influencing efficacy and safety outcomes of chimeric antigen receptor T-cell (CAR-T) therapies in diffuse large B-cell lymphoma (DLBCL) patients.

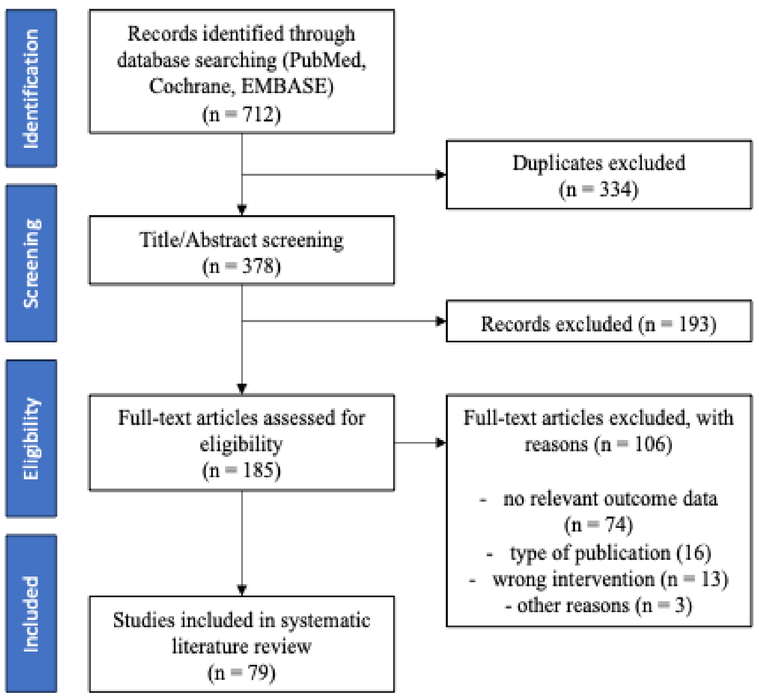
METHODS

A systematic literature review was conducted using PubMed, Cochrane, and EMBASE databases. Studies reporting on prognostic factors for overall survival (OS), progression-free survival (PFS), complete response rate (CRR), objective response rate (ORR), duration of response (DoR), best overall response (BOR), and safety outcomes (cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]) in DLBCL patients treated with CAR-T therapy were included. Data were extracted and analysed according to PRISMA guidelines.

RESULTS

From 712 articles, 79 met inclusion criteria. Key prognostic factors for efficacy included ECOG PS, LDH levels, IPI, disease histology, and Ann Arbor stage. High LDH, ECOG PS ≥2, and higher disease burden were associated with poorer outcomes. CAR-T expansion and persistence correlated with improved efficacy.

For safety, elevated interleukins, high ferritin, and high tumour burden were associated with increased CRS risk. Various blood markers, including ferritin and neurofilament light chain levels, were linked to higher ICANS risk.



Safety

Classification	Prognostic Factor Category	CRS	ICANS
Patient-Related	Age	-	1↑
	Gender male vs. female (binary endpoint)	1↑	1↑
	Clinical markers: Low Albumin, High Ferritin, High Fibrinogen, elevated bilirubin (> 1.5 g/dL), Granzyme B, Interleukins [IL-2Rα/IL-6/IL-10/IL-15], high PLT, higher Serum peak level ANG2/ANG1, higher Serum peak level, higher Serum peak level IFNγ, higher peak level of noradrenaline, higher Serum peak level TNFα, High NfL levels, High pre-lymphodepletion ctDNA, High CRP, Low PLT	8↑	6↑
	HCT-CI (0–2)	1↓	-
	CGA score (fit vs. unfit/frail)	1↑	-
	High ECOG PS	2↑	-
	Low mHLA-DR D14, Ab/c after CAR T-cell infusion	-	1↑
	High EASIX score	2↑	1↑
Disease Related	High LDH	3↑	3↑
	Maximum SUV	-	1↑
	IPI score (3-5), Tumor burden	2↑	1↑
	Imaging: Evidence of pleural effusions, Thoracic images with abnormal findings	1↑	-
	Extent of disease: Disease Sites, >1 Lesions	1↑	-
Adverse Event Related	Adverse event treatment: ≥ 2 doses of tocilizumab, G-CSF application, higher Serum peak level GM-CSF	3↑	-
	Atelectasis	1↑	-
	High CRS	-	1↑
Treatment before CAR-T cells	Number of treatment lines and prior autologous transplantation (for CRS grades 2-4)	2↓	1↑
	Bridging Therapy	1↑	-
CAR-T cell Response	C_{max}	2↑	-
CAR-T cell Product Related	CAR-T cell type Axi-cel vs. Tisa-cel	1↑	1↑
Legend	The figure next to the arrow (↓or ↑) means the number of publications identifying the prognostic factor.		
↑	"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 assocatiated with the variable.		
↓	"negative" means either (1) that a specific biomarker was significantly associated with lower grades of CRS (less than grade 3), or (2) that the variable was associated with lower rates of ICANS, or (3) the proportion of patients who had CRS was negatively associated with the variable.		

Acronyms: ANG: Angiopoietin; CGA: comprehensive geriatric assessment score; C_{max}: peak cell expansion; CRP: c-reactive protein; CRS: Cytokine release syndrome; ctDNA: circulating tumor DNA; EASIX: Endothelial Activation and Stress Index; ECOG PS: Eastern Cooperative Oncology Group Performance Score; G-CSF: Granulocyte colony stimulating factor; GM-CSF: granulocyte–macrophage colony-stimulating factor; HCT-CI: hematopoietic cell transplantation comorbidity index; ICANS: Immune-effector-cell-associated-neurotoxicity-syndrome; IFN: interferone; IPI: International Prognostic Index; LDH: Lactate Dehydrogenase; mHLA-DR: monocyte HLA-DR; NfL: Neurofilament light chain; PLT: platelets; SUV: standardized uptake values; TNF: Tumor necrosis factor.

Efficacy

Classification	Prognostic Factor Category	BOR	ORR	DoR	CRR	PFS	OS
Patient-Related	Age > 60 (CRR) / ≥65 (ORR, PFS) Age > 60 (OS)	-	1↑	-	1↑	1↑	2↓
	Demographics: Ethnicity African American vs. Caucasian, Male Gender	-	1↓	1↓	-	4↓[1]	4↓[1]
	ECOG status 1 vs 0 (BOR), ECOG PS ≥1 (PFS) / ≥2 (OS/DOR) + Charlson Comorbity index (CCI >5) eligibility for ZUMA-1, HCT-CI 3-7	1↓	2↓	1↓	-	10↓	13↓
	Glasgow prognostic score (1-2 vs. 0)	-	-	-	-	1↓	1↓
	Clinical markers: Inflammatory markers: Increased baseline ferritin, baseline IL-6, peak serum IL-10 and IL-15, IFN, elevated CRP. Hematological markers: low haemoglobin (<6 mmol/L), low haematocrit, low platelet (<150/nL), low absolute lymphocyte count at leukapheresis (ALCLeuk), low eosinophil, granulocytes 2 months after CAR-T cell infusion. Hepatic and metabolic markers: bilirubin (>1.5 g/dL), serum albumin, insufficient vitD	-	5↓	2↓	1↓	10↓[3]	16↓[4]
	LDH > ULN (ORR, CRR, PFS, OS) or baseline LDH (DoR)	-	3↓	1↓	2↓	22↓	19↓
	Comorbidities: Sarcopenia by skeletal muscle index, hepatic disease, heart valve disease, elevated liver enzymes, renal insufficiency (moderate/severe), pulmonary disease, comprehensive geriatric assessment score, (unfit/frail vs fit)	-	2↓	1↓	-	3↓	4↓
	Increased adipose tissue (abdominal, subcutaneous, visceral)	-	-	-	-	1↑	1↑
	Prognostic nutritional index <33.5	-	-	-	-	1↓	1↓
	mHLA-DR D−7 < 13,500 Antibodies per cell	-	-	-	-	1↓	1↓
Disease-Related	Histology: double/triple hit, immunophenotype, cMyc, high focal copy number alteration score, low immunoscore, low Immunosign 21, TP53 altered, PD-L1 expression on tumor cells	-	-	1↓	1↑	2↓	5↓
	Disease Characteristics at initial diagnosis: B-symptoms, bulky mass, no history of indolent lymphoma, IPI (incl. aaIPI >2), Ann Arbor Stage, Extranodal sites >1, higher MTV	-	-	1↓	-	19↓	18↓
	Refractoriness Status: primary refractory status, PIF, chemoresistance	-	1↓	1↓	1↓	3↓	5↓
	Pre-infusion profile: High tumor burden, size of tumor, diameter of the largest lesion, CR/PR status before infusion, necrosis, pre-LDC SPD, low ctDNA, STL, higher MTV	--	1↓	1↓	1↓	7↓	10↓
Adverse Event Related	Pulmonary complications, presence of AKI, hepatic diseaseGrade 3 ICANS or other neurotoxicities	--	--	--	--	1↓	2↓
	Short duration of cytopenia, severe cytopenia (anemia, leukopenia, lymphopenia, thrombocytopenia), thrombocytopenia (CTCAE grade 3-4 vs. 1-2)	--	1↓	--	--	2↓	--
	Grade 3 ICANS or other neurotoxicities	--	--	--	--	2↓	2↓
	Absence or lower grade of CRS (CRR, PFS), CRS <2 vs ≥2 (ORR) or grade 1-2 vs. 3-5 CRS (OS)	--	1↓	--	1↓	2↓	1↑
Treatment before CAR-T	Number of Prior treatment lines	-	2↓	-	-	5↓	2↓[7]
	Time from diagnosis (≥12 months), from last treatment (<91 days), or time to relapse (≥12 months) from initial diagnosis, short interval from apharesis/indication to CAR-T cell treatment	-	1↑	-	-	3↑	4↑
	Use and/or no response to BT, use of corticosteroids, G-CSF application	-	-	-	-	10↓	12↓
CAR-T Response	Number of CAR-T cells after infusion, high CAR-T cells level at D7, persistence at 6 months, CR/PR at D28, peak expansion, subjects given CD8+ 19-28z CAR T cells, subjects given fewer naive- like (CD45RA1CCR71) CD41, ΔTLG, ΔTMTV, ΔSUVmean, Peak CAR + PBMC/µL, Peak CAR -T cells <1 x 10 ^5 vs ≥ 1x 10^5	-	5↑	2↑	3↑	10↑[8]	5↑[9]
CAR-T Product Related	CAR-T cell type (Axi-cel vs. Tisa-cel)	-	1↑	-	-	6↑	3↑
	Cytotoxicity (low effector to target ratio)			-	-	1↓	-
Legend	The figure next to the arrow (↓or ↑) means the number of publications identifying the prognostic factor.						
↓	Negative association of variable on endpoint was observed. ”Negative" means that variable is associated with worse ORR/DOR/CR/PFS/OS/BOR.						
↑	Positive statistically significant association of variable on endpoint was observed. ”Positive" means that variable is associated with higher ORR/DOR/CR/PFS/OS/BOR. SAFETY endpoints: "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 assocatiated with the variable.						

Acronyms: aaIPI: age adjusted International Prognostic Index; AKI: acute kidney injury; ALC_{Leuk}: absolute lymphocyte count at leukapheresis; ASCT: autologous Stem cell transplantation; BT: Bridging therapy, CCI: Charlson Comorbity index; CR/PR: complete response/partial response; CRP: c-reactive protein; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: circulating tumor DNA; ECOG PS: Eastern Cooperative Oncology Group Performance Score; G-CSF: Granulocyte colony stimulating factor; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; HSCT: Hematopoietic Stem cell transplantation; ICANS: Immune-effector-cell-associated-neurotoxicity-syndrome; IFN: Interferon; IL: Interleukin; IPI: International Prognostic Index; LDH: Lactate Dehydrogenase; LDC: leukocyte differential count; mHLA-DR: monocyte expression of human leukocyte antigen; MTV: Metabolic Tumor Volume; PIF: Primary Induction Failure; SCT: Stem cell transplantation; SPD: sum of the product of perpendicular diameters; STL: Sum of Target Lesions; SUVmean: mean standardized uptake value; TLG: total lesion glycolysis; TMTV: total metabolic tumor volume; ULN: upper limit of normal; vitD: Vitamin D.

Footnotes: [1] Among 5 publications, one raised positive impact with male sex. [3] 1 Publication found that CRP ≤30 mg/mL is a negative prognosis factor, in contradiction to other authors. 1 Publication identified a positive association of low haematocrit for PFS. [4] 1 Publication identified a positive association of low haematocrit for OS. [5] Absence of prior SCT is associated with positive impact in 2 articles, but also with negative impact in 2 articles. [6] Absence of prior SCT is associated with positive impact in one article and with negative impact in another. [7] A third article found positive impact due to prior treatment line. [8] Among 10 publications, only one had negative impact due to CAR-T treatment. [9] Among the 6 publications, only one had negative impact due to CAR-T treatment

CONCLUSION

This review identified six categories of prognostic factors for CD19 CAR-T therapy in DLBCL. Established predictors such as LDH, tumor burden, ECOG/IPI and adverse histology consistently correlate with inferior PFS and OS and confirm the robustness of our search. More recent evidence highlights additional influences: age shows variable impact, with some studies reporting comparable or even better outcomes in older patients, while others note higher progression risk and treatment-related mortality. The need for and refractoriness to bridging therapy predicts poorer survival, whereas early metabolic response on PET-CT and favorable CAR-T kinetics strongly indicate improved outcomes. Inflammatory and endothelial stress markers such as CRP, IL-6 and EASIX scores are associated with toxicity and worse survival. Together, these findings suggest that beyond established clinical risk factors, emerging predictors may refine patient selection and guide individualized prognostic assessment.

Jonas Jost
jonas.jost@marketaccess-pricingstrategy.de

Dr. Stefan Walzer – CEO & Founder
stefan.walzer@marketaccess-pricingstrategy.de

Miltenyi Biomedicine

MArS Market Access & Pricing Strategy