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High efficacy of CD19 CAR T-cells in patients with transformed Waldenström macroglobulinemia

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Abstract:

Histological transformation of Waldenström macroglobulinemia (HT-WM) carries a poor prognosis with standard treatments. Here, we report the first series of HT-WM treated with CAR T-cells showing a high efficacy and no unexpected toxicity.

Conflict of interest: COI declared - see note

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45 **Abstract**

46 Histological transformation of Waldenström macroglobulinemia (HT-WM) carries a poor prognosis
47 with standard treatments. Here, we report the first series of HT-WM treated with CAR T-cells showing
48 a high efficacy and no unexpected toxicity.

49

50 Histological transformation (HT) of Waldenström macroglobulinemia (WM)/lymphoplasmacytic
51 lymphoma represents a rare but severe event occurring in less than 5% of the cases. Patients usually
52 present with adverse prognostic features, including extra-nodal involvement and elevated lactate
53 dehydrogenase levels.^{1,2,3} These patients carry a poor prognosis after standard treatments with
54 frequent refractory disease, short duration of response and/or central nervous system (CNS) relapses,
55 with a median overall survival of 1.5 to 2.7 years.^{4,5} Chimeric antigen receptor T-cells (CAR-T) have
56 been approved for the treatment of aggressive B-cell lymphomas, including *de novo* large B-cell
57 lymphoma (LBCL) and transformed follicular lymphoma (tFL).⁶ However, little is known about the
58 efficacy of CAR-T in patients with transformed WM. Only a few cases have been reported in the
59 literature including two cases from the TRANSCEND study, one reaching a partial response (PR),⁷ and
60 one case reported by Bansal et al.⁸ who achieved a complete response (CR) for 12 months at the time
61 of publication.

62 Here, we conducted a retrospective collaborative study to evaluate the efficacy and safety of CAR-T in
63 patients with HT-WM. Patients from the French DESCAR-T registry (NCT04328298, n=19 patients)
64 and from two U.S. centers (n=4 patients) were included if they met all of the following criteria: age
65 over 18, refractory/relapsed (R/R) HT-WM, biopsy- proven LBCL, and had received treatment with a
66 commercial CAR-T. Patients received CAR-T as standard of care and all provided informed consent
67 prior to the treatment. The primary endpoint was to evaluate the best CR rate (CRR), according to the
68 Lugano 2014 classification.⁹ Secondary endpoints included overall response rate (ORR), progression-
69 free survival (PFS), overall survival (OS) and safety, including cytokine-release syndromes (CRS),
70 immune effector cell-associated neurotoxicity syndrome (ICANS), infections, and hematological
71 toxicity. CRS and ICANS were graded according to the American Society for Transplantation and
72 Cellular Therapy (ASTCT) grading system. Other adverse effects were graded according to the National
73 Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0).

74 Patient characteristics are provided in **Table 1**. A total of 23 patients were treated between June 2017
75 and October 2023. The median age at WM diagnosis was 58 years (range, 35-72). *MYD88*^{L265P} and
76 *CXCR4* mutations were detected in 86% (12/14) and 25% (2/8) of patients with available data,
77 respectively. The median time from WM to HT diagnosis was 4.5 years (interquartile range (IQR), 0.3-
78 16.7), including five cases (22%) with concurrent diagnosis of WM and LBCL. Patients received a
79 median of 1 line of treatment (range, 0-4) for WM and 2 lines (range, 1-4) for HT before CAR-T
80 infusion, and eight patients (35%) had undergone prior autologous stem cell transplantation (SCT)
81 (two as part of WM treatment and six for HT) and one allogeneic SCT after HT (**Supplemental Table**
82 **1**). CNS involvement due to LBCL was present in three patients at HT and two at the time of CAR-T
83 therapy. The median time from HT diagnosis to CAR-T infusion was 26 months (IQR, 8-40). Median
84 age at the CAR-T infusion time was 66 years (range, 41-82). Nearly half of the patients (48%) were
85 refractory to the last therapy before CAR-T. Seventeen patients (74%) received a bridging therapy, of
86 whom only six (35%) responded (CR or PR) (**Supplemental Table 2**). Lymphodepletion consisted of
87 fludarabine/cyclophosphamide for 20 patients and bendamustine for 3 patients (due to renal failure).
88 Patients received axicabtagene-cileucel (axi-cel, n=14) or tisagenlecleucel (tisa-cel, n=9).

89 The best ORR was 96% (95% CI, 78-100), including 87% CR (95% CI, 66-97) (**Table 1, Supplemental**
90 **Figure 1, and Supplemental Table 3**). Two out of four patients with a PR at 1 month converted to a CR
91 at 3 and 6 months without additional treatment. At 6 months, 73% of the patients remained in CR. Of
92 note, the two patients with CNS involvement achieved a CR at 1 month: one relapsed at 3 months,
93 and one remained in CR at 12 months. Regarding WM disease evaluation, serum IgM levels before
94 and after CAR-T were available for 18 patients (**Supplemental Figure 2**). IgM peak at CAR-T infusion
95 was undetectable in 8 patients. Among the 10 remaining patients, the mean IgM level before CAR-T

96 was 6.1 g/L (IQR, 4-10). All the 5 patients with IgM level > 5 g/L before CAR-T achieved a PR after CAR-
97 T. Of note, low serum IgM levels is a common feature in HT-WM.^{1,4}

98 After a median follow-up of 28 months (range, 3-57), the estimated PFS rates at 1 and 2 years were
99 73.4% (95% CI, 50.2-87.1) and 67.5% (95% CI, 42.9-83.2), respectively (**Figure 1A**). The estimated OS
100 rates at 1 and 2 years were 80.5% (95% CI, 50.6-89.2) and 69.5% (95% CI, 44.6-85.3), respectively
101 (**Figure 1B**). Eight patients experienced relapse/progression during follow-up. Among them, six
102 occurred within the first 6 months following CAR-T infusion and were related to LBCL relapse. Of
103 note, one patient presented with a late relapse (4.5 years) of LBCL. Only one patient relapsed with
104 non-transformed WM at 28 months. Among the 7 patients who relapsed with LBCL after CAR T-cells,
105 salvage therapy consisted of lenalidomide (+/- rituximab or tafasitamab) in 4 patients, glofitamab in 1
106 patient, epigenetic agent in 1 patient and ibrutinib in 1 patient with CNS relapse. Only 1 patient
107 treated with lenalidomide obtained a sustained response for 2 years. At the time of data cut-off, eight
108 patients have died, seven from lymphoma progression (LBCL) and one from COVID-19 infection.

109 There was no unexpected toxicity with 74% CRS (9% grade 3-4) and 39% ICANS (9% grade 3-4)
110 (**Supplemental Table 4**). The median time to onset of CRS was 2 days (IQR, 1-4) after CAR-T infusion
111 and the median duration was 5 days (IQR, 3-8). The median time to onset of ICANS was 5 days (IQR,
112 4-11) after CAR-T infusion and the median duration was 7 days (IQR, 4-13). Four patients (17%) were
113 admitted to the intensive care unit because of CAR-T toxicities. Twelve patients experienced
114 infections, including 4 grade 3-4 events. Between 22% and 35% of the patients developed grade \geq 3
115 prolonged cytopenias (i.e. not resolved within 30 days post-infusion).

116 Although cross-trial comparison cannot be formally performed, these data compare favorably with
117 the results of the ZUMA-1^{10,11} and the JULIET trials¹² with axi-cel and tisa-cel, respectively. The CRR
118 was 58% in ZUMA-1 and 40% in JULIET, vs. 87% in our study. The 1 year-PFS and OS rates were 44%
119 and 59% in ZUMA-1 and unknown (83% among responders at 3 months) and 49% in JULIET,
120 respectively, vs. 73.4% and 80.5% in our study.¹³ The good efficacy of CAR-T in HT-WM seems to be in
121 line with the results in transformed FL^{14,15,16} but contrasts with the poor efficacy of CAR-T in Richter
122 transformation^{17,18,19}. This suggests that CAR-T efficacy may not be influenced by the transformation
123 itself but rather by the underlying disease and/or the host immune system or microenvironment.

124 Overall, CAR-T therapy is associated with high efficacy in HT-WM, especially given the poor outcome
125 of these patients with standard treatments. Furthermore, CAR-T therapy seems to be well tolerated
126 in these patients, with no unexpected toxicity. Although these results need to be confirmed in a larger
127 cohort, they support the use of CAR T-cells in this population. Extended follow-up is needed to
128 confirm the long-term efficacy of CAR-T in HT-WM.

129 Patients included in the French DESCAR-T registry (NCT04328298) and IRB approval for the two
130 American centers.

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Contribution: E.D. and R.H. analyzed and interpreted data, and wrote the manuscript, E.D., D.R.W, A.C., J.D., R.D.B, T.G., H.B., M.C., C.J., S.G., F.X.G, E.B., A.C., P.C.M., S.P.T., A.D., R.R., S.L.G., J.J.C, and R.H. collected data, and all authors agreed to the final version of the manuscript.

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230 **Table 1. Patient characteristics and outcome**

Variable	n = 23
Sex male/female (ratio)	12/11 (1.1)
WM characteristics	
Median age at WM diagnosis (years, range)	58 [35-72]
<i>MYD88</i> ^{L265P} mutation	12/14 (86%)
<i>CXCR4</i> mutation	2/8 (25%)
Median number of lines for WM (range)	1 (0-4)
HT characteristics	
Median age at HT (years, range)	65 [41-81]
Histology	
DLBCL, not otherwise specified	22 (96%)
HGBL (<i>MYC</i> and <i>BCL6</i> translocations)	1 (4%)
Hans algorithm	
Non-GC	18 (86%)
GC	3 (14%)
Extranodal involvement	19 (83%)
CNS involvement	3 (13%)
Median serum IgM level (g/L, range)	6.1 [0-31.1]
Ann Arbor stage III-IV	22 (96%)
IPI ≥ 3	10/20 (50%)
Median number of lines for HT (range)	2 (1-4)
Characteristics at lymphodepletion	
Median age at lymphodepletion (years, range)	66 [41-82]
> 70 years	8 (35%)
Refractory to last therapy	11 (48%)
ECOG performance status ≥ 2	5/22 (23%)
Elevated LDH	11 (48%)
Ann Arbor stage III-IV	12/15 (80%)
CNS involvement	2/23 (9%)
Bridging therapy	17 (74%)
Response to bridging therapy (n = 17)	
CR	3 (18%)
PR	3 (18%)
SD	5 (29%)
PD	6 (35%)
Lymphodepleting chemotherapy	
Flu/Cy	20 (87%)
Bendamustine	3 (13%)
CAR T-cell product	
Axicabtagene-ciloleucel	14 (61%)
Tisagenlecleucel	9 (39%)
Outcome after CAR-T infusion	
Best OR	22 (96%)
Best CR	20 (87%)
1 year PFS (95% CI)	73.4% (50.2-87.1%)
1 year OS (95% CI)	80.5% (50.6-89.2%)
Grade ≥ 3 CRS	2 (9%)
Grade ≥ 3 ICANS	2 (9%)

231 *WM: Waldenström macroglobulinemia; HT: histological transformation; DLBCL: diffuse large B-cell*
232 *lymphoma; HGBL: high grade B-cell lymphoma; GC: germinal center; CNS: central nervous system;*
233 *ECOG: Eastern cooperative oncology group; CR: complete response; PR: partial response, SD: stable*
234 *disease; PD: progressive disease; Fly/Cy: fludarabine cyclophosphamide; OR: overall response; PFS:*
235 *progression-free survival; OS: overall survival; CRS: cytokine release syndrome; ICANS: immune*
236 *effector cell-associated neurotoxicity syndrome.*

237

238 **Figure 1. Outcomes after CAR T-cell infusion.** Kaplan-Meier estimates of progression-free survival (A)
239 and overall survival (B) from CAR T-cell infusion.

240

Figure 1

