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Abstract

Background and Objectives

Anti-CD19 CAR T-cell therapy is a promising treatment in relapsing B-cell lymphoma, but is frequently associated with acute neurotoxicity. Neurological long-term safety has not been thoroughly assessed.

Methods

All consecutive refractory lymphoma patients admitted in our center for CAR T-cell therapy underwent neurological examination, extensive neuropsychological assessment, brain MRI (except one patient) and completed self-administrated questionnaires at baseline. The patients who remained disease-free at 2 years were re-evaluated similarly. All neurological assessments were conducted by senior neurologists.

Results

None of the 19 disease-free patients developed new neurological deficits or MRI changes when compared to baseline. There was no difference in cognitive performances before and two years after, even for the 11 patients who had developed acute neurotoxicity after CAR T-cells.

In self-questionnaire assessments, cognitive complaint was stable, reported by 32% of patients at 2 years. We observed a reduction in HADS anxiety scores two years after treatment when compared to baseline (median score: 7/21 vs 4/21, p=0.01).

Discussion

In conclusion, no significant neurocognitive or neurological disorders were observed in this cohort of patients, two years after treatment with anti-CD19 CAR T-cells.

Chimeric antigen receptor (CAR)-T cells are genetically engineered T-lymphocytes targeting selected tumor antigens. Anti-CD19 CAR T- cell therapy is now approved for relapsed/refractory B-cell lymphoma. However, these treatments are associated with significant and sometimes life-threatening toxicities, the most frequent being cytokine released syndrome and neurotoxicity [1-5]. Neurotoxicity or ICANS (Immune effector Cell–Associated Neurotoxicity Syndrome), is observed in approximately half of the patients and usually occurs within the first two weeks [1-4]. Almost all patients rapidly recover within a median of six days, although severe forms might lead to death in rare cases [1-5].

Given this high rate of acute neurotoxicity, assessing long-term neurological sequelae needs to be studied. A preliminary report on a prospective cohort of patients followed in our center did not show any mid-term neurological side effects [6] but with a limited follow-up (six to twelve months) after CAR T-cell administration. We here reported the results of the neurological and cognitive evaluations on this prospective cohort of patients, two years after anti-CD19 CAR T-cell treatment.

Methods

All relapsed B-cell lymphoma patients without cerebral involvement admitted in our center for CAR T-cell therapy from October 2018 to August 2019, were prospectively included. This study was approved by the local institutional review board for ethics and clinical research (CLEA-2019-74). Written informed consents were collected in all patients.

All patients had complete neurological examination, brain MRI, neuropsychological tests and self-administered questionnaires, within two weeks before CAR T-cell injection. If acute neurotoxicity occurred, patients were monitored on a daily basis and received steroids/anticonvulsants when required. Patients were fully re-evaluated 22-26 months later. In this study, we considered only disease-free patients to avoid any bias related to progression or neurotoxicity due to other treatments. None of these patients were lost to follow-up (see Figure 1 for flowchart). All neurological assessments were standardized and conducted by senior neurologists.

Results

Nineteen patients were disease-free at 2 years and analyzed in this study (characteristics in table 1). After treatment, eleven patients developed an acute neurotoxicity within 18 days, cognitive disorders being the most frequent (8 patients), as previously reported [6]. Steroids and anticonvulsants were administered in six and five patients, respectively. Neurotoxicities were reversible within 42 days in all patients.

Two years after treatment, no episodic disorders were collected; neurological examination was similar to baseline in all patients. One patient was fully investigated because he complained of mild and fluctuating paresthesia; all investigations were however normal: blood tests (assessing vitamin deficiencies, metabolic disorders, infections, and auto-immunity), CSF study, electromyogram, brain and spinal MRI.

MRIs at 2 years, done in all patients but one (claustrophobic patient), were similar to baseline. Neuropsychological tests did not show any cognitive differences before and two years after CAR T-cells (Table 2), and this, whether the patients had ICANS (n=11) or not (n=8).

In self-questionnaire assessments, cognitive complaint was the most frequent one, reported by 21% of the patients at baseline, and 32% of patients at 2 years (p=n.s). Anxiety and depression HADS scores were improved two years after treatment (Table 2). The percentage of patients with an abnormal level of anxiety (HADS score ≥ 8/21) was high at baseline and lower at two years (42% vs 11%, p=0.05).

Discussion

Acute neurological toxicities are frequently associated with CAR T-cells and usually recover within two weeks [1-5]. Yet, the long-term neurological safety of this new treatment remains insufficiently described.

In this cohort of 19 patients, no objective long-term neurological or cognitive deficits were identified when compared to baseline, even in patients who had acute neurotoxicity. Another study reported neurological events occurring more than 90 days after CAR T-cell infusion in 10% of patients [7]. However, no neurological examination was made at baseline in these heavily pre-treated patients and most of them had tumor recurrence, thus making the relationship between the reported neurological events and CAR T-cells questionable.

In our patients, anxiety, frequent at baseline, significantly improved at two years and reached a level (11%) similar to that of the general French population [7], a fact that can be easily explained by the long period of remission.

The main limitation of our study is the small number of patients. However, none of our patients were lost to follow-up, a frequent situation in larger studies that induces major bias. Another limitation comes from the small number of patients with severe neurotoxicity (n=3) who might be more at risk to develop neurological sequelae. Larger series on long-term safety after severe ICANS are needed to address this point.

In conclusion, neither neurocognitive disorders, nor neurological impairments, nor imaging abnormalities on brain MRI were observed two years after anti-CD19 CAR T-cell infusions. Similar studies should be extended to other types of CAR T-cells.

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Tables and figure legends:

Table 1:

Patients' characteristics.

Table 2:

Neuropsychological tests (administered by a trained neuropsychologist) and self-assessment questionnaires of anxiety, depression and cognitive complaints performed at baseline and at two years after CAR T-cell injection.

Figure 1:

Flowchart of the patients included in the study.

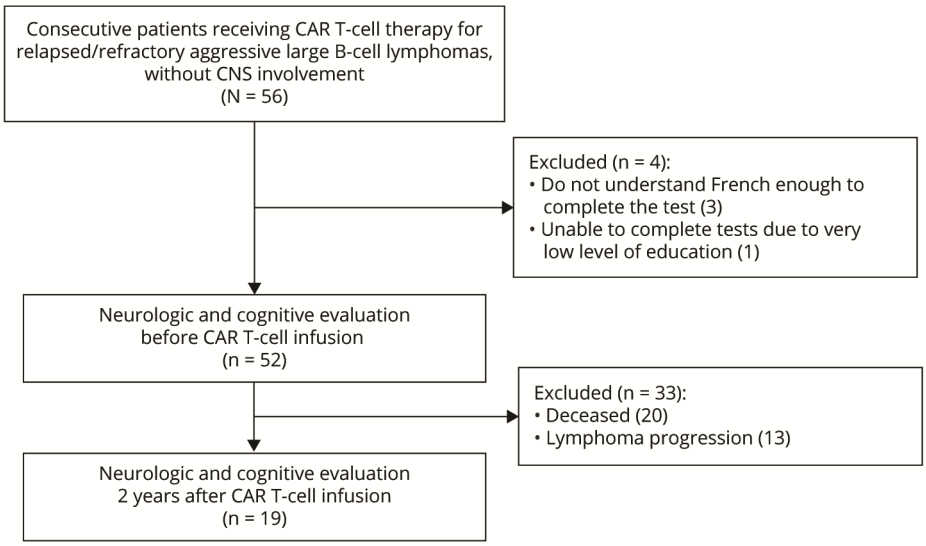

Table 1 :

	Patients with long-term evaluation n=19
Age, years (median, min-max)	69 (26-72)
Sex	
Male	10 (53%)
Female	9 (47%)
Past neurological history	5 (26%)
Meningitis and sciatica	1 (5%)
Herniated disc (L5-S1)	2 (11%)
Bell's palsy	1 (5%)
Transient vascular ischemic attack	1 (5%)
Baseline neurological examination	
Normal	8 (42%)
Abnormal	11 (58%)
Chemotherapy-induced neuropathy	6 (32%)
Radiculopathy (L4,L5,S1)	4 (21%)
Horner syndrome related to lymphoma localization (compressive lymph node)	1 (5%)
CRS	

Grade 1	10 (53%)
Grade 2	7 (37%)
Grade 3	0
Grade 4	0
Neurotoxicity	
No neurotoxicity	8 (42%)
Grade 1	3 (16%)
Grade 2	5 (26%)
Grade 3-4	2 (11%)
Grade 4	1 (5%)
Treatment at intensive care units	9 (47%)

Table 2:

Name of neuropsychological tests*	**Baseline evaluation, median (min-max) n=19**	**Long-term evaluation, median (min-max) n=19**	***P***
Mini–Mental State Examination* (Score/30)	28 (25-30)	29 (25-30)	*p=0.12*
Episodic memory*			
French Free and Cued Selective Reminding Test (learning score %)	50% (-14 to 78)	50% (-50 to 100)	*p=0.69*
French Free and Cued Selective Reminding Test (cueing score %)	98% (89-100)	98% (88 to 100)	*p=0.71*
French Free and Cued Selective Reminding Test Delayed Free Cued consolidation score – % of forgetfulness)	0% (-21 to 75)	0% (-29 to 33)	*p=0.34*
Visuo-spatial Memory (Recall of the Rey-Osterrieth Complex Figure - score/36)	18 (5-31)	22.5 (14-31)	*p=0.06*
Short-term Memory*			
Forward and backward Digit Span (score/19)	7 (4-15)	10 (3-16)	*p=0.03*
Executive functions*			
Trail Making Test part A (seconds)	29 (18-71)	35 (16-59)	*p=0.76*
Trail Making Test part B (seconds)	86 (42-291)	78 (39-420)	*p=0.23*
Trail Making Test part B (time) - Trail Making Test part A (seconds)	61 (20-253)	42 (11-389)	*p=0.23*
Stroop test: time of interference part – time of denomination part (seconds)*	61 (32-190)	58 (22-97)	*p=0.19*
Language*			

Oral naming task of 80 images (score /80)	79 (66-80)	80 (74-80)	*p=0.2*
Semantic verbal fluency (number of items in 2 minutes)	30 (16-52)	27 (15-49)	*p=0.1*
Dictation of the Boston Diagnostic Aphasia Examination (score/3)	3 (1-3)	3 (1-3)	*p=0.3*
Repetition (words/sentences) of the Boston diagnostic aphasia examination (score/26)	26 (24-26)	26 (23-26)	*p=0.78*
Praxis*			
Copy of the Rey-Osterrieth Complex Figure – score/36 (constructive praxis)	34 (28-36)	35 (30-36)	*p=0.11*
Symbolic gestures of the Mahieux gestural praxis battery – score/5 (gestural praxis)	5 (5-5)	5 (4-5)	*p=1*
Pantomimes of the Mahieux gestural praxis battery – score/10 (gestural praxis)	10 (10-10)	10 (6-10)	*p=1*
Imitation of abstract gestures of the Mahieux gestural praxis battery – score/8 (gestural praxis)	8 (7-8)	8 (7-8)	*p=1*
Mood evaluations with self-assessment of anxiety, depression and cognitive complaints**			
STAI – anxiety state (score/80)	34 (20-61)	28 (20-44)	*p=0.5*
STAI – anxiety trait (score/80)	38 (21-52)	35 (20-53)	*p=0.4*
HADS – anxiety (score/21)	7 (1-11)	4 (1-9)	**p=0.01**
HADS – depression (score/21)	3 (1-14)	3 (0-6)	**p=0.04**
QMRP Prospective memory (score/40)	17 (11-24)	16 (10-30)	*p=0.9*
QMRP Retrospective memory (score/40)	14.9 (11-26.3)	14.9 (8-30)	*p=0.6*

* *Cognitive performances were compared before and two years after the infusion with a non-parametric paired comparison (Wilcoxon test) as the acceptance of the normality was not respected. Given the large number of comparisons (n=17), the significance level was lowered to 0.003 (Bonferroni's correction).*

***The self-administered-questionnaire measures were compared with a non-parametric paired comparison (Wilcoxon test) as the acceptance of the normality was not respected. The significance level was 0.05.*

All statistical analyses were performed using Jamovi software (Version 1.2).

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