ELSEVIER

Blood 142 (2023) 3088–3091

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Secondary Central Nervous System Large B-Cell Lymphoma (SCNSL): A Multicenter Retrospective Analysis

Gulrayz Ahmed, MD FACP[1], Aseel Alsouqi, MD[2], Aniko Szabo, PhD[1], Alexandra E. Rojek, MD[3], Peter A. Riedell, MD[4], Farrukh T. Awan, MD[5], Laura Samples, MD[6], Mazyar Shadman, MD MPH[7], Marie Hu, MD[8], Veronika Bachanova, MD PhD[8], William Wesson, MPH[9], Nausheen Ahmed, MD[10], Madiha Iqbal, MD[11], Mohamed A. Kharfan-Dabaja, MD MBA[12], Michael Scordo[13], Patrick Connor Johnson, MD[14], Yi-Bin Chen, MDMS[15], Sawa Ito, MD[16], Mehdi Hamadani, MD[17], Matthew J. Frigault, MD MS[18]

[1] Medical College of Wisconsin, Milwaukee, WI
[2] University of Pittsburgh Medical Center, Pittsburgh, PA
[3] Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL
[4] David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL
[5] Division of Hematologic Malignancies and Cellular Therapy, Dept of Internal Medicine, Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX
[6] Fred Hutchinson Cancer Center and University of Washington School of Medicine, Seattle, WA
[7] Fred Hutchinson Cancer Center, Seattle, WA
[8] Division of Hematology, Oncology, and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN
[9] University of Kansas School of Medicine, Kansas City, KS
[10] University of Kansas Cancer Center, Westwood, KS
[11] Mayo Clinic Florida, Jacksonville, FL
[12] Department of Hematology/Oncology, Mayo Clinic, Jacksonville, FL
[13] Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[14] Cancer Center, Massachusetts General Hospital, Boston, MA
[15] Massachusetts General Hospital, Boston, MA
[16] Hematology and Oncology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA
[17] Division of Hematology and Oncology, The Medical College of Wisconsin Inc, Milwaukee, WI
[18] Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA

Introduction

Secondary central nervous system (CNS) involvement develops in 2-10% of large B-cell lymphoma (LBCL) cases. Current treatment approaches for relapsed or refractory CNS disease generally do not provide durable responses. Limited data suggest efficacy and feasibility of CAR-T therapy in SCNSL. We report here the largest multicenter retrospective analysis of the safety and efficacy of CD19-directed CAR-T therapy in SCNSL patients.

Methods

This study included SCNSL patients who received commercial CD19-directed CAR-T therapy at 9 academic institutions in the United States between 2016 and 2022. SCNSL was defined as history of parenchymal and/or leptomeningeal/cerebrospinal fluid (CSF) involvement by lymphoma at any time prior to receiving CAR-T therapy. Systemic response was assessed using the Lugano criteria while CNS response was assessed as per International PCNSL Collaborative Group criteria. Kaplan-Meier curves were generated for progression-free survival (PFS) and overall survival (OS) for entire cohort, as well as subsets of patients with and without active CNS disease at the time of CAR-T infusion.

Results

Ninety patients were included in the analysis, with baseline characteristics shown in **Table 1**. CAR-T products utilized include axicabtagene ciloleucel (n= 38, 42%), tisagenlecleucel (n=37, 41%) and lisocabtagene maraleucel (n= 15, 14%). Fludarabine/cyclophosphamide was used as lymphodepletion in 84 patients (93%). 28 patients received CNS directed radiation therapy (RT) prior to CAR-T infusion (31%) within a median time of 28.5 days (range 5 - 906) from last day of RT. Amongst all

patients at the time of CAR-T infusion 82 (91.1%) had active CNS and/or systemic involvement while 8 (8.9%) had no evidence of disease; 68 (75.5%) had active CNS involvement while 22 (24.5%) had a prior history of CNS involvement but no active at the time of CAR-T infusion. (**Table 1**)

Median follow up all patients was 0.5 year (range 0.01 - 4.7). 71 patients (79%) developed cytokine release syndrome (CRS; median time to onset 3 days) with 3.3% patients developing Grade 3-4. Immune effector cell-associated neurotoxicity syndrome (ICANS; median time to onset 5 days) was reported in 55 patients (61%), with 28.8% developing Grade 3-4. No patients died due to CRS or ICANS. At 1-month post CAR-T, 80 patients were evaluable for CNS response and 71 patients in the entire cohort were evaluable for systemic response. Similarly, at 3-months these numbers were 66 and 60, respectively. Objective response rates (ORR) were 75% and 80% at 1-month for CNS and systemic disease respectively, while corresponding ORRs at 3-months were 68% and 76.7%. At 1- and 3-months timepoint 36 (45%) and 33 (50%) patients, respectively achieved CNS complete remission (CR), while 44 (62%) and 42 (70%) patients respectively achieved systemic CR. 1- and 2-year PFS for entire cohort were 25% (95%CI 15% - 34%) and 16% (95%CI 8.5% - 28%) respectively, while 1- and 2-year OS were 46% (95%CI 36% - 59%) and 31% (95%CI 22% - 46%). Non-relapse mortality (NRM) were 4.6% (95%CI, 1.8% -12%) and 7.2% (95%CI 2.9% - 18%) at 1- and 2-year. Cumulative incidence of relapse at 1- and 2-year were 73% (95%CI 63% - 83%) and 77% (95%CI 68% - 88%), respectively.

ORRs for CNS response in patients with active CNS disease at 1-month and 3-month interval were 71% (n=45) and 60% (n=31). Similarly, ORR for systemic response with active CNS disease at 1-month and 3-month interval were 85% (n=43) and 74.3% (n=32).The 2-year PFS for patients with and without active CNS disease at CAR-T infusion were 12% (95%CI 5.4% - 27%) and 28% (95%CI 12% - 65%) respectively, with a corresponding OS of 25% (95%CI 15% - 41%) and 58% (95%CI 37% - 91%). (**Figure 1**) The 2-year NRM rates for patients with and without active CNS disease at CAR-T infusion were 4.6% (95%CI 1.5% - 14%) and 14% (95%CI 3.6% - 53%) respectively, while the cumulative incidence of relapse in similar order were 83% (95%CI 73% - 95%) and 58% (95%CI 39% - 88%).

Conclusion

In this largest known case series to date, CAR-T therapy appeared safe and feasible in patients with SCNSL, but is associated with high rates of treatment failure, particularly in patients with active CNS disease at CAR-T infusion. This warrants further study of optimal CNS-directed treatment strategies prior to CAR-T, development of novel cellular therapy platforms or consideration of post CAR-T maintenance therapy in these high-risk patients.

Disclosures Riedell: *Nurix Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bristol Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Genmab:* Membership on an entity's Board of Directors or advisory committees; *Celgene/ Bristol-Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *CVS Caremark:* Consultancy; *Sana Biotechnology:* Consultancy; *CRISPR Therapeutics:* Research Funding; *Takeda:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Calibr:* Research Funding; *Fate Therapeutics:* Research Funding; *Nkarta:* Research Funding; *Pharmacyclics:* Consultancy; *Genmab:* Consultancy; *Janssen:* Consultancy; *Intellia Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *MorphoSys:* Research Funding; *Nektar Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *Roche:* Research Funding; *Tessa Therapeutics:* Research Funding; *ADC Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Kite/Gilead:* Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Xencor:* Research Funding; *Karyopharm Therapeutics:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Awan:** *Pharmacyclics LLC, an AbbVie Company.:* Other: Contracted Research; *Janssen, Gilead, Kite pharmaceuticals, Karyopharm, MEI Pharma, Verastem, Incyte, Johnson and Johnson, Merck, Epizyme, Loxo Oncology, Adaptive Biotechnologies, Genmab:* Other: Consulting Agreements; *AstraZeneca Pharmaceuticals LP:* Other: Advisory Committee; *AbbVie Inc, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol-Myers Squibb Company, Cardinal Health, Caribou Biosciences Inc, Celgene Corporation, Cellectar Biosciences Inc, DAVA Oncology, Epizyme Inc, Genentech, a member of the Roche:* Other: Consulting Agreements. **Shadman:** *Pharmacyclics:* Consultancy, Research Funding; *MEI Pharma:* Consultancy; *TG Therapeutics:* Research Funding; *Mustang Bio:* Consultancy, Research Funding; *Kite, a Gilead Company:* Consultancy; *Vincerx:* Research Funding; *ADC therapeutics:* Consultancy; *Janssen:* Consultancy; *Fate Therapeutics:* Consultancy; *MorphoSys/Incyte:* Consultancy, Research Funding; *Bristol Myers Squibb:* Consultancy, Research Funding; *BeiGene:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *AstraZeneca:* Consultancy, Research Funding; *AbbVie:* Consultancy, Research Funding; *Eli Lilly:* Consultancy; *Genmab:* Consultancy, Research Funding; *Regeneron:* Consultancy. **Hu:** *AbbVie:* Membership on an entity's Board of Directors or advisory committees. **Bachanova:** *Gamida Cell:* Research Funding; *AstraZeneca:* Membership on an entity's Board of Directors or advisory committees; *ADC:* Membership on an entity's Board of Directors or advisory committees; *Allogene:* Membership on an entity's Board of Directors or advisory committees; *Miltenyi:* Other: DSMB; *BMS:* Research Funding; *Citius:* Research Funding; *Incyte:* Research Funding. **Ahmed:** *BMS:* Consultancy; *Kite:* Consultancy, Research Funding. **Scordo:** *Angiocrine Bioscience, Inc.:* Research Funding; *CancertNetwork (Intellisphere LLC):* Honoraria; *Medscape, LLC:* Honoraria; *Omeros Corporation:* Consultancy, Research Funding; *Amgen, Inc.:* Research Funding. **Johnson:** *Abbvie:* Consultancy; *ADC Therapeutics:* Consultancy; *Incyte:*

Consultancy, Research Funding; *AstraZeneca:* Consultancy, Research Funding; *Seagen:* Consultancy; *Medically Home:* Research Funding. **Ito:** *Horizon Therapeutics:* Other: Clinical trial drug supply ; *BlueSphere Bio:* Patents & Royalties: Patent , Research Funding. **Hamadani:** *SeaGen:* Consultancy; *BeiGene:* Speakers Bureau; *Myeloid Therapeutics:* Honoraria; *Sanofi Genzyme:* Speakers Bureau; *Astellas:* Research Funding; *Spectrum Pharmaceuticals:* Research Funding; *Takeda:* Research Funding; *Astra Zeneca:* Speakers Bureau; *Genentech:* Honoraria; *Novartis:* Consultancy; *MorphoSys:* Consultancy; *Legend Biotech:* Consultancy; *Kadmon:* Consultancy; *Genmab:* Consultancy; *Caribou:* Consultancy; *AstraZeneca:* Speakers Bureau; *Kite, a Gilead Company:* Consultancy, Speakers Bureau; *BeiGene:* Speakers Bureau; *Incyte:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Gamida Cell:* Consultancy; *Genmab:* Consultancy; *CRISPR:* Consultancy; *Omeros:* Consultancy; *Abbvie:* Consultancy; *ADC therapeutics:* Consultancy, Honoraria, Research Funding, Speakers Bureau. **Frigault:** *Arcellx:* Research Funding; *Covance:* Consultancy; *Kite:* Consultancy, Research Funding; *BMS:* Consultancy; *Novartis:* Consultancy, Research Funding.

Table 1. Demographics and Clinical Characteristics of CAR-T infused patients.

Characteristics	N = 90
Age (Range)	61.5 (28-82)
Male Sex (%)	57 (63)
Race (%)	
White	83 (92)
African American	1 (1.1)
Others/Unknown	6 (6.6)
Lymphoma Type (%)	
Burkitt Lymphoma	3 (3.3)
Diffuse Large B-Cell Lymphoma	74 (82.3)
High Grade Large B-Cell Lymphoma	13 (14.4)
Stage 3-4 at diagnosis (%)	75 (84.2)
Prior Lines of Therapy, median (Range)	3 (1 – 7)
History of prior HSCT (Auto or Allo) (%)	17 (19)
No	73 (81)
Yes	17 (19)
Interval to CAR-T therapy from diagnosis in months (Interquartile range)	12.91 (8.33 – 27.85)
Active Disease Status at CAR-T infusion (%)	
CNS and Systemic	39 (43.3)
CNS only	29 (32.2)
Systemic only	14 (15.6%)
None	8 (8.9%)
Systemic disease active at CAR-T infusion (%)	
No	37 (41)
Yes	53 (59)
CNS disease active at CAR-T (%)	
No	22 (24)
Yes	68 (76)
Site of active CNS Disease prior to CAR-T (%)	
Leptomeningeal/CSF	27 (30)
Parenchymal	24 (27)
Both	17 (19)
None	22 (24)
BTKi use within 30 days prior to CAR-T (%)	
No	74 (82.2)
Yes	16 (17.7)

DLBCL = Diffuse Large B-Cell Lymphoma, HGBCL = High Grade B-Cell Lymphoma, GCB = Germinal Center B-Cell, IPI = International Prognostic Index, HSCT = Hematopoietic Stem Cell Transplant, CNS = Central Nervous System, RT = Radiation, WBRT = Whole Brain Radiation, CSF = Cerebrospinal Fluid, CNS = Central Nervous System, CRS = Cytokine Release Syndrome, ICANS = Immune effector cell-associated neurotoxicity syndrome, BTKi = Bruton's Tyrosine Kinase Inhibitor

Figure 1 Progression Free Survival of patients with and without active CNS disease at CAR-T infusion

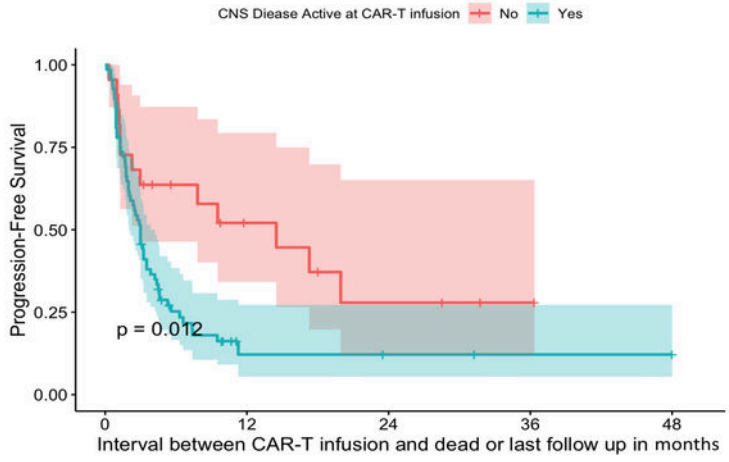

Figure 1

https://doi.org/10.1182/blood-2023-184345