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Authors

Larue, Marion
Bouvier, Amélie
Maillard, Alexis
et al.

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Neurofilament light chain levels as an early predictive biomarker of neurotoxicity after CAR T-cell therapy

Marion Larue ,[1] Amélie Bouvier,[1] Alexis Maillard,[2] Alexis Cuffel,[1,3] Vincent Allain,[1,3] Renata Ursu,[4] Antoine F Carpentier,[4] Elie Azoulay,[2] Catherine Thieblemont,[5] Roberta Di Blasi,[5] Sophie Caillat-Zucman [1,3]

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[1]Laboratoire d'Immunologie, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Cité, Paris, France
[2]Médecine intensive et réanimation, Hôpital Saint-Louis, AP-HP, Université Paris Cité, Paris, France
[3]INSERM UMR976, Institut de Recherche St-Louis, Université Paris Cité, Paris, France
[4]Service de Neurologie, Hôpital Saint-Louis, AP-HP, Université Paris Cité, Paris, France
[5]Service d'Hémato-Oncologie, Hôpital Saint-Louis, AP-HP, Université Paris Cité, Paris, France

Correspondence to
Professor Sophie Caillat-Zucman;
sophie.caillat-zucman@aphp.fr

ABSTRACT

Immune effector cell-associated neurotoxicity syndrome (ICANS) remains a significant cause of morbidity associated with CD19-targeted chimeric antigen receptor (CAR) T-cell therapy. Early prediction of patients who will develop ICANS would be crucial to better guide individualized management of high-risk patients, but specific predictive markers are still missing. Serum neurofilament light chain (NfL) levels are a sensitive indicator of neuroaxonal injury in neurological diseases. Elevated NfL levels at the time of CAR T-cell infusion have been associated with the severity of ICANS, but their utility for earlier identification of patients with subclinical neurological damage has not been evaluated.

We studied all consecutive adult patients who received commercial CAR T cells for relapsed/refractory B-cell lymphomas at Saint-Louis Hospital between January 2019 and February 2023. Patients with pre-existing or current neurological disease were excluded. NfL levels were quantified in frozen serum collected at the time of the decision to treat (ie, the day of leukapheresis) and at the time of treatment (ie, the day of infusion).

Of the 150 study patients, 28% developed ICANS of any grade, including 15.3% of grade 2–4. Receiving a CAR construct with a CD28 domain (58% of patients) was the strongest predictor of grade 2–4 ICANS. Serum NfL levels were significantly higher in patients with grade 2–4 ICANS than in those with grade 0–1 ICANS, both at the time of leukapheresis and infusion. In multivariate models, NfL above the cut-off value was independently associated with grade 2–4 ICANS at leukapheresis (NfL>75 pg/mL, OR 4.2, 95% CI 1.2 to 14.2, p=0.022) and infusion (NfL>58 pg/mL, OR 4.3, 95% CI 1.3 to 13.7, p=0.015).

In conclusion, high NfL levels at the time of the decision to proceed with CAR T-cell manufacturing may represent an early surrogate of underlying loss of neuroaxonal integrity that increases the risk of subsequent neurotoxicity. Incorporating NfL levels into the decision-making process based on each patient's risk profile could help determine the appropriate CAR product when possible, and guide the prophylactic or therapeutic management of ICANS.

BACKGROUND

CD19-targeted chimeric antigen receptor (CAR) T cells have been a breakthrough in the treatment of refractory or relapsed B-cell lymphoma (rrBCL).[1] However, their use remains hampered by the emergence of immune-mediated toxicities, in particular cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[2] ICANS occurs in 20–70% of patients treated with CD19-directed CAR-T cells and remains a significant cause of CAR T-cell-related morbidity, prolonged hospitalization and increased supportive care.[3–6] Optimal management of ICANS is based on patient characteristics and toxicity grade according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.[7–10] Corticosteroids are recommended to treat clinically significant ICANS (grade≥2), but they have their own set of adverse effects and may affect CAR T-cell efficacy.[10] Therefore, early prediction of patients who will develop ICANS would be crucial to better guide individualized management of high-risk patients.

The mechanisms leading to ICANS are not fully elucidated and involve increased cytokine levels, endothelial activation, and impaired blood-brain barrier permeability.[11–13] Currently, beyond older age, pre-existing neurological disease and factors also associated with CRS, such as high tumor burden, inflammatory markers and CARs equipped with a CD28 costimulatory domain,[5 12–14] specific risk factors for ICANS remain poorly described. Several risk scores based on pre-infusion laboratory parameters have been associated with the occurrence and severity of CAR T-cell-related toxicities,[15–18] but they have limited specificity for ICANS.

Neurofilament light chain (NfL), a neuroaxonal cytoskeletal protein released into both cerebrospinal fluid and blood, has emerged as a valuable biomarker for assessing neuronal damage and predicting outcomes in several neurological disorders.[19] Interestingly, recent

studies showed that elevated serum NfL levels prior to CAR T-cell infusion correlated with subsequent ICANS severity.[20 21] However, the utility of NfL as a surrogate for early identification of patients with latent neuroaxonal injury at the time of the clinical decision to proceed with CAR T-cell manufacturing has not been evaluated.

We therefore sought to determine the association between NfL levels before leukapheresis and before CAR T-cell infusion and the subsequent occurrence of ICANS.

METHODS

Study population and data collection

This single-center retrospective study included all consecutive adult patients who received commercial CAR T cells as second-line or third-line therapy for rrBCL at St-Louis Hospital between January 2019 and February 2023, and had archived serum samples available at the time of treatment decision (TD) and at the time of treatment (TT). Patients with pre-existing neurological disease or central nervous system (CNS) localization of lymphoma were excluded from the study. Patients received axicabtagene-ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), or tisagenlecleucel (tisa-cel), depending on slot availability and underlying disease. All patients received lymphodepletion with cyclophosphamide and fludarabine. Baseline patient and tumor characteristics were prospectively collected through the electronic medical record. Disease burden was evaluated based on lactate dehydrogenase (LDH) and total metabolic tumor volume (TMTV) before lymphodepletion. Baseline laboratory values, including C-reactive protein (CRP), albumin and ferritin, were determined before CAR T-cell infusion, and the modified Endothelial Activation and Stress Index (mEASIX) was calculated as reported.[15] No prophylactic corticosteroids and/or tocilizumab were used. CRS and ICANS were graded according to the ASTCT consensus criteria.[7]

NfL quantification

Patient's frozen serum samples were stored at the immunology laboratory. Samples at the time of TD were collected on the day of leukapheresis. Samples at TT were collected on the day of CAR T-cell infusion. NfL levels were quantified (triplicate measurements) using the Ella automated simple plex immunoassay system (lower limit of quantification 1.09 pg/mL) (Bio-Techne).

Statistical analysis

Standard descriptive statistics were used to summarize baseline demographic, clinical and biological characteristics. Categorical variables were presented as number and percentage, and quantitative variables as median and IQR. Patients with clinically significant ICANS (grade 2–4) were compared with those with no or mild ICANS (grade 0–1), with the intention of having a sufficient number of events to allow for statistical power and of identifying a clinically relevant toxicity level. Comparisons between groups were performed using the Mann-Whitney U test, and χ^2 or Fisher's exact test, as appropriate. Association between variables was assessed using Spearman's rank correlation test. Cumulative incidence curves were calculated for grade 2–4 ICANS. OR associated with the occurrence of grade 2–4 ICANS were computed using logit-regression models. Since risk factors and patient characteristics may vary between TD and TT, we built two statistical models with distinct variables. Quantitative biological variables were dichotomized in subsequent statistical models using receiver operating characteristics to select the best threshold for discriminating subsequent grade 2–4 ICANS. All variables significantly associated with grade 2–4 ICANS in the univariate analysis were included in the multivariate analysis. Full multivariate models were subjected to variable selection using a backward stepwise procedure with a stopping rule based on the Akaike criterion to build parsimonious risk prediction models. Missing data were not imputed. All tests were two-tailed with α=0.05. Analyses were performed using R statistical software (V.4.1.1).

RESULTS

Of the 187 patients with rrBCL who received standard-of-care CAR T cells between January 2019 and February 2023, 150 met the inclusion criteria (online supplemental figure S1). Of these, 52.7% were over 60 years old and 68.7% were men (table 1). Overall, 87 (58.0%) patients received CD28-containing CAR (79 axi-cel, 8 brexu-cel) and 63 (42.0%) received 4-1BB-containing CAR (tisa-cel). The mean time between leukapheresis and CAR T-cell infusion was 42 days, and most patients (86%) received bridging therapy. One-third of patients had a high disease burden defined by TMTV>80 mL before lymphodepletion.

Altogether, 42 (28%) patients developed ICANS of any grade, including 19 grade 1 (12.7%), 15 grade 2 (10%), 4 grade 3 (2.7%), 4 grade 4 (2.7%) and no grade 5. Due to the low rate of grade≥3 ICANS precluding biomarker analysis for this subgroup, we compared patients with clinically significant ICANS (grade 2–4, n=23) to those with mild or no ICANS (grade 0–1, n=127), as previously performed in similar studies[20 22 23] (table 1). Grade 2–4 ICANS occurred in 21 of 87 (24%) patients who received CD28 CAR, and 2 of 63 (3%) of those who received 4-1BB CAR.

Of the clinical factors evaluated, Eastern Cooperative Oncology Group performance status≥2 was the only factor significantly associated with grade 2–4 ICANS on univariate analysis (tables 1 and 2). Of note, high tumor burden, defined by LDH above the upper limit of normal or TMTV>80 mL before lymphodepletion, was not associated with more severe ICANS (table 1).

To address the ability of NfL levels to predict ICANS at the time of decision to proceed with CAR T-cell manufacturing, we quantified NfL in serum samples collected at the time of leukapheresis. NfL levels were significantly

Table 1 Characteristics of the patients

	Overall	ICANS 0–1	ICANS 2–4	P value
n	150	127	23	
Background				
Age	61.0 (52.0–67.0)	60.0 (51.0–67.0)	64.0 (58.0–69.5)	0.083
Male	103 (68.7)	89 (70.1)	14 (60.9)	0.563
Histology				0.489
DLBCL	107 (71.3)	93 (73.2)	14 (60.9)	
PMBCL	2 (1.3)	2 (1.6)	0 (0.0)	
tFL	33 (22.0)	26 (20.5)	7 (30.4)	
MCL	8 (5.3)	6 (4.7)	2 (8.7)	
GC phenotype	60 (51.7)	54 (53.5)	6 (40.0)	0.486
Previous lines≥4	26 (17.3)	23 (18.1)	3 (13.0)	0.782
CAR T-cell product				**0.002**
axi-cel	79 (52.7)	60 (47.2)	19 (82.6)	
brexu-cel	8 (5.3)	6 (4.7)	2 (8.7)	
tisa-cel	63 (42.0)	61 (48.0)	2 (8.7)	
CD28 costimulatory domain	87 (58.0)	66 (52.0)	21 (91.3)	**0.001**
Characteristics at the time of treatment decision				
ECOG performance status≥2	14 (11.0)	9 (8.2)	5 (29.4)	**0.029**
Ann Arbor stage 3–4	112 (78.3)	93 (76.2)	19 (90.5)	0.239
IPI high-intermediate or high	57 (38.0)	49 (38.6)	8 (34.8)	0.911
LDH>N	73 (57.9)	63 (57.3)	10 (62.5)	0.901
Characteristics before lymphodepletion				
ECOG performance status≥2	23 (16.1)	14 (11.6)	9 (40.9)	**0.002**
Ann Arbor stage 3–4	107 (80.5)	90 (78.9)	17 (89.5)	0.448
IPI high-intermediate or high	45 (30.0)	37 (29.1)	8 (34.8)	0.767
TMTV	46.6 (19.3–135.1)	44.5 (18.6–135.1)	54.5 (26.0–121.9)	0.515
Bridging	129 (86.0)	108 (85.0)	21 (91.3)	0.638
Biological tests on the day of CAR-T infusion				
Lymphocyte count (/mm3)	30.0 (0.0–62.5)	30.0 (0.0–70.0)	20.0 (2.5–50.0)	0.514
CRP (mg/L)	14.0 (6.0–36.0)	14.0 (5.5–31.0)	13.5 (6.0–70.8)	0.699
Albumin (g/L)	38.0 (35.0–40.0)	38.0 (36.0–40.0)	36.5 (33.2–40.0)	0.126
Ferritin (mg/L)	630.5 (330.5–1127.5)	599.5 (333.5–1050.8)	922.0 (373.2–2975.2)	0.077
LDH (U/L)	311.5 (207.8–435.5)	309.0 (208.2–431.5)	334.0 (204.8–454.2)	0.782
mEASIX	2.2 (1.1–4.1)	2.2 (1.4–4.1)	2.8 (1.1–3.8)	0.755
Serum NfL levels				
NfL before leukapheresis (pg/mL)	53.8 (34.2–91.7)	48.8 (32.7–82.1)	79.2 (49.0–126.5)	**0.015**
NfL before infusion (pg/mL)	51.2 (36.4–93.0)	49.0 (35.4–84.9)	81.0 (49.9–101.0)	**0.025**
Outcomes after infusion				
CRS	117 (78.0)	95 (74.8)	22 (95.7)	0.051
CRS grade≥2	41 (27.3)	27 (21.3)	14 (60.9)	**<0.001**
Total duration of ICANS (days)	5.0 (3.0–10.0)	3.5 (1.0–5.5)	7.0 (4.0–10.5)	0.032
Admission to the ICU	45 (30.6)	26 (21.0)	19 (82.6)	**<0.001**
Death at D90	48 (32.0)	40 (31.5)	8 (34.8)	0.946

Continued

Table 1 Continued

	Overall	ICANS 0–1	ICANS 2–4	P value

Results are presented as n (%) for categorical variables and median (IQR) for quantitative variables. No patient was lost to follow-up at 90 days. Significant P values are indicated in bold.
CAR, chimeric antigen receptor; CRP, C-reactive protein; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GC, Germinal Center; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; mEASIX, modified version of the Endothelial Activation and Stress Index; NfL, neurofilament light chain; PMBCL, primary mediastinal large B-cell lymphoma ; tFL, transformed follicular lymphoma; TMTV, total metabolic tumor volume.

higher in patients who developed grade 2–4 ICANS than in patients with grade 0–1 ICANS (79.2 pg/mL (IQR 49.0–126.5) vs 48.8 pg/mL (IQR 37.2–82.1), p=0.015) (figure 1A). Using a cut-off value of 75.1 pg/mL, NfL at TD could stratify ICANS severity (grade 2–4 vs 0–1) with a sensitivity of 0.57 and specificity of 0.71 (area under the curve (AUC), 0.66) (online supplemental figure S2). The cumulative incidence of grade 2–4 ICANS was 28% and 11% for NfL values above or below the cut-off value, respectively (p=0.012) (figure 1B). In a parsimonious multivariate model, NfL>75 pg/mL was independently associated with grade 2–4 ICANS (OR 4.2, 95% CI 1.2 to 14.2, p=0.022) (figure 1C and table 2).

In parallel, NfL was quantified in serum samples collected at the time of CAR T-cell infusion. Here again, NfL levels were higher in patients who developed grade 2–4 ICANS than in those with grade 0–1 ICANS (81.0 pg/mL (IQR 49.9–101.0) vs 49.0 pg/mL (IQR 35.4–84.9 pg/mL), p=0.025) (figure 1D). Using a cut-off of 58.2 pg/mL, NfL at TT could stratify ICANS severity (grade 2–4 vs 0–1) with a sensitivity of 0.66 and specificity of 0.70 (AUC, 0.65) (online supplemental figure S2). Additional laboratory factors associated with grade 2–4 ICANS included high ferritin levels (OR for levels above>803 mg/mL, 2.7, 95% CI 1.1 to 6.9) and low albumin levels (OR for levels<35 g/L, 3.36 95% CI 1.3 to 8.9) (table 2). Pre-infusion mEASIX score was not associated with more severe ICANS. The cumulative incidence of ICANS 2–4 was 25% and 8% for NfL values above or below the cut-off value, respectively (p=0.005) (figure 1E). As in the analysis at TD, a parsimonious multivariate model showed that NfL>58 pg/mL was independently associated with grade 2–4 ICANS (OR 4.3, 95% CI 1.3 to 13.7, p=0.015) (figure 1F and table 2). Furthermore, NfL levels at TD and TT were strongly correlated (r=0.74, p<0.0001) (figure 2A) and were not significantly different (figure 2B,C), suggesting that NfL release in the serum is a stable process. Of note, receiving a CAR construct with a CD28 domain was the strongest predictor of grade 2–4 ICANS (table 2). Characteristics of patients with and without increased NfL levels at TD and TT are shown in online supplemental tables 1 and 2.

DISCUSSION

Recent efforts to identify biomarkers or develop risk scores based on clinical laboratory parameters are of great interest to better predict the risks of CAR T-cell-related toxicities. Such models usually incorporate host or tumor factors analyzed just before lymphodepleting chemotherapy or before infusion.[15–18] To date, no laboratory test makes it possible to specifically identify patients at high risk for ICANS long in advance, when the decision to proceed to CAR T-cell manufacturing is made. Such information could help clinicians in their decision-making to consider different therapeutic options or anticipate preventive strategies in high-risk patients.

Patients with pre-existing neurological disease or known CNS damage are at higher risk of developing ICANS.[11] NfL is a widely used sensitive and specific marker of neuroaxonal injury in neurological diseases. Following axonal damage in the CNS, NfL levels increase in the blood where they remain elevated for weeks or months.[19] We therefore assessed whether NfL levels, by reflecting an underlying loss of neuroaxonal integrity, could predict the risk of ICANS well in advance of CAR T-cell infusion in patients without known neurological disease or CNS lymphoma. We show here that elevated serum NfL levels at the time of leukapheresis are significantly associated with the subsequent occurrence of grade 2–4 ICANS. Moreover, we confirm previous studies showing that elevated NfL levels at the time of CAR T-cell infusion are associated with more severe ICANS.[20 21] The strong correlation we observed between NfL levels at the time of leukapheresis and infusion suggests that NfL levels are not significantly altered by bridging and lymphodepletion chemotherapies. These results demonstrate for the first time, to our knowledge, the usefulness of NfL as an early predictor of ICANS in patients without objective neurological damage.

In our cohort, only 28% of patients developed ICANS of any grade, including 15% with ICANS of grade≥2, a lower rate than reported in clinical trials and real-life studies.[1 3 5] This may be explained by our deliberate exclusion of patients with neurological history in order to better assess the value of NfL as a surrogate for subclinical neurological damage. Moreover, more than 40% of study patients were given tisa-cel, which may also explain the paucity of severe ICANS, rarely observed in patients given this product.[5] Indeed, receiving CD28-equipped CAR T cells was the strongest predictor of subsequent ICANS.

Among other clinical or biological factors analyzed at the time of the decision to treat, only a poor performance status was associated with severe ICANS. Quantification of tumor burden by TMTV was only performed before lymphodepletion, making it impossible to incorporate

Table 2 Risk factors for grade 2–4 ICANS at the time of CAR T-cell treatment decision and time of treatment

	Univariate model		Multivariate model		Parsimonious model	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
At the time of treatment decision (TD)						
Male	0.66 (0.26 to 1.67)	0.383				
Age>60 years	1.85 (0.73 to 4.66)	0.194				
DLBCL (vs others)	0.57 (0.23 to 1.43)	0.232				
GC lymphoma	0.58 (0.19 to 1.75)	0.334				
Previous lines≥4	0.68 (0.19 to 2.48)	0.557				
IT chemotherapy	1.75 (0.52 to 5.9)	0.370				
Poor IPI	3.16 (0.94 to 10.65)	0.064				
Ann Arbor>2	2.96 (0.65 to 13.48)	0.160				
PS≥2	**4.68 (1.34 to 16.26)**	**0.015**	3.69 (0.79 to 17.25)	0.097	3.69 (0.79 to 17.25)	0.097
LDH>N	1.24 (0.42 to 3.66)	0.693				
NfL at TD>75 pg/mL	**3.11 (1.24 to 7.8)**	**0.016**	**4.17 (1.23 to 14.17)**	**0.022**	**4.17 (1.23 to 14.17)**	**0.022**
CAR with CD28 domain	**9.7 (2.18 to 43.13)**	**0.003**	**10.6 (2.04 to 55.15)**	**0.005**	**10.6 (2.04 to 55.15)**	**0.005**
At the time of treatment (TT)						
Male	0.66 (0.26 to 1.67)	0.383				
Age>60 years	1.85 (0.73 to 4.66)	0.194				
DLBCL (vs other histology)	0.57 (0.23 to 1.43)	0.232				
GC lymphoma	0.58 (0.19 to 1.75)	0.334				
Previous lines≥4	0.68 (0.19 to 2.48)	0.557				
Poor IPI	2.96 (0.79 to 11.18)	0.108				
Ann Arbor>2	2.27 (0.49 to 10.5)	0.295				
PS≥2	**5.29 (1.92 to 14.62)**	**0.001**	3.34 (0.83 to 13.36)	0.088	**4.64 (1.31 to 16.4)**	**0.017**
High TMTV	1.26 (0.48 to 3.31)	0.634				
IT chemotherapy	1.75 (0.52 to 5.9)	0.370				
Lymphocyte count>35/mm3	0.50 (0.19 to 1.33)	0.164				
LDH>N	0.50 (0.18 to 1.36)	0.175				
CRP>67 mg/L	0.91 (0.37 to 2.26)	0.837				
Albumin level<35 g/L	**3.36 (1.27 to 8.88)**	**0.014**	1.42 (0.37 to 5.52)	0.610		
Ferritin level>803 ng/L	**2.72 (1.08 to 6.87)**	**0.034**	2.23 (0.71 to 6.99)	0.171		
mEASIX>2.2	1.35 (0.49 to 3.68)	0.560				
NfL at TT>58 pg/mL	**4.01 (1.54 to 10.49)**	**0.005**	**3.52 (1 to 12.4)**	**0.050**	**4.27 (1.32 to 13.74)**	**0.015**
CAR with CD28 domain	**9.7 (2.18 to 43.13)**	**0.003**	**9.77 (1.99 to 47.91)**	**0.005**	**8.38 (1.78 to 39.37)**	**0.007**

For quantitative variables, variables were dichotomized and receiver operating characteristics were calculated to select the optimal threshold for discriminating subsequent grade 2–4 ICANS.
Variables with significant P values are indicated in bold.
CAR, chimeric antigen receptor; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; GC, Germinal center; ICANS, immune effector cell-associated neurotoxicity syndrome; IPI, International Prognostic Index; IT, Intra Thecal; LDH, lactate dehydrogenase; mEASIX, modified Endothelial Activation and Stress Index; NfL, neurofilament light chain; PS, performance status; TMTV, total metabolic tumor volume.

this information in early risk score. Unfortunately, we were also unable to determine the mEASIX score at the time of leukapheresis because the required parameters were not available. At the time of treatment, mEASIX was not associated with ICANS, as expected given the lack of predictive value of LDH and CRP levels in our cohort. In support of our observation, mEASIX was shown to discriminate severe ICANS at early post-infusion time points, but not before infusion.[15]

Our observations have potentially important practical consequences. First, the availability of a reliable predictive biomarker at the time of decision to treat could facilitate proactive prevention of ICANS by choosing, when possible, the type of CAR T constructs which have a lower

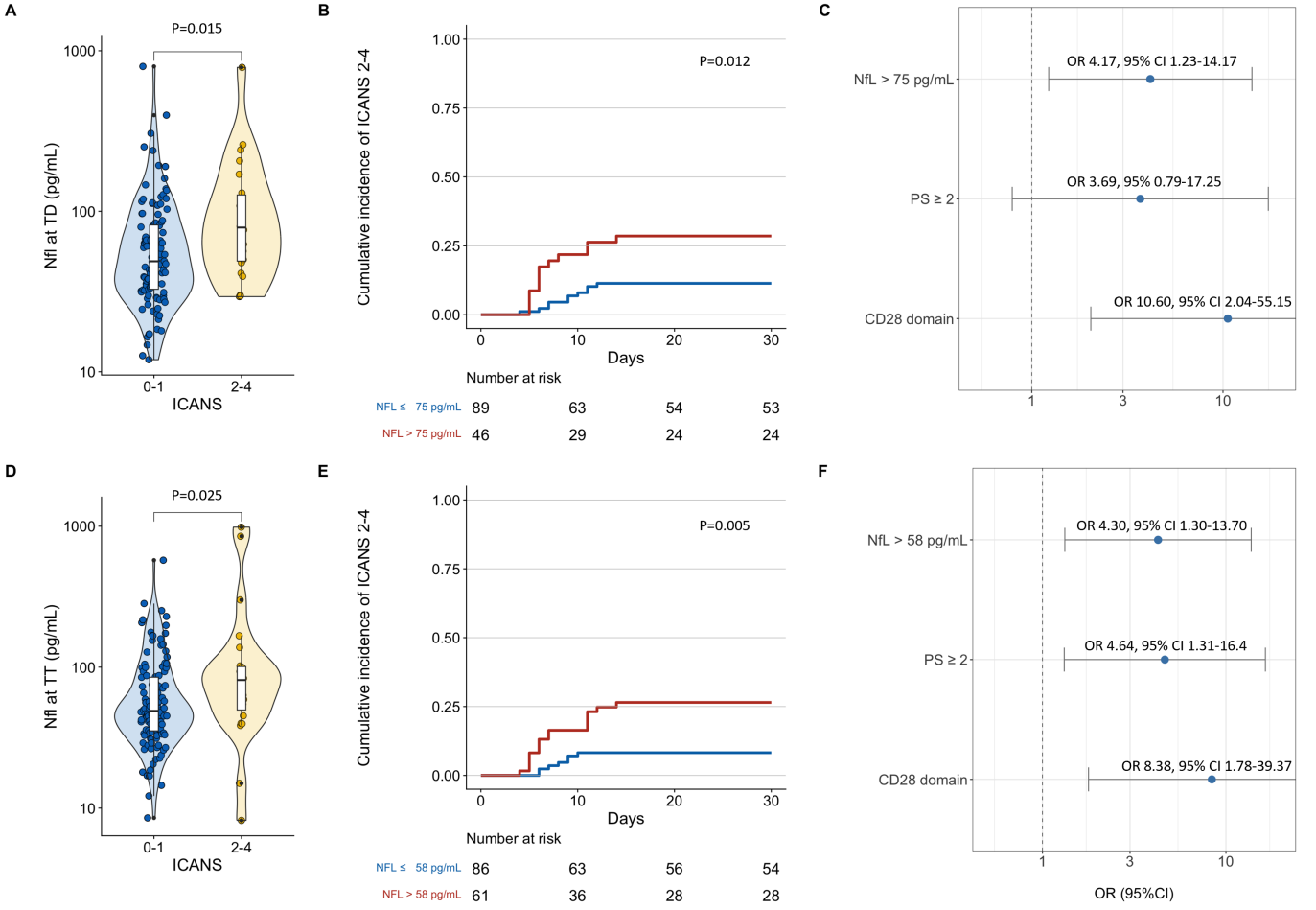

Figure 1 Association between serum NfL levels and occurrence of moderate-to-severe ICANS. Upper panel: At the time of decision (TD) to proceed to CAR T-cell therapy: (A) Serum NfL levels were significantly higher in patients who developed moderate-to-severe ICANS (grade 2–4) than in patients with no or mild ICANS (grade 0–1). (B) Cumulative incidence of ICANS 2–4 according to NfL levels above or below the cut-off value (75 pg/mL). (C) Factors associated with occurrence of subsequent grade 2–4 ICANS. Lower panel: At the time of treatment (TT): (D) Serum NfL levels were significantly higher in patients who developed moderate-to-severe ICANS (grade 2–4) than in patients with no or mild ICANS (grade 0–1). (E) Cumulative incidence of ICANS 2–4 according to NfL levels above or below the cut-off value (58 pg/mL). (F) Factors associated with occurrence of subsequent grade 2–4 ICANS. CAR, chimeric antigen receptor; ICANS, immune effector cell-associated neurotoxicity syndrome; NfL, neurofilament light chain; PS, performance status.

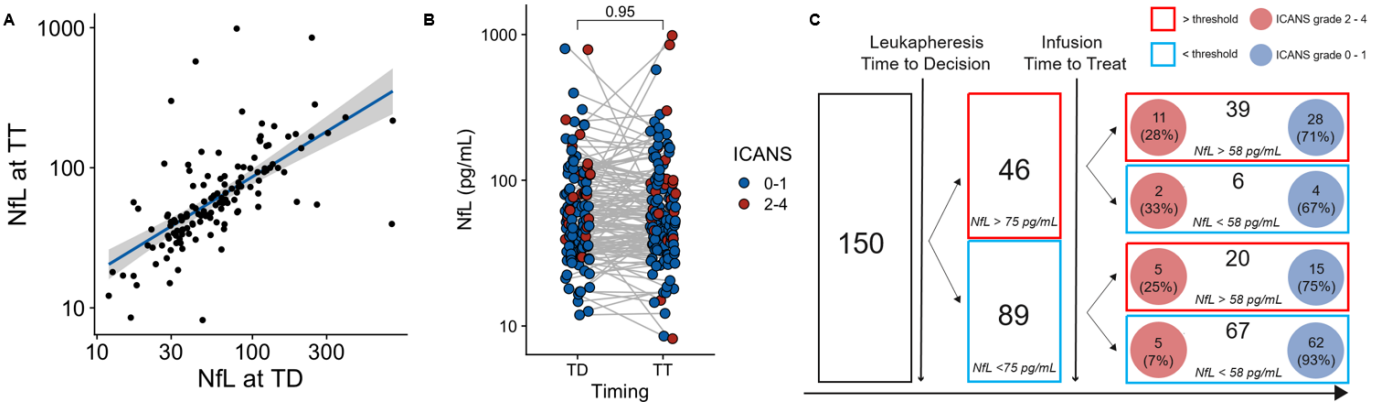

Figure 2 Correlation between NfL levels at TD and TT. (A) Regression curve and best fit line are shown. (B) Dynamic changes of NfL levels between TD and TT. (C) Correlation between NfL level at TD, at TT and occurrence of ICANS. ICANS, immune effector cell-associated neurotoxicity syndrome; NfL, neurofilament light chain; TD, time of treatment decision; TT, time of treatment.

risk of neurotoxicity (4-1BB vs CD28). Second, early risk assessment of ICANS would allow for risk-adapted prophylactic or preemptive therapies. Although the systematic administration of corticosteroids could be effective in preventing neurotoxicity, it also has several deleterious side effects, notably an increased risk of infection. In addition, the potential impact of corticosteroids on CAR T-cell efficacy remains controversial.[10] Based on the contribution of interleukin (IL)-1 signaling in the pathogenesis of ICANS,[22 24] the IL-1 receptor antagonist anakinra is increasingly used to treat refractory ICANS. Furthermore, as the question of prophylactic anakinra has recently been raised,[23 25] it seems even more important to identify those patients who would be most likely to benefit from it. Finally, tocilizumab, a cornerstone in the treatment of CAR-T-associated CRS, may increase the incidence and severity of ICANS by leading to increased circulating IL-6 in the CNS. Patients identified as being at high risk of ICANS could thus be scrutinized prior to tocilizumab administration.

Our study has several strengths. First, our cohort is larger than previous studies focusing on NfL at CAR T-cell peri-infusion time points[20 21] and is, to the best of our knowledge, the first to evaluate NfL as early as the time of treatment decision. Second, it focuses on patients without objective neurological disease and therefore suggests that NfL is a surrogate marker of subclinical neuroaxonal damage that may promote the occurrence of ICANS.

However, our study has several limitations due to its single center and retrospective nature, as well as the low rate of ICANS and the inclusion of patients treated with different CAR T-cell products. Therefore, further validation in a replication cohort of patients given CD28-equipped CAR T cells is warranted.

In conclusion, our study underlines the role of NfL as a potential biomarker for predicting the risk of ICANS with a more personalized and proactive approach in the management of this complication. By adding NfL levels both at the time of the decision to treat and the time of treatment to already existing ICANS risk prediction scores, clinicians might have a decision-making tool for determining the appropriate CAR product when possible, and guide the preventive and therapeutic management of ICANS. This approach would be even more useful in the absence of obvious clinical risk factors for neurotoxicity.

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Contributors SC-Z, ML and AB conceived and designed the study. ML and AB collected the data. SC-Z, ML, AB and AM analyzed the data. ML, AB, AM and SC-Z wrote the manuscript. All authors critically revised and approved the final manuscript. SC-Z, is the guarantor of the study, had full access to all the data, and took responsibility for the integrity of the data and the accuracy of the data analysis.

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ORCID iDs
Marion Larue http://orcid.org/0000-0003-4810-045X
Sophie Caillat-Zucman http://orcid.org/0000-0002-4535-3550

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