Anti-CD19 Chimeric Antigen Receptor T-cell therapy for Richter's Transformation: A Multicenter Retrospective Study - Abstract ID: 1550392

Authors: Adam S Kittai[1], David Bond[1], Ying Huang[1], Seema A Bhat[1], Emily Blyth[2], John C Byrd[3], Julio Chavez4, Matthew S Davids[5], Jamie P Dela Cruz[5], Mark Dowling[6], Caitlyn Duffy[5], Carrie Ho[7], Caron Jacobson[5], Samantha Jaglowski[1], Nitin Jain[8], Kevin Lin[9], Christine McCarthy[10], Erin Parry[5], Manoj Rai[11], Kerry A Rogers[1], Aditi Saha[4], Levanto Schachter[11], Hamish Scott[6], Mazyar Shadman[7], Tanya Siddiqi[10], Deborah M Stephens[12], Vinay Vanguru[13], William Wierda[8], Omer Zulfa[3], Jennifer A Woyach[1], Philip A Thompson[6]

Affiliations: [1]Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA, [2]Blood Transplant and Cell Therapies Program, Westmead Hospital Department of Haematology, Westmead, NSW, Australia, [3]Department of Internal Medicine, University of Cincinnati, Cincinnati, OH, USA, [4]Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA, [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [6]Department of Clinical Haematology, Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, Australia, [7]Division of Medical Oncology, University of Washington, Seattle, WA, USA, [8]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA, [9]Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA, [10]City of Hope National Medical Center, Duarte, CA, USA, [11]Center for Hematologic Malignancies, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA, [12]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, [13]Institute of Haematology, Royal Prince Alfred Hospital, NSW, Australia

The James

The Ohio State University Comprehensive Cancer Center

Background

-Aggressive lymphoma, most commonly large B-cell lymphoma (LBCL), arising in the setting of chronic lymphocytic leukemia (CLL) is known as Richter's transformation (RT)

-RT is associated with poor outcomes, with overall survival measured in months with standard of care approaches.

-Anti-CD19 Chimeric Antigen Receptor T-cell therapy (CART) has revolutionized the treatment of relapsed/refractory (R/R) LBCL, with impressive durable responses for patients with relapsed/refractory and high-risk disease.

-Patients with RT have been excluded from most major anti-CD19 CART clinical trials.

-We previously reported on 9 patients who received axicabtagene ciloleucel for RT, showing an impressive response rate.

-There are minimal available data describing outcomes of RT following anti-CD19 CART. Therefore, we performed a multicenter study, evaluating the use of CART for RT.

Objectives

-Determine the overall response rate, progression free survival, and overall survival of patients who receive currently approved anti-CD19 CART products for the treatment of RT

-Determine prognostic factors for survival for patients receiving anti-CD19 CART for RT

-Assess toxicity of CART when used for RT

Methods

-We conducted a multicenter, retrospective analysis of patients with RT who received anti-CD19 CART currently approved for hematologic malignancies at 7 academic centers in the United States.

-RT was defined as patients with LBCL with preceding or concurrently diagnosed CLL.

-We collected patient, disease (including molecular features of both CLL and RT), and treatment characteristics.

-Response was assessed by Lugano criteria by individual investigators.

-Progression-free survival (PFS) was measured from anti-CD19 CART infusion to progression, death or last known follow-up, and overall survival (OS) was measured from date of anti-CD19 CART infusion to death or last known follow-up and both were estimated using the Kaplan-Meier method.

-Cox regression model was used to associate prognostic factors with PFS and OS.

Table 1 – Patient Characteristics

Patient Characteristic	Total N=55
Age at CART infusion, median (range)	64 (27-78)
# of CLL therapies prior to RT, median (range)	2 (0-10)
# of RT therapies prior to CART, median (range)	2 (0-7)
Ever Received BTKi or Venetoclax for CLL or RT, n (%)	49 (89.1)
CLL Molecular Features	
IGHV, n (%)	
Mutated	7 (13.7)
Unmutated	44 (86.3)
Unknown	4
del(17p) , n (%)	17 (38.6)
Unknown	11
del(11q) , n (%)	12 (27.3)
Unknown	11
Tri 12, n (%)	8 (18.2)
Unknown	11
del(13q), n (%)	20 (45.5)
Unknown	11
TP53 mut, n (%)	15 (46.9)
Unknown	23
RT and CART Treatment Features	
KI67 (%), median (range)	80 (40-100)
Unknown	9
LDH >/= Upper Limit Normal, n (%)	35 (63.6)
Highest SUV on PET prior to CART, median (range)	14.5 (3-50.6)
Unknown	6
Largest LN (cm) prior to CART, median (range)	4.1 (0-16)
Unknown	7
Clonal relationship to CLL, n (%)	
Related	19 (100)
Unknown	36
Received concurrent BTKi with CART, n (%)	21 (38.2)
Days from Apheresis to CART infusion, median (range)	33 (24-100)
Received bridging therapy after apheresis, n (%)	45 (81.8)
CART product given, n (%)	
Axicabtagene ciloleucel (axi-cel)	35 (63.6)
Brexucabtagene autoleucel (brexu-cel)	1 (1.8)
Lisocabtagene maraleucel (liso-cel)	6 (10.9)
Tisagenlecleucel (tisa-cel)	13 (23.6)

Table 2 – Response rate and survival outcomes

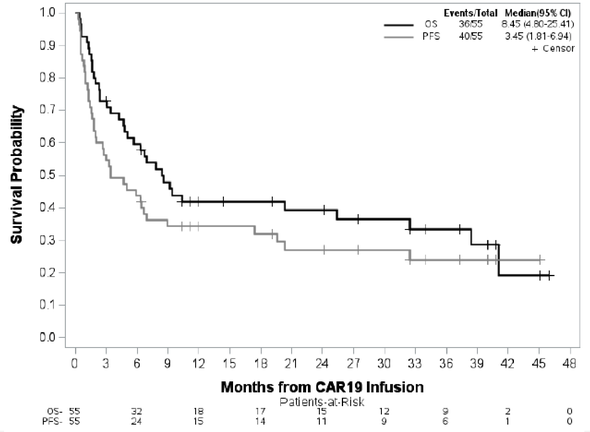
Outcome	
Best response to CART (Lugano 2014), n (%)	
CR	25 (45.5)
PR	9 (16.4)
SD	1 (1.8)
PD	18 (32.7)
Passed prior to assessment	2 (3.6)
Progression Free Survival	
Number of events	40
Median in months (95% CI)	3.45 (1.81-6.94)
Overall Survival	
Number of events	36
Median in months (95% CI)	8.45 (4.80-25.41)
Median follow-up in months among survivors (range)	27.45 (2.96-46.02)
Cause of Death, n (%)	
Disease	24 (70.6)
Non-relapse Mortality, % (95% CI)	
6-month estimate	9.1% (3.3-18.6)
12-month estimate	17.1% (8.3-28.6)

Table 3 – Univariable and Multivariable Cox Model for Overall Survival

	Univariable Models		Multivariable Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at anti-CD19 CART infusion, 5-years older	1.01 (0.87-1.19)	0.87	-	-
# prior lines of therapy for CLL prior to RT	1.09 (0.91-1.31)	0.34	-	-
# prior lines of therapy for RT prior to CART	1.30 (0.99-1.70)	0.06	1.59 (1.19-2.11)	0.0014
Total prior lines of therapy	1.15 (1.00-1.33)	0.06	-	-
Ever received prior BTKi or Ven for CLL or RT	1.80 (0.53-6.18)	0.35	-	-
Ki-67, 10% higher	1.45 (1.11-1.88)	0.0060	1.66 (1.27-2.17)	0.0002
LDH, 2-fold increase	1.85 (1.31-2.61)	0.0005	1.75 (1.17-2.61)	0.0064
SUV, 1-unit increase	1.02 (0.99-1.05)	0.20	-	-
Size of LN, 1-cm increase	0.98 (0.89-1.08)	0.66	-	-
Received BTKi concurrently with RT*	0.83 (0.43-1.61)	0.59	-	-
Days from apheresis to anti-CD19 CART, 5 more days	1.02 (0.89-1.16)	0.78	-	-
Received bridging therapy	1.35 (0.52-3.49)	0.53	-	-
Types of anti-CD19 CART therapy, vs Brexu-cel or Liso-cel				
Axi-cel	0.93 (0.32-2.72)	0.90	-	-
Tisa-cel	0.78 (0.24-2.53)	0.67	-	-

* Received BTKi as part of the most recent therapy prior to apheresis, or as part of the bridging treatment or concurrently with anti-CD19 CART.

Figure – Progression-free Survival and Overall Survival



Results

Fifty-five patients were included.

-Overall response rate was 61.9%, with 25 (45.5%) and 9 (16.4%) patients attaining complete response (CR) and partial response, respectively.

-After a median follow up of 27.5 months from anti-CD19 CART infusion, the median PFS was 3.45 months (95% CI: 1.81-6.94), and median OS was 8.5 months (95% CI: 4.80-25.4) (Figure).

-Among 34 patients who died with known cause of death, twenty-four (70.6%) died due to progression of disease, and 10 (29.4%) died for other reasons including 8 infections (4 COVID), 1 stroke, and 1 respiratory failure.

-The cumulative incidence of non-relapse mortality at 12-months was 17.1% (95% CI: 8.3-28.6).

-Three patients in a CR underwent allogeneic stem cell transplantation: two were alive at last known follow up (3.9- and 24.2-months post-transplant), and 1 patient died from progression of disease 21 months post-transplant.

-Forty-eight (87%) patients had CRS, with 9 (16.3%) grade ≥3 events. Thirty-six (66.7%) patients had ICANS, with 21 (38.9%) grade ≥3 events.

-On multivariable analysis, increasing Ki-67, increasing LDH, and greater number of prior lines of therapy for RT were independent prognostic variables for worse PFS and OS. All other variables, including type of anti-CD19 CART product received, were not correlated with PFS or OS.

Conclusions

We report the largest cohort of patients with RT who received anti-CD19 CART. RT remains a disease of unmet need, as the median OS was 8.5 months in this study. However, the 8.5 months observed was in patients who had already received 2 prior lines of therapy for RT. Although the CR rate is lower than what would be expected for patients with R/R LBCL, there were durable remissions observed. Early relapse was prevalent, therefore allogeneic stem cell transplantation at response should be considered, however our data was limited on post-CART transplant. Given more lines of therapy was prognostic for survival, consideration of CART earlier in the treatment paradigm for RT may be necessary. Rates of CRS and ICANS, and treatment-related mortality were also higher than expected, thus developing better supportive care for this patient population is warranted. Prospective clinical trials evaluating anti-CD19 CART with novel agents, including BTKi, for RT are currently ongoing.

Contact

Adam.Kittai@osumc.edu, @AdamKittai