Eleven cases of laryngeal edema after tisagenlecleucel infusion: a 3-year single center retrospective study of CD19-directed chimeric antigen receptor T-cell therapy for relapsed and refractory B-cell lymphomas

Authors

Erina Hosoya,[1] Jun Ando,[1,2] Shintaro Kinoshita,[1] Yoshiki Furukawa,[1] Yuko Toyoshima,[1,2] Yoko Azusawa,[2] Toru Mitsumori,[3] Eriko Sato,[4] Hina Takano,[5] Yutaka Tsukune,[1] Naoki Watanabe,[1] Tomoiku Takaku,[1] Hajime Yasuda,[1] Yasuharu Hamano,[1] Makoto Sasaki,[1] Shuko Nojiri,[6] Midori Ishii[1] and Miki Ando[1]

[1]Department of Hematology, Juntendo University School of Medicine, Hongo, Bunkyo-ku; [2]Division of Cell Therapy & Blood Transfusion Medicine, Juntendo University School of Medicine, Hongo, Bunkyo-ku; [3]Department of Hematology, Juntendo University Urayasu Hospital, Tomioka, Urayasu-shi, Chiba; [4]Department of Hematology, Juntendo University Nerima Hospital, Takanodai, Nerima-ku, Tokyo; [5]Department of Hematology, Juntendo University Shizuoka Hospital, Nagaoka, Izunokuni-shi, Shizuoka and [6]Medical Technology Innovation Center, Juntendo University, Hongo, Bunkyo-ku, Tokyo, Japan

Correspondence:
MIKI ANDO - m-ando@juntendo.ac.jp

https://doi.org/10.3324/haematol.2024.286169

Received: July 11, 2024.
Accepted: October 10, 2024.
Early view: October 17, 2024.

Supplementary Table 1

A. Patient characteristics

	DLBCL		FL	
	n=53		n=6	
Age				
median, years (range)	66	(35-79)	69	(60-74)
≥65, no. (%)	31	(58%)	5	(83%)
Sex				
Male	33	(62%)	3	(50%)
Female	20	(38%)	3	(50%)
ECOG performance status				
0	50	(94%)	5	(83%)
1	3	(6%)	1	(17%)
Disease stage at initial diagnosis				
I or II	8	(15%)	2	(33%)
III or IV	45	(85%)	4	(67%)
Histological subtypes				
de novo DLBCL	37	(70%)	-	-
transformed DLBCL	16	(30%)	-	-
Number of previous lines of therapy before apheresis				
2 lines	22	(42%)	2	(33%)
≥3 lines	31	(58%)	4	(67%)
median (range)	3	(2-10)	4	(2-7)
Previous ASCT	16	(30%)	0	(0%)
Primary refractory	20	(38%)	3	(50%)

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; ECOG: Eastern Cooperative Oncology Group; ASCT: autologous stem cell transplantation

B. Patient status before infusion

	DLBCL		FL	
	n=38		n=3	
Bridging chemotherapy	33	(87%)	3	(100%)
Radiation therapy after apheresis	9	(24%)	1	(33%)
LDH at lymphodepletion >ULN	18	(47%)	1	(33%)
Bulky disease at infusion (>5 cm)	6	(16%)	1	(33%)
Status before infusion				
CR	7	(18%)	0	(0%)
PR	11	(29%)	1	(33%)
SD	16	(42%)	0	(0%)
PD	4	(11%)	2	(67%)

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; LDH: lactate dehydrogenase; ULN: upper limit of normal; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

C. Adverse events

	n=41	
Infusion reaction	7	(17%)
Cytopenia over 3 months, grade ≥3	8	(20%)
Hypogammaglobulinemia	5	(12%)
CRS		
Any grade	30	(73%)
Grade ≥3	14	(34%)
Median time to onset, day (range)	2	(0-5)
Details of manifestations		
Fever	30	(73%)
Hypotension	10	(24%)
Hypoxia	4	(10%)
Acute kidney injury	1	(2%)
Laryngeal edema	11	(27%)
ICANS		
Any grade	3	(7%)
Grade ≥3	2	(5%)
Median time to onset, day (range)	4	(4-7)
Details of manifestations		
Confusional state	2	(5%)
Seizure	1	(2%)
Aphasia	1	(2%)
Peripheral neuropathy	1	(2%)
Tocilizumab use	21	(51%)
Corticosteroid use	10	(24%)
Admission to intensive care unit	15	(37%)
Treatment-related mortality	0	(0%)

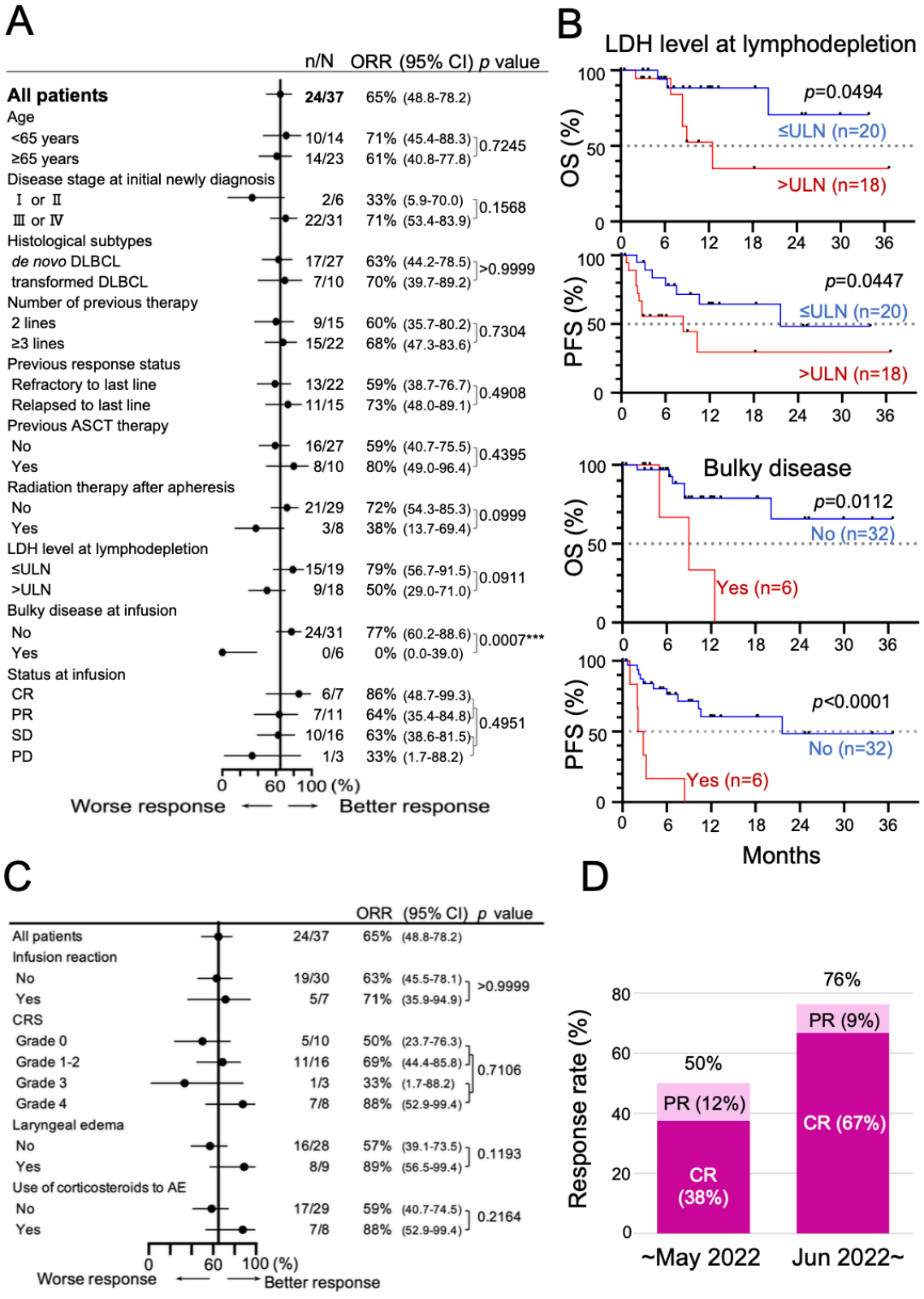
CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome

D. Characteristics of patients with laryngeal edema

		n=11	
CRS grade			
0		1	(9%)
1~2		0	(0%)
3~4		10	(91%)
Mean duration to onset, day (range)		3.4	(2~5)
Presence of cervical tumor		5	(45%)
Tocilizumab		11	(100%)
Corticosteroids		7	(64%)
DEX	10 mg/body×1 dose	2	(18%)
	10 mg/body×2 doses	2	(18%)
	20 mg/body×3 doses	1	(9%)
mPSL	2 mg/kg×1 dose	1	(9%)
Combination of DEX and mPSL		1	(9%)
Emergency airway management		9	(82%)
Admission to intensive care unit		11	(100%)

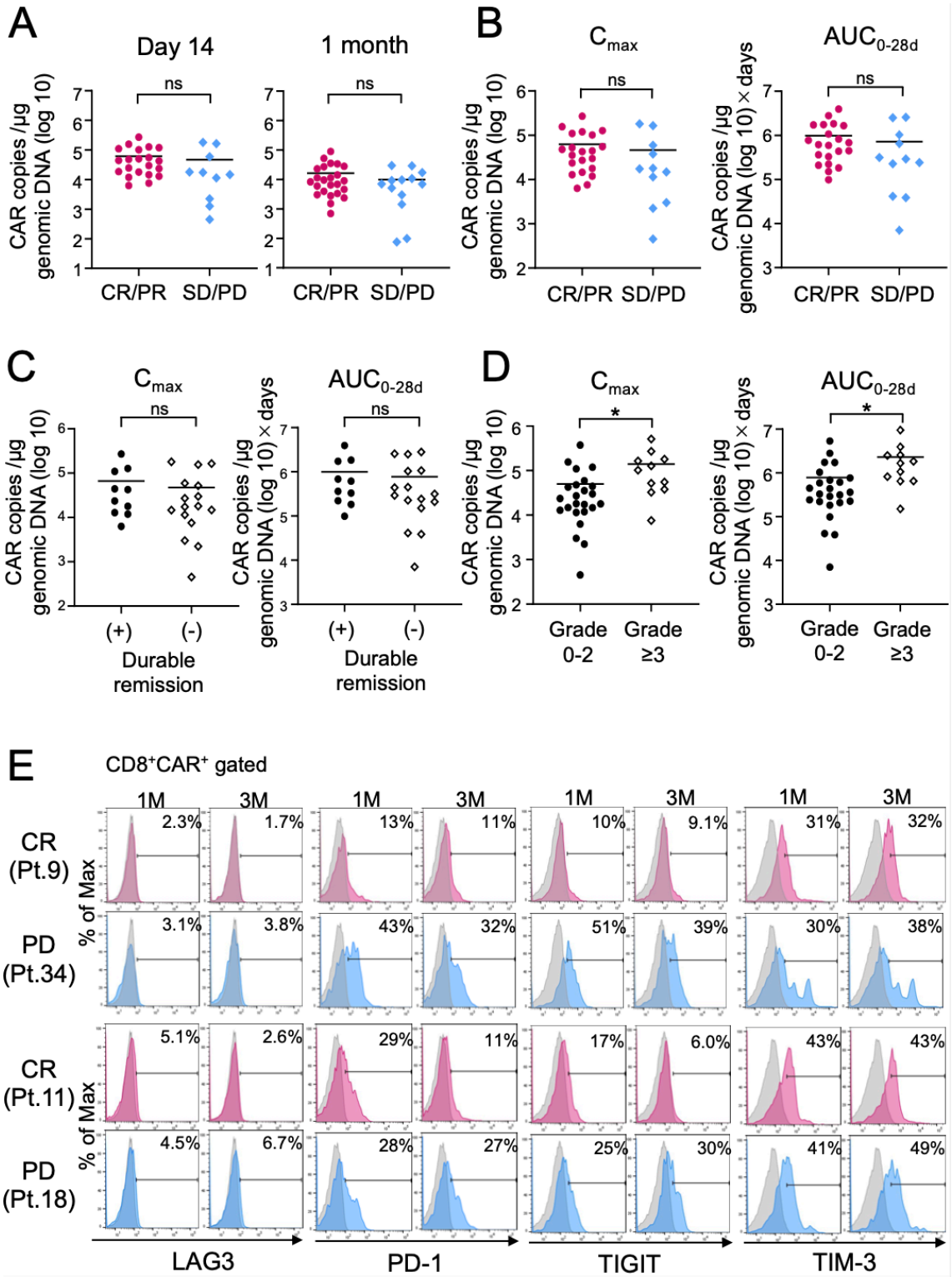
CRS: cytokine release syndrome; DEX: dexamethasone; mPSL: methylprednisolone

Supplementary Figure 1



(A) Univariate analyses affecting overall response rate (ORR). The vertical line represents the ORR for all patients. ***, $p<0.001$ by χ^2 / Fisher's exact test. (B) Subgroup analyses of overall survival (OS) and progression-free survival (PFS) classed by LDH level at onset of lymphodepletion and by bulky disease. (C) Univariate analyses affecting ORR. The vertical line represents the ORR for all patients. comparison by χ^2 / Fisher's exact test. (D) ORR of patients infused with tisa-cel before May 2022 and after Jun 2022.

Supplementary Figure 2



(A) Mean chimeric antigen receptor (CAR) copy number of complete response (CR)/ partial response (PR) patients in pink and of stable disease (SD)/ progressive disease (PD) patients in blue. (Day 14, p=0.1864; 1 month, p=0.4793) ns, not significant by unpaired t-test. (B) C_{max} (left) and $AUC_{0\text{-}28d}$ (right) of CAR copy number according to patient disease status. Patients with CR and PR in pink and patients with SD and PD in blue. Ns, not significant by unpaired t-test. (C) C_{max} (left) and $AUC_{0\text{-}28d}$ (right) of CAR copy number according to patient disease status (with durable remission or without durable remission). (D) C_{max} (left) and $AUC_{0\text{-}28d}$ (right) of patients with grade 0-2 cytokine release syndrome (CRS) (black) and grade ≥3 CRS (white). Maximum concentration of CAR copy number after infusion; C_{max}, Area under curve of CAR copy number from day 0 to day 28; $AUC_{0\text{-}28d}$ (C_{max}; p=0.0215, $AUC_{0\text{-}28d}$; p=0.0217) *, p<0.05 by unpaired t-test. (E) Flow cytometric analysis of LAG3, PD-1, TIGIT, and TIM-3 expression on tisa-cel at 1 month, 3 months after infusion. All analysis are CR patients in red, PD patients in blue, negative control in grey.