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Case Report

IL-31: A Potential Implication in CAR T Cells Neurotoxicity?

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Abstract

67-year-old female with a refractory CNS lymphoma received axi-cel therapy, leading to grade III neurotoxicity but a complete and persistent response. Cerebro-spinal fluid (CSF) was obtained before CAR T cell injections, at day +3, day +7, and 2 months after. Strikingly, we observed a total disappearance of lymphoma cells at day +3 while CAR T cells expansion peak in CSF occurred later at day +7. Additionally, multiplex ELISA showed an intense inflammatory profile that quickly reduced suggesting that CAR T cells are the most efficient within the first days following injection. IL-31 was the most prominent cytokine in CSF far ahead of IL-1β and remained elevated during neurotoxicity deterioration suggesting that this cytokine, whose receptor is expressed on neuronal cells, may be important in ICANS physiopathology.

Keywords: Cerebro-Spinal Fluid; ELISA; Chemotherapy; Cytokine Release Syndrome; Neurotoxicity

Insights: IL-31 is the most prominent cytokine found in CSF from a patient with CNS lymphoma treated with CAR T cells.

Introduction

Adoptive immunotherapy with chimeric antigen receptor (CAR) T cell therapy has emerged as a promising treatment option for patients with relapsed or refractory Diffuse Large B Cell Lymphoma (DLBCL) [1-3]. However, the presence of endothelial activation and systemic capillary leak was demonstrated after CD19 CAR-T cell therapy and was associated with disruption of the blood brain barrier and the occurrence of neurotoxicity [4]. This explains the exclusion of patients with central nervous system (CNS) lymphoma from landmark trials ZUMA and JULIET [1,3]. As for the registration trial of Liso-cel TRANSCEND-NHL-001, only 7 patients with CNS involvement were included [2]. Evidence of safety and toxicity of anti-CD19 CAR T cells derives from case reports, case series and post-hoc analysis of prospective studies [5]. We herein present the case of a patient treated with axicabtagen ciloleucel (axi-cel) for refractory DLBCL with CNS involvement and demonstrate CAR-T expansion in CNS that correlates with cytokine overproduction, followed by a severe but reversible neurotoxicity. Most particularly, IL-31 was the most prominent cytokine found in CSF followed by IL-1β.

Case Report

This is a previously healthy 67-year-old female patient who was diagnosed on March 2022 with stage IV DLBCL with pleural, peritoneal, hepatic, and bone involvement. There was no CNS involvement at diagnosis. The disease was refractory to a first-line treatment with 6 R-CHOP and 4 intrathecal injections of methotrexate, with an end-of-treatment MRI in July 2022 revealing right parietal and left cerebellar suspicious lesions with leptomeningeal dissemination, while the other initial localizations of lymphoma had totally disappeared. Pathological analysis of a left cerebellar lesion obtained with surgical biopsy was compatible with the prior diagnosis of DLBCL. The patient received salvage treatment with R-ICE chemotherapy which did not allow a reduction of the CNS lesions. The disease was also refractory to a third-line treatment with Rituximab-Revlimid-Ibrutinib, with clinical and radiological progression after only one cycle. Despite a poor performance status, which was attributed to disease progression, the indication of treatment with axi-cel was approved by our multidisciplinary tumor board. The patient underwent bridging therapy with Cytarabine and high-dose Methotrexate, with slight clinical improvement of neurological symptoms. Baseline brain MRI was performed before axi-cel injection and displayed a partial response (Figure 1). Cerebrospinal fluid (CSF) analysis showed a persistent massive infiltration with lymphomatous cells (950 cells/mm^3 with 67 % of tumoral B cells) (Figure 2 B and C). CAR-T cells were injected after lymphodepleting chemotherapy with 30 mg/m^2 Fludarabine and 500 mg/m^2 Cyclophosphamide. Of note, the patient received 3 days of 0,5 mg/kg of Dexamethasone during lymphodepletion because of clinical progressive disease (left facial paresis with left oculomotor nerve VI palsy and important headache), that allowed a brief clinical improvement.

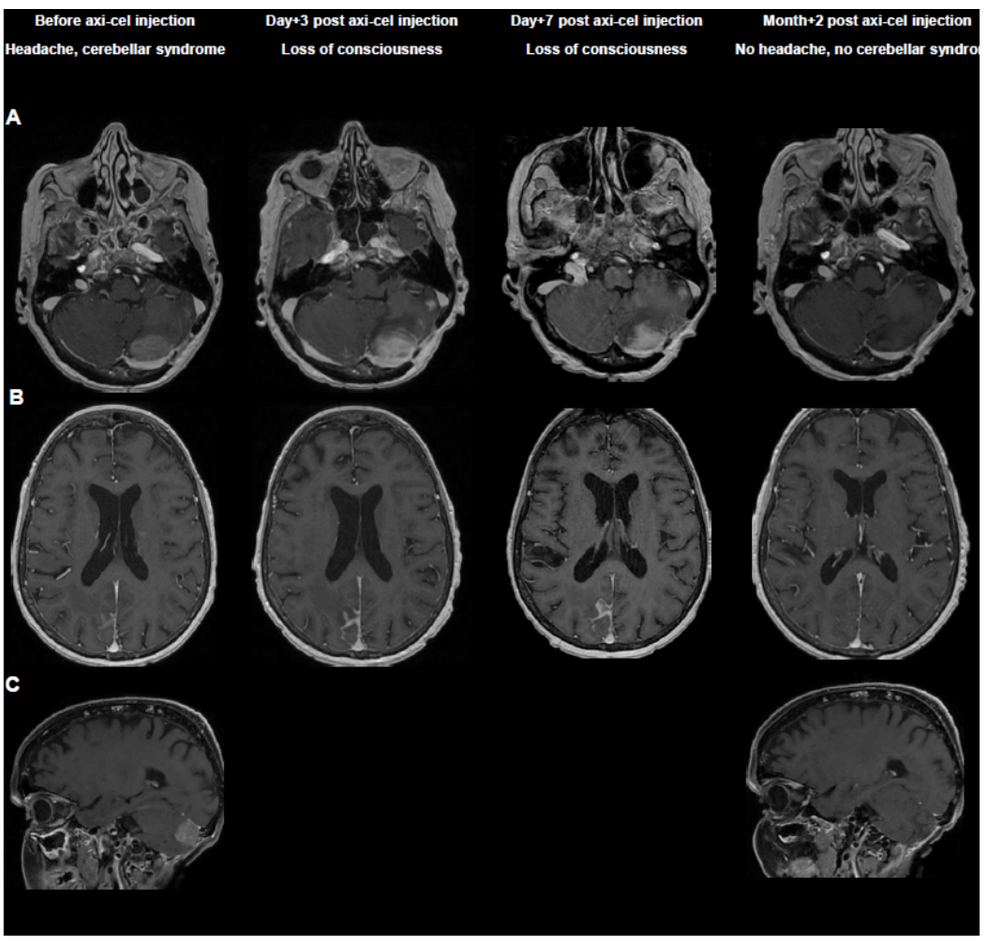

Figure 1: Representative post-contrast T1-weighted images of brain MRI before CAR T cells injection, at day +3 and day +7, corresponding to neurotoxicity, and finally 2 months after CAR T cells injection showing an excellent response. A. Axial sections of infratentorial compartment of the brain: left cerebellar mass that increased on day+3 and day+7 MRI but dramatically disappeared on month+2 MRI. B. Axial sections of supratentorial compartment of the brain: right parieto-occipital meningeal contrast that increased on day+3 and day+7 MRI but decreased on month+2 MRI. C. Sagittal reconstruction centered on the left cerebellar contrast that disappeared on month +2 MRI.

Grade II Cytokine Release Syndrome (CRS) occurred starting at day 2 after injection and persisting for up to 3 days, with hypoxemia requiring transitory oxygen supplementation. This toxicity improved after initiation of Tocilizumab at day 3 and large spectrum anti-bacterial coverage with Meropenem, that was rapidly de-escalated to Piperacillin-Tazobactam. Neurological evolution was marked by grade III immune effector cell-associated neurotoxicity syndrome (ICANS) with dizziness, aphasia and impaired handwriting appearing on day 2. Dexamethasone 10 mg QID was started, and the patient transferred to Intensive Care Unit for monitoring. Because of neurological deterioration (altered mental status with Glasgow coma score 11/15), Anakinra and high dose corticosteroids (Methylprednisolone 1g for 3 days) were started on day 6. This treatment resulted in neurological improvement. Anakinra was continued for a total of 7 days and corticosteroids were gradually tapered after obtaining neurological stability. Assessment after 2 months with brain MRI showed a near complete response with almost complete regression of all contrast-enhancing leptomeningeal lesions (Figure 1). Additionally, CSF analysis showed no evidence of disease progression (Figure 2B). This was compatible with the significant clinical improvement, as all neurological symptoms resolved except for a persistent ataxic gate. The patient is so far still in complete remission (12 months post CAR T cells injection).

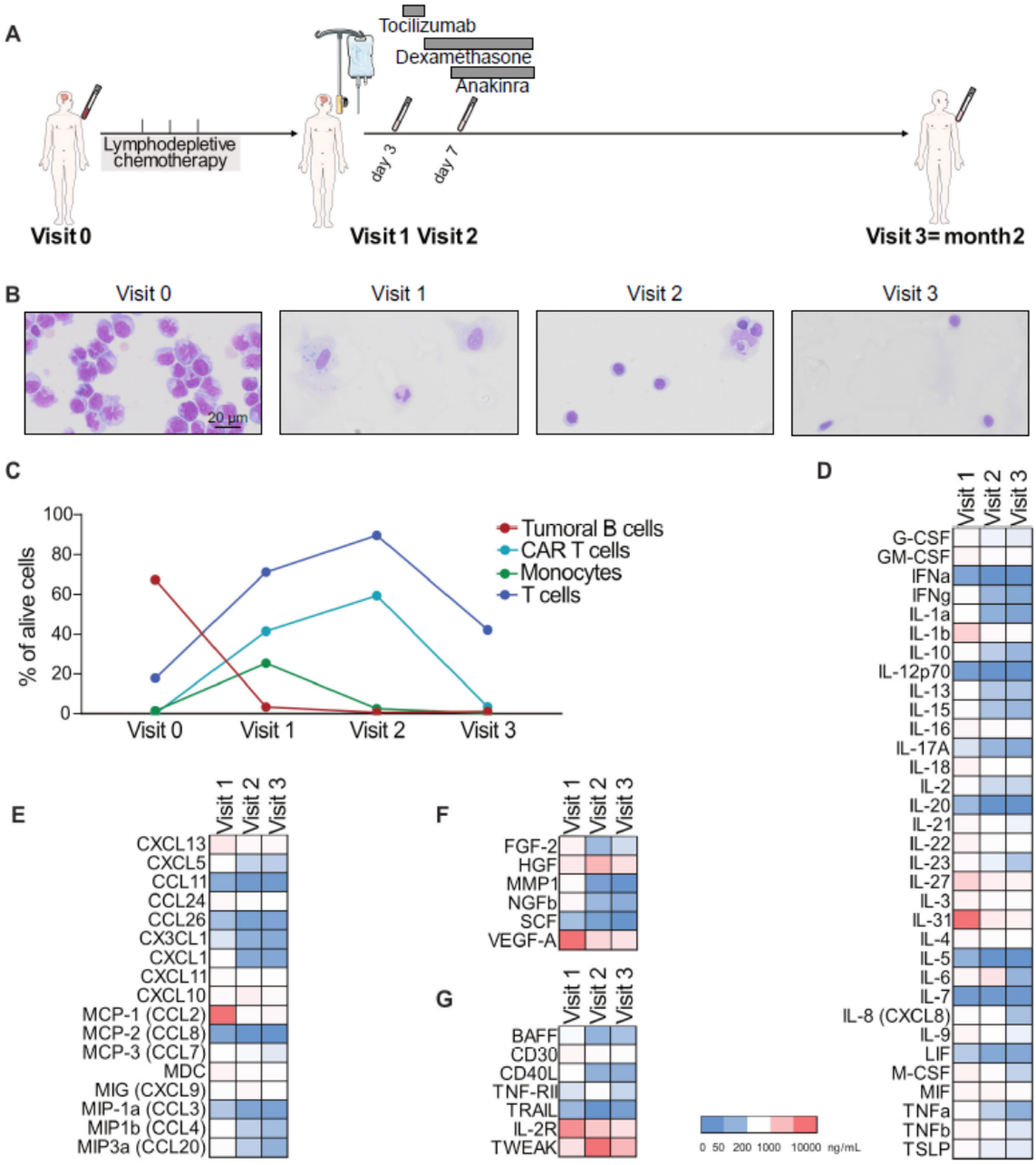

Figure 2: A. CSF samples collection schedule. B. Representative images of May-Grünwald-Giemsa colored CSF. C. Quantification of the different immune cell populations observed by flow cytometry in CSF. We can observe that the peak of CAR T cells expansion occurred at day +7, coinciding with neurological deterioration, while tumoral B cells were eliminated extremely rapidly after CAR T cells injection. D. Representation of cytokines concentration at visits 1, 2 and 3. E. Representation of chemokines concentration at visits 1, 2 and 3. F. Representation of growth factors concentration at visits 1, 2 and 3. G. Representation of soluble receptors concentration at visits 1, 2 and 3.

Methods

Biological samples: Cerebrospinal fluids (CSF) were obtained in the context of the PIONEER study (NCT05481502). A lumbar punction was performed before lymphodepletive chemotherapy, at day +3 following axi-cel injection, at day +7 and finally, at month +2, as described in Figure 2A. Cytospins were obtained after centrifugation and colored with May-Grünwald-Giemsa.

Flow cytometry: After centrifugation, cells from CSF were stained in Phosphate Buffer Saline (PBS) with flow cytometry monoclonal antibodies for 20 min at 4°C. The supernatant obtained after centrifugation was immediately frozen at -80°C. Flow cytometry was performed using a Fortessa analyzer (BD). Flow cytometry data analysis was performed using Flow Jo software. Antibodies used are listed in the below table.

antibodies	fluorochrome	clone
CD45	KrO	J33
CD3	Pacific Blue	UCH T1
CD4	PE	13B8.2
CD8	FITC	B9.11
CD19	ECD	HD237
CD5	AF700	BL1a
CD10	PC7	ALB1
CD20	AA750	B9E9
CD16	PC5	3G8
CD56	PC5.5	N901
CD19 CAR	PE	REA746

Multiplex ELISA: 25 µL of frozen CSF were used for 65-plex human ProcartaPlex according to manufacturer's protocol. Acquisitions and analyses were performed on BioPlex 200 from BioRad.

Results

CSF analysis before lympho-depletive chemotherapy showed, as expected, a massive infiltration of lymphomatous cells with irregular nuclei and basophilic cytoplasm accompanied by rare reactive lymphocytes (Figure 2B). At day+3 following axi-cel injection, CSF analysis showed poor cellularity containing mainly monocytes, few neutrophils, and lymphocytes. Tumoral cells were not observed anymore which was confirmed by flow cytometry analysis. Interestingly, 40% of the lymphocytes were actually CAR T cells. Analysis of multiplex ELISA displayed an intense inflammatory reaction (Figures 2D and E). Most particularly, IL-31, IL-1β, and IL-27 were the most prominent cytokines. MCP-1 (CLL2) chemokine was also particularly expressed which is concordant with monocyte infiltration. Moreover, VEGF and TWEAK elevations (Figure 2F and G), which are respectively a growth factor and a soluble receptor associated with angiogenesis, were indicative of vascular leak. At day+7 following axi-cel injection, the intense inflammatory profile observed with multiplex ELISA rapidly reduced (Figure 2D and E) while CAR T cells infiltrating the CFS continued to expand (Figure 2C) and monocytes disappeared, suggesting that monocytes may play a role in this intense inflammatory reaction and that CAR T cells activation is observed extremely early after their injection. Finally, at month+2 following axi-cel injection, cytokines were almost all found at a very low level, except IL-31 that keeps being elevated although decreased compared to day+3 and day+7 CSF samples. CAR T cells were still found but at a very low proportion in CSF, revealing that CAR T cells are invading CSF very early on but do not reside in CSF. Finally, BAFF, a fundamental survival factor for B cells constantly decreased in linked with B cells disappearance. IL-2R that is mostly expressed on T cells also decreased over the time with the disappearance of T cells. These two values indicate the robustness of our data.

Conclusion

Based on the analysis of our case report, we can conclude that 1) CAR T cells rapidly invade the CNS after injection but do not reside for a long term, as previously demonstrated [6]; 2) tumoral B cells are eliminated within the first 3 days following CAR T cells injection and finally 3) a specific pattern of inflammatory cytokines is found in CSF (increase of IL-31, IL-1β and IL-27) following CAR T cells injection. While IL-1β has been extensively studied in ICANS and is now targetable by anakinra [7], an IL-1R antagonist, little is known about IL-31. Additionally, our patient presented a rapid neurological deterioration caused by CNS inflammation despite dexamethasone, one might speculate that blocking IL-31 could be a good therapeutic option, although this suggestion must absolutely be confirmed by larger cohorts. IL-31 belongs to the IL-6 cytokine family that includes IL-6, IL-11 and IL-27 and has been mainly studied in the context of dermatitis, a skin inflammation mostly mediated by Th2 cells. IL-31 is thought to be produced by CD4+ Th2 T cells [8] and interacts with a heterodimer complex that is composed of the IL31RA subunit and oncostatin M receptor β (OSMRβ). The OSMRβ is widely expressed, whereas IL31RA expression is predominantly observed in epithelial and neuronal cells. More precisely, IL-31R is expressed in adult dorsal root ganglia [9], a type of neurons. Therefore, we could hypothesize that IL-31, likely produced by CAR T cells, may be implicated in the pathophysiology of CAR T cells neurotoxicity, through bonding to its receptor expressed on certain neurons. Nemolizumab, an anti IL31R antibody, has recently shown promising results for atopic dermatitis [10] and

could be an interesting therapeutic option in severe CAR T cell neurotoxicity.

While the use of CAR T cells in patients with B cell tumors involving CSF is restrained because of fear of neurotoxicity, our case provided an insight on the pathophysiology of CAR T cells expansion and action in the CSF of an affected patient. A better understanding the mechanisms of ICANS in these patients might further improve managing toxicities.

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