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BRIEF COMMUNICATION

Pre-existing frontal lobe dysfunction signs as predictors of subsequent neurotoxicity in CAR T cell therapy: insights from a case series

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Abstract

Background Chimeric Antigen Receptor (CAR) T cell therapies are innovative treatments against hematological malignancies, with increasing therapeutic indications. Despite their great efficacy, these therapies are hampered by high rates of neurotoxicity (immune effector cell–associated neurotoxicity (ICANS)). In the past few years, several risk factors have been associated with ICANS and grouped together in the attempt to build validated models able to predict neurologic complications. However, little is known about pre-existing neurologic conditions possibly related to the development of neurotoxicity.

Methods and results In our case series, including sixteen consecutive patients treated with CAR T cells, we observed that (i) neurotoxicity only occurred in the two patients who presented subtle clinical signs of frontal lobe impairment at baseline and (ii) neurologic manifestations of ICANS consisted of language disturbances and cortical frontal myoclonus, which were both manifestations of a frontal predominant dysfunction.

Discussion Based on our experience, we suggest that a pre-existing frontal lobe impairment, even if at a subclinical level, may eventually drive to ICANS, which in turn shows symptoms compatible with a frontal encephalopathy. It is remarkable that this focal neurotoxicity involved the same CNS regions that were responsible of subtle neurological signs at baseline. Future studies on larger numbers of patients are needed to confirm the possible role of baseline frontal lobe dysfunction as a predictor of ICANS, in order to enhance efforts to safely deliver CAR T cell therapy.

Keywords CAR T cell therapy · Neurotoxicity · Immune effector cell–associated neurotoxicity syndrome (ICANS) · Frontal encephalopathy

Introduction

Chimeric antigen receptor (CAR) T cell therapies are innovative immunotherapy treatments consisting of patient's autologous T cells genetically engineered to elicit an immune response toward cancer cells. Since the approval of the first CAR-T therapy, i.e., tisagenlecleucel in 2017, five new drugs have been introduced in clinical use so far (i.e., brexucabtagene autoleucel, axicabtagene ciloleucel, idecabtagene vicleucel, lisocabtagene maraleucel, ciltacabtagene autoleucel) for the treatment of acute lymphoblastic leukemia and certain subtypes of non-Hodgkin lymphomas, such as diffuse large B cell lymphoma and mantle cell lymphoma. In addition, several lines of research are currently investigating the efficacy of CAR T cell therapies on follicular lymphoma, multiple myeloma, and solid tumors [1]. Despite a great efficacy in treating refractory malignancies, these therapies are hampered by high rates of adverse events encompassing systemic and neurologic toxicities, as occurring in the cytokine release syndrome (CRS) and in the immune effector cell–associated neurotoxicity syndrome (ICANS), respectively.

Clinical manifestations of neurotoxicity reflect a diffuse involvement of central nervous system (CNS). Common symptoms include waxing and waning encephalopathy, headache, delirium, language disturbances, tremor, and seizures [2].

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Considering that ICANS has usually a good outcome when treated early, its prompt identification is crucial to provide adequate management. Since the release of CAR T cell therapies, multiple grading systems have been proposed for an early recognition of neurotoxicity. Recently, the use of immune effector cell–associated encephalopathy (ICE) score, a 10-point screening tool assessing multiple neurologic domains, has been endorsed by the American Society for Transplantation and Cellular Therapy (ASTCT), since it was recognized as objective, accurate, and easy to use [3]. Current recommendations suggest to perform ICE at least every 8 h in patients treated with CAR T cell therapies [4].

Along with the implementation of effective tools to detect early neurotoxicity, extensive studies have been carried out to identify risk factors for developing ICANS [5, 6]. Indeed, risk factors of neurotoxicity could be categorized as (1) related to tumor (e.g., type and burden of disease), (2) related to patient (e.g., weight of subject, platelets count, serum albumin), (3) related to treatment (e.g., type of CAR T therapy, dose of CAR T cells, pharmacokinetics of CAR T therapy), and (4) related to interplay patient-treatment (e.g., fever, hemodynamic instability, grading of CRS). Taking into account some of these features that were significantly associated with the development of neurotoxicity in their large case series, Rubin and colleagues developed a multivariate score to predict the risk of ICANS [7]. In more details, the authors proposed a predictive score ranging from 0 (lowest probability of ICANS) to 14 (highest probability of ICANS), by assigning 0–3 points to specific clinical and laboratory markers (i.e., age of subject, lymphoma indolent/aggressive, maximum daily body temperature, serum levels of C-reactive protein, white blood cell count, fibrinogen, ferritin, procalcitonin, lactate dehydrogenase, IL-6, and number of doses of tocilizumab administered) [7]. However, it is well accepted for various types of cancer that a high disease burden at the time of CAR T cell infusion implies a higher risk of ICANS [6]. Although with less evidence, several data from clinical trials and small case series suggest that also other factors may predispose to neurotoxicity, such as the preconditioning with fludarabine and cyclophosphamide, or specific clinical and biohumoral features (e.g., increased patient weight, low platelets count, low serum albumin) [8, 9].

Indeed, inflammation after CAR T cell infusion has a crucial role in determining neurotoxicity, as proved by the tight association between CRS severity and ICANS. The hypothesized mechanism linking CRS and ICANS could rely on an increased permeability of blood–brain barrier (BBB) due to a cytokine-mediated disruption, thus leading cytokines and immune effector cells to enter the CNS [10]. In this regard, the decisional tree designed by Gust et al., based on early onset of high fever and high concentration of specific serum inflammatory biomarkers (e.g., interleukin 6 and monocyte chemoattractant protein-1) after the CAR T cell infusion, was able to predict subjects who were likely to develop severe neurotoxicity [6].

Compared to the extensive research performed on inflammation, little is known about pre-existing neurologic conditions possibly related to the development of neurotoxicity. In particular, Gust and colleagues underlined the need of considering pre-existing neurologic comorbidities as risk factors for ICANS; in their study, the authors demonstrated that different pre-existing neurologic comorbidities—including headache, seizures, cognitive impairment, peripheral neuropathies, and intracranial hemorrhages—resulted in an increased risk of neurotoxicity when considered as a whole, but none of them was specifically linked to ICANS when considered alone [6]. Undoubtedly, the idea of considering pre-existing neurologic comorbidities as potential risk factors for a subsequent neurotoxicity was very interesting but a limitation of the study was related to not distinguish central and peripheral neurologic conditions, with different pathogenesis and organic substrates [6].

More recently, Pensato and colleagues demonstrated that the presence of electroencephalogram (EEG) abnormalities—even if mild—at baseline (i.e., one day before the infusion) correlated with the development of ICANS [11].

Given this background, the aim of our study was to analyze our cohort of patients treated with CAR T cell therapy, with a specific focus on neurologic anamnestic history and baseline full neurologic examination, in order to look for, even subtle, signs of neurologic involvement which could eventually predict the onset of neurotoxicity.

Methods

We conducted a retrospective study on subjects who received CAR T cell therapy in the Hematology Unit at Azienda Ospedaliero-Universitaria Pisana (Pisa, Italy), from December 2020 to December 2022. All data were collected from medical records. Demographic features included sex and age at treatment, while clinical features included tumor histologic type, tumor grade, previous chemotherapy treatments, CAR T therapy used, onset and maximum grade of CRS (if applicable), onset and maximum grade of ICANS (if applicable), pre-existing non-neurologic and neurologic conditions, and abnormal signs at baseline neurologic examination. CRS and ICANS occurrence was graded according on the ASTCT consensus [3].

All patients underwent a thorough neurologic examination and a brain CT scan in the week before the CAR T cell infusion. From the day of the infusion, ICE scale was administered by a trained nurse every 8 h (i.e., at every shift change) as per current guidelines and revised by a

neurologist if any of the items were compromised. All patients were hospitalized for at least 7 days after the infusion. If ICANS occurred, daily neurologic examinations and further tests, following the clinical manifestations, were performed and recorded. In particular, for patient no. 11, we recorded simultaneous EEG and electromyography (EMG) while he was hospitalized in the cleanroom of the Hematology Unit; the EEG recording was performed with 6 needle electrodes placed according to the 10–20 international system and referenced to the ipsilateral mastoid (F3, C3, O1, F4, C4, O2); sample rate was 128 Hz. Signal back averaging was obtained using a custom script on MATLAB (The Math Works, Inc. MATLAB. Version 2022b) and Brainstorm for EEG visualization and event markers placement (freely available for download online under the GNU general public license http://neuroimage.usc.edu/brainstorm).

Results

Sixteen consecutive patients (7 females, 9 males), with a median age at treatment of 62.7 years, were included in the study. Fourteen patients were affected by resistant diffuse large B cell lymphoma and were treated either with tisagenlecleucel (11 patients) or axicabtagene ciloleucel (3 patients), while 2 patients were affected by mantle cell lymphoma and received brexucabtagene autoleucel. Considering the day of CAR-T infusion as day 0 (T_0), all patients underwent a standard lymphodepletion treatment with fludarabine and cyclophosphamide since T_{-5} to T_{-3}, followed by a washout in T_{-2} and T_{-1}.

None of the patients had cerebral localizations of disease. Table 1 lists the patients in order of infusion, providing details on tumor histotypes, pre-existing neurological comorbidities, signs at full neurologic examination before the CAR T cell infusion, type of CAR T cell treatment, and onset and maximal grade of CRS and ICANS. Further information on patient characteristics and serum values, tumor grade, previous non-neurologic conditions, and previous chemotherapy can be found in supplementary material (Table S1).

CRS was observed in 15/16 patients (grade 1 in 12 cases, grade 2 in 2 cases, grade 3 in 1 case), with a median onset time of 4.2 days (range: 1–11 days). Two patients (no. 3 and no. 11) developed ICANS.

Concerning pre-existing neurologic conditions, patient no. 12 had suffered from chronic inflammatory demyelinating polyneuropathy (CIDP), which had started 20 years before, but had not progressed for 10 years. His neurologic examination revealed mild gait ataxia with symmetric deficit in feet dorsiflexion, bilateral calf and foot hypoesthesia, reduced patellar, and Achilles reflexes.

Even though neurologic history was unremarkable in the other subjects, subtle signs at neurologic examination were found in two patients at screening visit, who interestingly were the two patients who developed ICANS (subjects 3 and 11).

A detailed description of both these cases is provided below.

Patient no. 3

Patient no. 3 was a 69-year-old woman suffering from DLCBL, stage IV. Although no history of neurologic diseases was reported, baseline neurologic examination revealed a slight cognitive-motor slowing with disorientation to time (she was unable to recall date and day of the week) and bilateral palmo-mental reflexes. Baseline brain CT was unremarkable. Twenty-four hours after the infusion of tisagenlecleucel (T_{+1}), she developed a writing disorder consisting of mild apraxic agraphia, literal paragraphia, and paligraphia. These symptoms had a rapid evolving course, and she became completely unable to write within a few hours. By that time, she was sleepy, disoriented in time and space, and unable to follow operator's instructions, to name objects, or do calculations. Of note, neurotoxicity was not preceded by any symptom related to CRS, but the patient developed low grade fever (37.8 °C) and mild oxygen saturation (92–93%) requiring low flow nasal cannula concomitantly to the onset of neurologic disturbances. A brain CT scan, performed on the same day, was normal. Tocilizumab was started (8 mg/kg intravenously, tris in diem) with complete remission of symptoms after a few hours from the first dose. Writing abilities fluctuated in the following two days with a complete recovery after T_{+3} (Fig. 1(a)).

Patient no. 11

Patient no. 11 was a 56-year-old man affected by DLBCL, stage IV. His past medical history was unremarkable, and his baseline CT scan was normal, while neurologic examination only revealed a slight motor impersistence in gaze fixation, accompanied by reduced saccade velocity. He was treated with axicabtagene ciloleucel and developed hyperpyrexia on day T_{+4}, unresponsive to paracetamol, requiring treatment with tocilizumab and low doses of dexamethasone. He experienced complete defervescence on day T_{+8}. However, on day T_{+11}, he started to develop bilateral jerky tremor along with action and stimulus-sensitive myoclonus in upper and lower limbs. Concomitantly, he developed a progressive disturbance in writing, characterized by apraxic agraphia and paragraphia (Fig. 1(b)). Brain CT and MRI, performed respectively on T_{+11} and on T_{+12}, were unremarkable. Simultaneous EEG and EMG recording from left flexor digitorum longus muscle was performed. On the EEG, we observed a diffuse

Table 1 Case series: main clinical characteristics of patients, baseline neurologic conditions, and complications after CAR T cell infusion

ID	Age and gender	Tumor histotype	Pre-existing neurologic conditions	Signs at full neurologic examination at screening visit	Type of CAR T cells treatment	CRS onset* and maximal grade°	ICANS onset* and maximal grade°
#1	56 M	DLBCL	–	Normal	Tisagenlecleucel	T_{+6} grade 1	–
#2	68 F	DLBCL	–	Normal	Tisagenlecleucel	T_{+3} grade 1	–
#3	68 F	DLBCL	–	Slight cognitive-motor slowing, slight disoriented to time, positive palmo-mental reflexes	Tisagenlecleucel	–	T_{+1} grade 2
#4	65 M	DLBCL	–	Normal	Tisagenlecleucel	T_{+1} grade 1	–
#5	66 M	DLBCL	–	Normal	Tisagenlecleucel	T_{+2} grade 2	–
#6	53 F	DLBCL	–	Normal	Tisagenlecleucel	T_{+2} grade 1	–
#7	65 M	DLBCL	–	Normal	Tisagenlecleucel	T_{+2} grade 3	–
#8	64 F	DLBCL	–	Normal	Axicabtagene ciloleucel	T_{+4} grade 1	–
#9	56 M	DLBCL	–	Normal	Axicabtagene ciloleucel	T_{+4} grade 2	–
#10	65 F	MCL	–	Normal	Brexucabtagene autoleucel	T_{+6} grade 1	–
#11	60 M	MCL	–	Slight motor impersistence in gaze fixation with reduced saccadic velocity	Brexucabtagene autoleucel	T_{+6} grade 1	T_{+11} grade 2
#12	53 M	DLBCL	CIDP	Mild gait ataxia, bilateral deficit in foot dorsiflexion, bilateral hypoesthesia of calf and foot, reduced patellar and Achilles reflexes	Tisagenlecleucel	T_{+2} grade 1	–
#13	54 F	DLBCL	–	Normal	Tisagenlecleucel	T_{+4} grade 1	–
#14	64 F	DLBCL	–	Normal	Tisagenlecleucel	T_{+3} grade 1	–
#15	26 M	DLBCL	–	Normal	Tisagenlecleucel	T_{+7} grade 1	–
#16	34 F	DLBCL	–	Normal	Axicabtagene ciloleucel	T_{+11} grade 1	–

Patients are listed in order of infusion. For each patient, table reports details on demographics, tumor histotypes, pre-existing neurologic comorbidities, signs at full neurologic examination before the CAR T cell infusion, type of CAR T cell treatment, onset and maximal grade of CRS and ICANS. Subtle signs at neurologic examination were found in two patients (no. 3 and no. 11) at screening visit, who interestingly were those who developed ICANS. In our series, anamnestic history of involvement of peripheral nervous system (i.e., CIDP in patient no. 12) was not associated with ICANS

Abbreviations: CIDP chronic inflammatory demyelinating polyneuropathy, *CRS* cytokine-related syndrome, *DLBCL* diffuse large B cell lymphoma, *ICANS* immune effector cell–associated neurotoxicity syndrome, *MCL* mantle cell lymphoma

*Onset of CRS and ICANS is expressed as T_{+n}, where *n* denotes the number of days after CAR T cell infusion

°Maximal grade of CRS and ICANS is determined according to ASTCT consensus grading

slowing without clear epileptiform activity. Then, we marked 8 larger jerks not preceded by baseline EMG activity and we used the EMG as a trigger pulse to back average the EEG signal. The jerk-locked back-averaging demonstrated a time locked biphasic sharp wave in right frontal and central regions which appeared 23 ms prior to jerks (Fig. 2). Levetiracetam, 1000 mg bis in diem, was started as prophylaxis of seizures, as indicated by current guidelines, along with corticosteroids. Symptoms gradually recovered within a few days. Two subsequent EEG at 7 days and 30 days apart showed progressive improvement in background rhythm until normalization.

Discussion

In this study, we described a case series of sixteen patients treated with CAR T cell therapies in Hematology Unit at our hospital, evaluating clinical features and, specifically, neurologic signs at baseline, in the attempt to find any aspects associated with the development of ICANS. Overall, we observed a relative low rate of ICANS, but what is interesting is that—in our series—this complication only occurred in patients who presented subtle abnormal signs of CNS involvement at baseline. In particular, even if single and subtle signs cannot be accounted to address

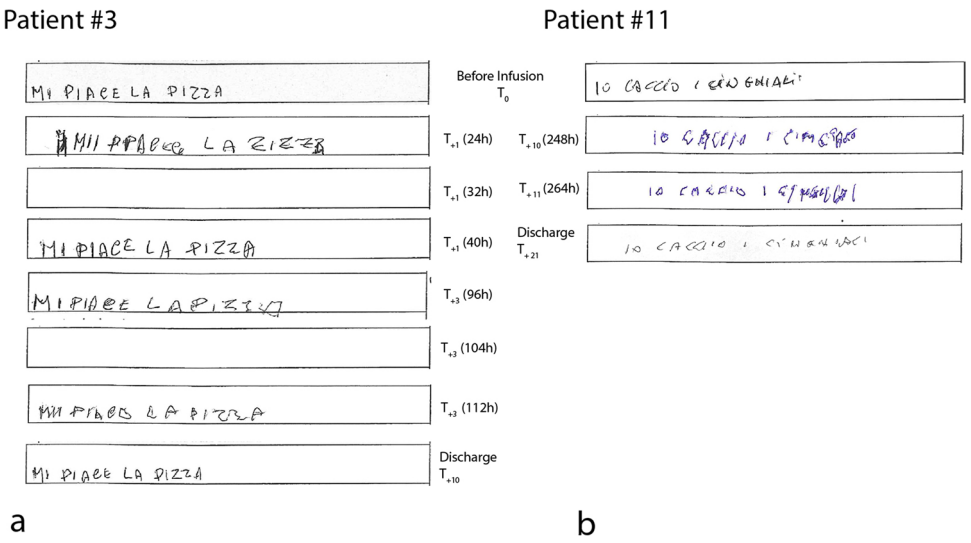

Fig. 1 Handwriting at different time points in the two subjects with ICANS during the hospitalization—as recorded in the ICE score. (**a**) Patient no. 3 chose as reference sentence "MI PIACE LA PIZZA" (English translation: "I LIKE PIZZA") and was asked to write the sentence at baseline (T_0). Twenty-four hours after CAR T cell infusion, she started to develop ICANS with typical paligraphia, paragraphia ("MII PPACICCE LA ZIZZZA"), and signs of graphic apraxia. Patient was completely unable to write at T_{+1} (32 h). She recovered soon after the administration of a dose of tocilizumab at T_{+1} (40 h), but writing abilities fluctuated in the following 2 days with signs of graphic apraxia and a new inability to write at T_{+3} (104 h). While recovering writing function, she experienced again a transient mild paligraphia ("MII PIACE LA PIZZA") at T_{+3} (112 h). Then, she fully regained her writing abilities. (**b**) Patient no. 11 chose as reference sentence "IO CACCIO I CINGHIALI" (English translation: "I HUNT WILD BOARS"). He developed shaky writing with signs of graphic apraxia 10 days after CAR T cell infusion without paligraphia. His symptoms recovered in the following days and he was asymptomatic at discharge. Abbreviations: ICANS, immune effector cell–associated neurotoxicity syndrome; T0, day of CAR T cell infusion; T_{+n}, *n* denotes the number of days after infusion, in brackets the exact number of hours after infusion

specific brain localizations, both patients developing neurotoxicity showed a combination of signs compatible with frontal lobe impairment, i.e., bilateral palmo-mental reflexes associated with slight cognitive-motor slowing in patient no. 3 [12] and motor impersistence associated with reduce saccade velocity in patient no. 11 [13].

Although most clinical manifestations of ICANS are consistent with nonspecific brain dysfunction without focal signs [5], emerging data suggest that neurotoxicity in some cases could be attributable to a frontal encephalopathy, particularly at early stages of the adverse event. This hypothesis has been recently supported by the study of Pensato and colleagues, who reported a frontal lobe dysfunction in 65% of patients developing ICANS after CAR T cell therapy, characterized by a variable association of behavioral disinhibition, verbal and motor perseveration or apathy, and motor signs. Frontal lobe involvement was further proven by brain FDG-PET, showing bilateral frontal-predominant hypometabolism, and by EEG, revealing frontal predominant EEG abnormalities [11]. Interestingly, the electroclinical features of the frontal lobe dysfunction in ICANS share several aspects with other encephalopathies associated to cytokine storm, i.e., SARS-CoV-2 and sepsis-related encephalopathies [14]. A possible explanation to this frontal predominant involvement is that frontal lobes are more susceptible to cytokine-induced inflammation via the NF-kB signaling pathway [14, 15].

Also in our experience, writing disturbances and myoclonic tremor observed as symptoms of ICANS are likely to arise by dysfunctions in frontal lobe. Concerning writing, both of our patients developed a writing disturbance variously constituted of apraxic agraphia, paragraphia, and paligraphia. In particular, (1) apraxic agraphia has been defined as resulting from the impairment in retrieving motor engrams that program the movements necessary to produce written letters [16]; (2) literal paragraphia implies the use of unintended letters in the word formation [17]; and (3) paligraphia consists of the repetition of letters, especially in words containing double or circular letters, due to a dysfunction in frontal lobe [18]. This latter was well described in the past as a feature of Gilles de la Tourette syndrome [19] and recently in patients treated with CAR T cells as an early sign of neurotoxicity [20].

Concerning tremor and myoclonus, they are commonly described as adverse events of CAR T cell therapy, both isolated and in combination with each other [2]. Previous studies evaluating EEG abnormalities in patients with myoclonus after CAR T cell infusion did not show univocal findings, ranging from epileptic discharges [21] to slow rhythms without epileptic activity [22]. In our patient, no.

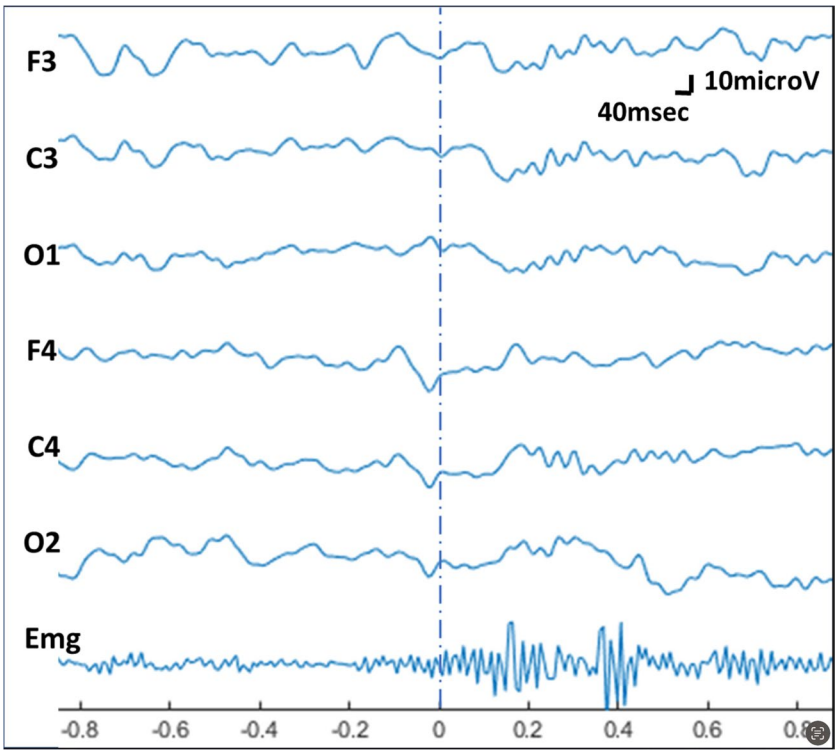

Fig. 2 Back averaging of EEG signal jerk-locked with EMG in patient no. 11 during myoclonus. Simultaneous recording of electroencephalogram (EEG) and electromyography (EMG) from left flexor digitorum longus muscle. EEG channels are placed according to the 10–20 international system and referenced to ipsilateral mastoid. The jerk-locked back-averaging of the EEG signal showed a time locked biphasic sharp wave, with the positive transient appearing on C4 23 ms prior jerk, thus indicating a cortical origin of the myoclonus

11, EEG recorded during myoclonic tremor showed diffuse slowing, which progressively resolved along with resolution of tremor. Interestingly, jerk locked back-averaging of the superimposed jerks showed a time locked sharp wave on the right fronto-central region which appeared 23 ms before left hand jerks. This finding is consistent with cortical myoclonus, as previously reported by Swinnen et al. [23] and points to a frontal origin of the clinical manifestation.

The reasons why some patients develop this frontal encephalopathy after CAR T cell infusion are still not fully understood. Indeed, systemic inflammatory response is of pivotal importance in this scenario, leading to a BBB disruption with leakage, and to the entrance of inflammatory molecules and cells in the CNS. However, pre-existing CNS conditions, even if at a subclinical level, may cause subtle chronic neuronal injury and BBB dysfunction, thus facilitating the passage of inflammatory molecules in the CNS. A recent study by Schoeberl and colleagues [24] correlated serum levels of neurofilament light chain (NfL), a marker of neuroaxonal injury in numerous CNS diseases [25], with the severity of neurotoxicity after CAR T cell treatment. The authors found that pre-existing neuroaxonal injury, which was characterized by higher serum NfL levels before treatment with CAR T, correlated with the severity of subsequent ICANS, thus suggesting that neuroaxonal integrity might also have an important role in determining the occurrence and the severity of ICANS.

Further evidence, supporting the possibility that pre-existing neurologic conditions may represent a risk factor for ICANS, came from the study by Gust and colleagues, in which the authors found an association between neurotoxicity and any pre-existing neurologic comorbidity. However, in this work, the authors failed to find any specific neurological comorbidity that was clearly linked to the development of ICANS, and they considered several central and peripheral neurological diseases all together, despite different and unrelated underlying pathogenesis. We hypothesize that mainly pre-existing conditions involving a BBB dysfunction may lead to a higher risk of neurotoxicity.

Conclusions

CAR T cells represent a revolutionary therapy, able to produce remarkably effective and durable clinical responses in some types of refractory hematologic tumors, whose prognosis have been otherwise extremely poor. Due to its high efficacy, it is being intensely considered a potential treatment for other types of cancer, including solid tumors. However, the risk of severe life-threatening systemic and neurologic toxicities represents a consistent barrier toward the use and spread of this innovative therapy.

The identification of factors able to predict the risk of such complications not only in an early symptomatic phase,

but also before the treatment administration, would be of pivotal importance to stratify patients and to promptly start appropriate treatment. Based on our experience, we suggest that subtle CNS abnormal signs at baseline neurological examination, especially those involving frontal lobe functions, may represent a risk factor for ICANS development. Future studies on larger numbers of patients are needed to confirm this finding.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-023-06841-6.

Data availability The authors take full responsibility for the data, the analysis, and the interpretation of the research, and they have full access to all of the data.

Declarations

Ethical standards All investigations were carried out according to the Declaration of Helsinki.

Consent to participate Informed consent was obtained from the patients for the inclusion of deidentified clinical data in a scientific publication, in accordance of the Declaration of Helsinki.

Consent for publication All authors agreed with this final version.

Conflict of interest The authors declare no competing interests.

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