blood advances

TO THE EDITOR:

CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy

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Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), with aggressive clinical behavior.[1] Approximately 40% to 50% of DLBCL patients are refractory to or relapse after frontline chemoimmunotherapies.[2] Management of relapsed/refractory DLBCL is challenging, and treatment options include salvage therapy followed by autologous hematopoietic cell transplantation (autoHCT), in younger, chemosensitive patients.[3] CD19-directed chimeric antigen receptor (CAR) modified T-cell therapy is another potentially curative option for patients with relapse after autologous hematopoietic cell transplantation or those with refractory disease.[4] Axicabtagene ciloleucel and tisagenlecleucel are 2 anti-CD19 CAR T-cell treatments approved by the US Food and Drug Administration for relapsed/refractory DLBCL.[5,6]

The CD19 antigen is an attractive target for immunotherapy in B-cell non-Hodgkin lymphoma. It is expressed during B-cell development only after B-lineage commitment and is thus not present on hematopoietic stem cells.[7] CD19 expression is lost during terminal plasma cell differentiation but maintained in hematologic B-cell malignancies.[7] Several clinical trials using monoclonal antibodies,[8] antibody-drug conjugates (ADCs),[9] and bispecific T-cell engagers targeting the CD19 antigen are ongoing in B-cell non-Hodgkin lymphoma. Studies investigating CD19-directed CAR T-cell therapies in aggressive lymphomas frequently excluded patients previously treated with CD19 targeting immunotherapies. Hence, the feasibility and efficacy of anti-CD19 CARs in lymphoma patients with prior CD19-directed immunotherapies are not known. Loncastuximab tesirine is an ADC comprising a humanized anti-CD19 monoclonal antibody stochastically conjugated to a pyrrolobenzodiazepine dimer toxin, SG3199.[10] A phase 1 first-in-human study of loncastuximab tesirine demonstrated encouraging clinical activity in patients with relapsed/refractory DLBCL,[9] and a phase 2 study recently finished patient accrual (#NCT03589469).

We sought to evaluate the outcomes of anti-CD19 CAR T-cell therapy in relapsed, refractory DLBCL previously treated with CD19-directed immunotherapy. Adult (age ≥18 years) DLBCL patients were identified from 2 multicenter, open-label studies of loncastuximab tesirine (phase 1: #NCT02669017 and phase 2: #NCT03589469), who subsequently received anti-CD19 CAR T-cell therapy. This retrospective analysis was approved by the institutional review board. Deidentified patient data were collected in collaboration with 6 academic medical centers (US centers = 4; United Kingdom = 1; Italy = 1) involved in the loncastuximab tesirine trials. Cytokine release syndrome was graded using Lee et al 2014 criteria,[11] and neurotoxicity was graded as per Common Terminology Criteria for Adverse Events, version 5.0.

A total of 14 DLBCL patients with disease relapsing or progressing after treatment with loncastuximab tesirine and subsequently undergoing CD19-directed CAR T-cell therapy were identified (Table 1). Among the 14 patients, 11 patients (79%) were male, and 13 patients (93%) were white. The median age was 58.5 years (range, 27 to 86). Ten had de novo DLBCL (germinal center B-cell–like = 4; non–germinal center B-cell = 2; not known = 4), and 4 patients had DLBCL transforming from indolent histologies (marginal zone lymphoma = 1; follicular lymphoma = 1; nodular lymphocyte predominant Hodgkin lymphoma = 1). Five patients (36%) had a high-intermediate international prognostic index at the time of diagnosis. c-MYC gene rearrangement was identified in 3 patients (21%) (1 patient had triple-hit lymphoma), whereas c-MYC status was unknown in 3 patients (21%). The median interval between diagnosis of DLBCL and initiation of loncastuximab tesirine was 21.5 months (range, 6.8 to 258). These patients received a median of 2 cycles (range, 1 to 7) of loncastuximab tesirine.

Table 1. Patient demographics and disease characteristics

	Patients (N = 14)
Age, median (range), y	58.5 (27-86)
Sex, n (%)	
Male	11 (79)
Female	3 (21)
Race, n (%)	
White	13 (93)
African American/black	1 (7)
Lymphoma subtype	
DLBCL*	10
Transformed DLBCL	4
IPI at diagnosis, n (%)	
Low (0, 1)	3 (21)
Low-intermediate (2)	3 (21)
High-intermediate (3)	5 (36)
Unknown	3 (21)
Advanced stage (III/IV) at diagnosis	4 (29)
c-MYC rearrangement, n (%)	
Yes	3 (21)
No	8 (57)
Unknown	3 (21)
Median interval between diagnosis and start of loncastuximab tesirine (range), mo	21.5 (6.8-258)
Best response to loncastuximab tesirine, n (%)	
Complete response	1 (7)
Partial response	5 (36)

Percentages may not add up to 100 due to rounding.
IPI, International Prognostic Index.
*One patient had mediastinal large B-cell lymphoma.

The antitumor response to loncastuximab tesirine in these 14 patients was as follows: 8 patients (57%) had refractory disease, 5 patients (36%) attained partial response, and 1 patient (7%) achieved a complete response (overall response rate [ORR] = 43%). All responding patients had progression of the disease before proceeding with CAR therapy.

Table 2 summarizes details of CAR T-cell therapy in these subjects. The median interval between loncastuximab tesirine and CAR T-cell therapy was 120 days (range, 22 to 600). Six patients received additional lines of therapy between loncastuximab tesirine and CAR T-cell treatment (median of 1 therapy line; range, 1 to 3). The CD19 expression was assessed by immunohistochemical staining on repeat biopsies in 10 patients (71%) in between loncastuximab tesirine and CAR administration. All 10 tested patients were positive for CD19 after ADC failure. This information was not available in 4 patients (29%). Before CAR T-cell administration, 13 patients had refractory or progressive disease, whereas 1 patient was in partial remission. All patients received standard lymphodepletion with fludarabine and cyclophosphamide before CAR T-cell therapy. The type of anti-CD19 CAR T-cell therapy received by the patients included axicabtagene ciloleucel (n = 5), tisagenlecleucel (n = 2), JCAR017 (n = 3), and investigational CARs targeting CD19 (n = 4; including 2 patients with CARs targeting dual antigens; Table 2).

Table 2. CAR T-cell therapy in DLBCL patients failing CD19-directed treatment

	Patients (N = 14)
CD19 expression on lymphoma cells after loncastuximab tesirine therapy, n (%)	
Positive	10 (71)
Not checked	4 (29)
Median interval between loncastuximab tesirine and CAR T-cell therapy (range), d	120 (22-600)
Additional therapy between loncastuximab tesirine and CAR T-cell therapy, n (%)	
Yes*	6 (43)
No	8 (57)
Disease status before CAR T-cell therapy, n (%)	
Refractory disease	5 (36)
Progressive disease	8 (57)
Partial remission	1 (7)
Flu/Cy lymphodepletion, n (%)	14 (100)
Type of CAR T-cell therapy, n (%)	
Axicabtagene ciloleucel	5 (36)
Tisagenlecleucel	2 (14)
Investigational targeting CD19†	4 (29)
JCAR017	3 (21)
Best response to CAR T-cell therapy, n (%)	
Complete response	6 (43)
Partial response	1 (7)
Refractory disease	7 (50)
CRS grade, n (%)	
None	6 (43)
1	3 (21)
2	4 (29)
3	1 (7)
ICANS grade, n (%)	
None	8 (57)
1	4 (29)
2	1 (7)
3	0 (0)
4	1 (7)

CRS, cytokine release syndrome; Flu/Cy, lymphodepletion with fludarabine/cyclophosphamide.
*Additional therapy between loncastuximab tesirine and CAR T-cell therapy included radiation alone (n = 3), radiation, ifosphamide/vinblastine/etoposide (n = 1), radiation; rituximab/methotrexate (n = 1), lenalidomide, anti-CD47 antibody, ibrutinib (n = 1).
†One patient each received a CD19/CD22-directed CAR, and a CD19/CD20-directed CAR. Neither patient responded to CAR treatment.

The median follow-up of survivors was 6 months (range, 3 to 22). Grade 1 to 2 cytokine release syndrome was common (n = 7; 50%). Grade 1 immune effector cell–associated neurotoxicity syndrome (ICANS) was identified in 4 patients (29%), and only 1 patient had grade 4 ICANS. Following CAR therapy, the best response at 3 months included 6 patients (43%) with a complete response and 1 patient (7%) with a partial response (ORR = 50%). Seven patients had refractory disease following CAR therapy. Five of 6 complete

remissions are ongoing at a median of 6 months (range, 6 to 11). One patient with complete remission relapsed after 11 months and was alive at last follow-up (+22 months), whereas the patient achieving a partial remission subsequently died because of progressive lymphoma. Six out the 7 patients not achieving a CR expired at a median of 5 months (range, 1 to 9) after CAR therapy. None of the 2 patients receiving dual-antigen targeting CARs (targeting CD19/CD22 and CD19/CD20) achieved a response. All 4 patients with unknown CD19 expression status after loncastuximab tesirine achieved a complete remission with anti-CD19 CAR T-cell therapy, making it unlikely that these patients had relapsed with a CD19-negative disease.

This is the first report, to our knowledge, evaluating the efficacy of anti-CD19 CAR T-cell therapy after anti-CD19 immunotherapy. In this series of 14 cases, favorable outcomes of CAR T-cell therapy (ORR = 50%) were seen in patients with relapsed/refractory DLBCL after anti-CD19–targeted treatment with a pyrrolobenzodiazepine dimer–based ADCs. The toxicity profile of CAR treatment in these subjects appears consistent with published data.[5,6] CD19 expression on DLBCL was reassessed in 10 patients after relapse or progression on loncastuximab tesirine treatment; no cases of CD19 antigen-negative relapse were seen. We wish to acknowledge that this report is limited by small sample size and retrospective design. In conclusion, our report suggests that prior treatment with anti-CD19 ADCs in relapsed/refractory DLBCL does not preclude subsequent responses to anti-CD19 CAR T-cell therapies. Additional data on the feasibility of CAR therapy in patients receiving CD19 monoclonal antibodies and bispecific T-cell engagers are needed.

Send data sharing requests to the corresponding author, Mehdi Hamadani (mhamadani@mcw.edu).

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References

1. Non-Hodgkin Lymphoma - Cancer Stat Facts. SEER. https://seer.cancer.gov/statfacts/html/nhl.html. Accessed 25 September 2019.
2. Sarkozy C, Sehn LH. Management of relapsed/refractory DLBCL. *Best Pract Res Clin Haematol*. 2018;31(3):209-216.
3. Hamadani M, Hari PN, Zhang Y, et al. Early failure of frontline rituximab-containing chemo-immunotherapy in diffuse large B cell lymphoma does not predict futility of autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(11):1729-1736.
4. Jain T, Bar M, Kansagra AJ, et al. Use of chimeric antigen receptor T cell therapy in clinical practice for relapsed/refractory aggressive B cell non-Hodgkin lymphoma: an expert panel opinion from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2019;25(12):2305-2321.
5. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56.
6. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
7. Scheuermann RH, Racila E. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. *Leuk Lymphoma*. 1995;18(5-6):385-397.
8. Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2018;29(5):1266-1272.
9. Kahl BS, Hamadani M, Radford J, et al. A phase I study of ADCT-402 (loncastuximab tesirine), a novel pyrrolobenzodiazepine-based antibody-drug conjugate, in relapsed/refractory B-cell non-Hodgkin lymphoma. *Clin Cancer Res*. 2019;25(23):6986-6994.
10. Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a PBD dimer-containing antibody drug conjugate targeting CD19-expressing malignancies. *Blood*. 2018;131(10):1094-1105.
11. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome [published correction appears in *Blood*. 2015;126(8):1048]. *Blood*. 2014;124(2):188-195.

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