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Intracranial pressure management in fulminant cerebral oedema after CAR T-cell therapy: Not all is lost!

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## Intracranial Pressure Management in Fulminant Cerebral Edema after CAR T-Cell Therapy: not all is lost!

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| Complete List of Authors:     | <p>Asioli, Gian Maria; IRCCS Istituto Delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica - NeuroMet</p> <p>Castioni, Carlo Alberto; IRCCS Istituto Delle Scienze Neurologiche di Bologna, UOC Anestesia e Rianimazione</p> <p>ZINZANI, PIER LUIGI; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Istituto di Ematologia "Seràgnoli"</p> <p>Casadio, Maria Chiara; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Intensive Care Unit</p> <p>Pierucci, Elisabetta; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Intensive Care Unit</p> <p>Casadei, Beatrice; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Istituto di Ematologia "Seràgnoli"</p> <p>Spinardi, Luca; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Diagnostic and Interventional Neuroradiology Unit</p> <p>Pellegrini, Cinzia; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Istituto di Ematologia "Seràgnoli"</p> <p>Bonafé, Massimiliano; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Istituto di Ematologia "Seràgnoli"</p> <p>Maffini, Enrico; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Istituto di Ematologia "Seràgnoli"</p> <p>Guarino, Maria; IRCCS Istituto Delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica - Rete Neurologica Metropolitana (NEUROMET)</p> <p>Cortelli, Pietro; IRCCS Istituto Delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica - Rete Neurologica Metropolitana (NEUROMET)</p> <p>Bonifazi, Francesca; IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola, Istituto di Ematologia "Seràgnoli"</p> |
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**Intracranial Pressure Management in Fulminant Cerebral Edema after CAR T-Cell Therapy: not all is lost!**

Gian Maria Asioli<sup>1</sup>, Carlo Alberto Castioni<sup>2</sup>, Pier Luigi Zinzani<sup>3,4</sup>, Maria Chiara Casadio<sup>5</sup>, Elisabetta Pierucci<sup>5</sup>, Beatrice Casadei<sup>3,4</sup>, Luca Spinardi<sup>6</sup>, Cinzia Pellegrini<sup>3</sup>, Massimiliano Bonafé<sup>3,4</sup>, Enrico Maffini<sup>3</sup>, Maria Guarino<sup>1</sup>, Pietro Cortelli<sup>1,7</sup>, Francesca Bonifazi<sup>3</sup>

1 UOC Clinica Neurologica - Rete Neurologica Metropolitana (NEUROMET),  
IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

2 UOC Anestesia e Rianimazione, IRCCS Istituto delle Scienze Neurologiche di  
Bologna, Bologna, Italy

3 Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di  
Bologna, Bologna, Italy.

4 Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna,  
Italy

5 Intensive Care Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna,  
Bologna, Italy

6 Diagnostic and Interventional Neuroradiology Unit, IRCCS Azienda Ospedaliero-  
Universitaria di Bologna, Bologna, Italy

7 Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna,  
Bologna, Italy

**Corresponding author**

Francesca Bonifazi  
Istituto di Ematologia "Seràgnoli", Policlinico Sant'Orsola – Malpighi,

Via Massarenti, 9 Bologna

e-mail: [francesca.bonifazi@unibo.it](mailto:francesca.bonifazi@unibo.it)

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a well-known complication after CAR-T therapy with a relevant impact on morbidity and even mortality.<sup>1</sup> ICANS manifestations may range from mild encephalopathy with predominant language disturbances to coma or death due to fulminant diffuse cerebral edema (FCE).<sup>2</sup>

FCE is the most extreme neurological complication after CAR T-cell therapy. It occurs with a rapid neurological deterioration which typically leads to brain death within 24 hours. Although it is a rare adverse event (estimated incidence 1-2%), the cases described so far have shown an almost invariably fatal evolution.<sup>1-6</sup>

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Hereby, we describe a case of CAR T-cell related FCE successfully treated with a prompt neuro-intensive support in addition to immunosuppressive anti-cytokine therapy.

The patient, a 55-year-old woman suffering from follicular non-Hodgkin B-cell lymphoma grade 3 B transformed from grade 2 follicular lymphoma, was candidate to CAR-T cell therapy as fifth line, after the fourth untreated relapse (infradiaphragmatic adenopathies). She was previously administered: R-CHOP, IEV, idelasinib, and an experimental protocol with obinutuzumab and a BTK-inhibitor. Her past medical history was also remarkable for a breast ductal carcinoma treated with quadrantectomy and radiotherapy three years before with a negative oncological follow-up.

Before admission, the patient underwent a neurological screening evaluation (including EEG, brain MRI and neuropsychological tests), which was fully negative, and started prophylaxis with levetiracetam (750 mg/q12h) according to the center's policy

After standard lymphodepleting chemotherapy with fludarabine and cyclophosphamide she was infused with axicabtagene ciloleucel (Axi-cel;  $2 \times 10^6$  anti-CD19 CAR T-cells/kg).

The day after CAR T-cells infusion, she developed grade I Cytokine Release Syndrome (CRS) with constant fever despite acetaminophen and was thus treated with three doses of tocilizumab (8 mg/kg, on days +2 and +3) according to the center's guidelines, which provides for therapeutic escalation in case of persistence of symptoms beyond 24hours in patients who develop CRS within 24 hours from the infusion. At the CRS onset, the patients also started an empiric large spectrum antibiotic therapy in addition to the standard infectious prophylaxis (sulfamethoxazole-trimethoprim, acyclovir and posaconazole).

The fever persisted with impact on general status, thus she was further treated with steroids (methylprednisolone - MPS, 1 mg/kg/q12h) on day +4. CRS did not progress to a higher grade and neurological evaluations (including EEG) were repeatedly unremarkable (ICE 10, ICANS grade 0). Inflammation markers were marginally altered (Figure 1).

Despite this, after 20 hours from steroids administration (day +5), she acutely developed headache and vomiting, becoming lethargic and then comatose about 3 hours later (Glasgow Coma Scale, GCS=9; ICE 0, ICANS 4). Even with a normal brain CT, FCE was suspected based on clinical features and high-dose MPS (1000 mg/q12h for 3 days and then tapered halving the dose every three days) along with both anakinra (100 mg/q12h, for 14 days) and siltuximab (11 mg/kg, single dose) was promptly started. The patient was sedated, intubated and transferred to the neurointensive care unit. About 8 hours after headache onset, the intraparenchymal pressure monitor showed an intracranial pressure (ICP) of 45 mmHg (normal values: 10-12 mmHg). A stepwise management of ICP was promptly started including hyperventilation, 30° head and trunk elevation, hypertonic saline solution, and pharmacological sedation with propofol and midazolam, then escalated to therapeutic hypothermia (34°C) and sodium thiopental because of refractoriness of hypertension. A normal ICP value was then reached within an hour.

A brain CT performed the next day showed diffuse brain edema.

Anesthetic treatment was progressively tapered targeting ICP and MPS was scaled over the next days (by halving about every 3 days).

At anesthetic withdrawal (day +9 from CAR-T cells infusion), the patient was comatose (GCS=3) with preserved truncal reflexes and slight generalized myoclonus. EEG showed sharp generalized periodic discharges at 3-4 Hz compatible with generalized status epilepticus. Thus, phenytoin (15 mg/kg bolus, then adjusted to plasmatic level) was started, levetiracetam was increased (2500

mg/day) and sedation (propofol) was reintroduced until suppression of epileptic activity.

Brain Magnetic Resonance Imaging (MRI) (day +13) showed diffuse vasogenic edema mainly involving the hemispheric white matter (Figure 2).

Anesthetic was gradually withdrawn and stopped on day +13 based on continuous EEG monitoring. The patient progressively woke up without evident cognitive impairment, only a mild proximal tetraparesis and distal dysesthesia were revealed on neurological examination. EEG showed a normal background with occasional generalized frontal intermittent rhythmic delta activity (FIRDA).

As the patient's neurological condition stabilized, she was extubated and transferred to the Transplant and Cellular Therapy Unit.

A control brain MRI (day +26) showed a subtotal resolution of cerebral edema; whole-body FDG-PET (day +30) disclosed a complete hematologic disease remission and a brain normal neuronal metabolism. The patients expanded successfully CAR-T cells reaching the peak of expansion at day +13 (1279 CAR-T cells/microliter) with an area-under the curve over the 30 days after infusion of 15997 cells/microliter x days.

Patient was discharged on +35 without significant neurological impairment; steroid therapy was tapered and discontinued on day +42. Her one-year follow-up whole-body FDG-PET confirm complete metabolic remission.

We report a case of FCE related to CAR-T therapy successfully treated with combination therapy of immunosuppression and neuro-intensive management of intracranial hypertension.

To date, fewer than ten FCEs related to CAR-T cell therapy have been reported in literature, and all but one have met an inauspicious end.<sup>2,4,6-9</sup> Although it is a rare complication, FCE has raised concerns since early studies with CD19-CAR T,

leading to the early termination of the Phase II ROCKET study in acute lymphoblastic leukemia patients after 5 fatal cases.<sup>10</sup>

The pathophysiology of FCE following CAR T-cell therapy remains not fully elucidated: histological and neuroimaging evidence supports cerebral vasogenic edema triggered by cytokine-mediated blood–brain barrier (BBB) dysfunction as the underlying mechanism.<sup>1,11</sup> The disruption of BBB allows systemic cytokines, including IL-6 and IFN- $\gamma$ , to diffuse into the cerebrospinal fluid and brain parenchyma thus inducing vascular pericyte stress and the secretion of endothelial cell-activating cytokines in a self-powered loop. Because tocilizumab cannot cross BBB some authors have hypothesized its potential role in neurotoxicity worsening because of an increase in diffusion of free IL-6 into the CNS due to the peripheral IL-6 receptors blockade.<sup>1,12</sup> This hypothesis appears to be supported by the increased incidence of severe ICANS (grade 3 and 4) with prophylactic use of tocilizumab after Axi-cel CAR-T therapy.<sup>13</sup>

The dysfunction of BBB leads to excessive accumulation of extracellular fluid which increases brain volume and then ICP. If uncontrolled, a significant rise in ICP lead to an irreversible brain injury due to brainstem compression and reduction in cerebral blood flow.

Therefore, reaching rapidly a normal ICP value is truly central in the management of FCE in order to ensure cerebral perfusion and prevent secondary brain injury, allowing time for the immunosuppressive therapy to shut down the cytokine storm that generated the edema. An approach with immunosuppressive therapy alone is not advisable as the elevation of ICP would lead to irreversible brain damage much earlier than the effects of either steroids or anticytokine drugs appear.

The rarity and the dramatic fatal course of FCE have severely limited its clinical characterization so far. Nevertheless, the cases previously reported in literature and those occurred in our hospital seem to display a different clinical course compared



to the “classic” ICANS.<sup>1-2,6</sup> Indeed, FCE typically presents in a hyperacute way with symptoms of intracranial hypertension (i.e., headache and vomiting), and it is not preceded by the typical subacute encephalopathy with predominant frontal dysfunction described in ICANS patient.<sup>14</sup>

Therefore, the appearance of signs suggestive of intracranial hypertension should be specifically pointed out. Given the dramatic rapidity of evolution, the diagnosis of FCE needs to be initially based on clinical suspicion only, without relying on neuroimaging, which is often unremarkable at the onset, in order to avoid any delay of the neuro-intensive approach.

Management of ICP elevation should begin at initial presentation and progressively escalate based on ICP value in a stepwise approach, up to barbiturate coma if required.<sup>15</sup> In the early days, intracranial pressure monitoring could be considered the main biomarker of response to therapy and indirectly of the ongoing cerebral inflammatory process since radiological evolution is not strictly time-related and serum inflammation mediator levels can be affected by immunosuppressive therapy.

The empiric aggressive immunosuppressive approach using a three-drug combination toward multiple molecular targets (siltuximab, anakinra and steroids) was justified by the severity of the clinical course, despite the potential increased risk of infection, which however did not occur. The absence of any infectious complication could be explained by the strong antimicrobial prophylaxis used in our center, which is similar to the highest-risk patients such as allogeneic recipients. The infectious risk is probably also reduced by laminar flow chamber with a positive pressure HEPA filter used in these patients. Intrathecal steroid therapy could also represent a valid therapeutic choice in patients with severe ICANS, as suggested in some reports.<sup>16</sup> In our case, however, we did not consider this option due to the potential risks associated with the procedure, deriving from the high intracranial

pressure and thrombocytopenia that the patient presented in the acute phase. Nonetheless, the lack of prospective studies does not currently allow further standardization of immunosuppressive regimen in this specific condition.

Whatever is the underlying pathophysiology still partially unknown, what is certain from our case is that FCE is a potentially reversible complication and the ICP management plays a key role. Signs of cerebral hypertension should alert the hematologist to a very fast management asking for aggressive neuro-intensive measures, in addition to immunosuppressive therapy, because it can prevent brain damage and let the poor prognosis of FCE become fully reversible.

### **Authorship Contributions**

GMA, MG, PC and FB contributed to conception of the study. GMA, CAC, MCC, EP, BC, LS, EM contributed to acquisition of the data. GMA, CAC, LS MG, PC and FB contributed to analysis of the data. GMA, MG, PC, FB, CP and MB contributed to interpretation of the results. GMA and FB contributed to drafting the manuscript. CAC, MG, PC, PLZ contributed to critically reviewing or revising the manuscript for important intellectual content.

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approach to the study of the nervous system in health and disease (DN. 1553  
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**Disclosure of Conflicts of Interest**

Authors declares no conflict of interest related to this paper.

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**Figure Legends**

**Figure 1. Timeline of serum inflammation marker and pharmacological interventions.** X-axis reports the number of days since CAR-T cell infusion (day 0), y-axis reports the values of inflammation markers in absolute value whose units are specified in the graph. Methylprednisolone (orange triangle), Tocilizumab (green square), Siltuximab (blue circle) and Anakinra (gray rectangle) detailed posology are reported in main text.

**Figure 2. Temporal evolution of Brain Magnetic Resonance Imaging in Fulminant Cerebral Edema.** Panel A: brain CT at neurotoxicity onset (day +5) resulted normal, while the next day (panel B) showed a mild diffuse white matter hypodensity and

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4 narrowing of cortical sulci suggestive for brain edema. Panel C-D: brain MRI at day  
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6 +13 after CAR-T cell infusion showed diffuse vasogenic edema mainly involving the  
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8 hemispheric white matter and, to a lesser extent, striatum nuclei, mesial thalamus,  
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10 and pontine tegmentum, with only subtle cortical sulci effacement. Panel E-F:  
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12 control brain MRI at day +26 showed a progressive reduction of vasogenic brain  
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14 edema and some small periventricular white matter T2-FLAIR hyperintensity  
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16 suggestive of neurotoxicity damage. Panel G-H: control brain MRI at day +96  
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18 showed a subtotal resolution of edema (C, E, G: axial FLAIR on basal ganglia level;  
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20 D, F, H: axial FLAIR on corona radiata level).  
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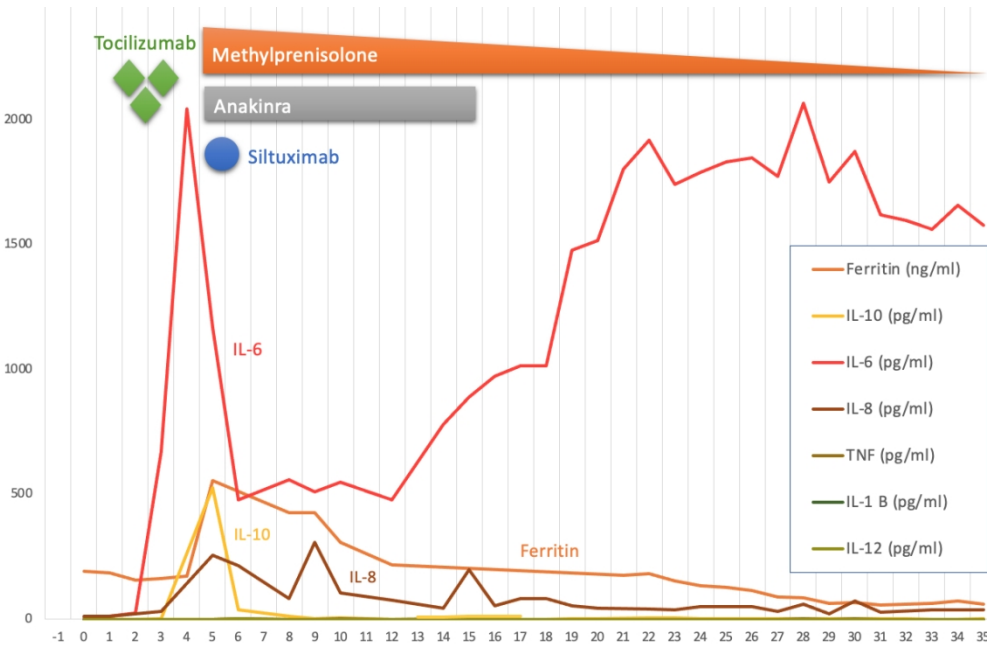


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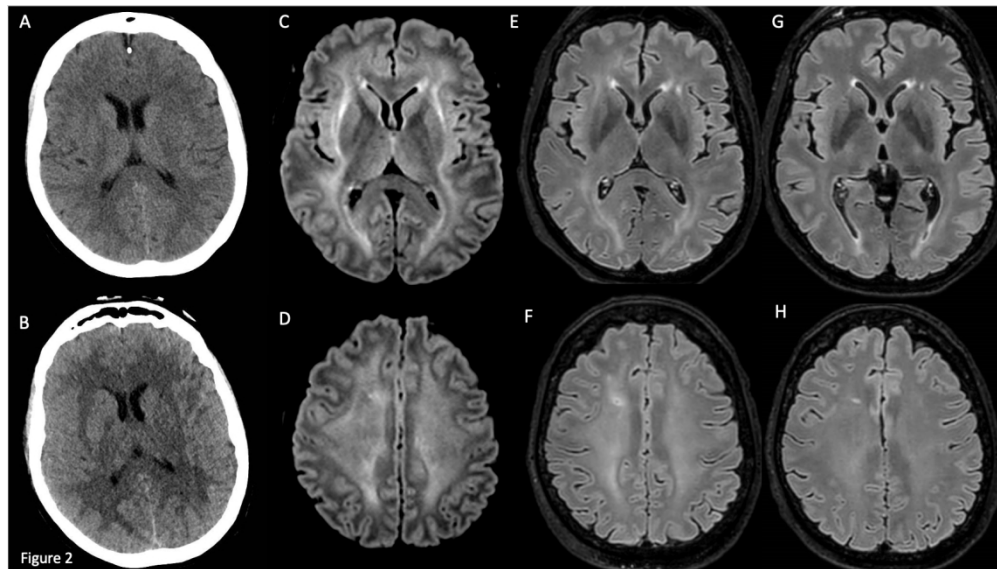


Figure 2. Temporal evolution of Brain Magnetic Resonance Imaging in Fulminant Cerebral Edema. Panel A: brain CT at neurotoxicity onset (day +5) resulted normal, while the next day (panel B) showed a mild diffuse white matter hypodensity and narrowing of cortical sulci suggestive for brain edema. Panel C-D: brain MRI at day +13 after CAR-T cell infusion showed diffuse vasogenic edema mainly involving the hemispheric white matter and, to a lesser extent, striatum nuclei, mesial thalamus, and pontine tegmentum, with only subtle cortical sulci effacement. Panel E-F: control brain MRI at day +26 showed a progressive reduction of vasogenic brain edema and some small periventricular white matter T2-FLAIR hyperintensity suggestive of neurotoxicity damage. Panel G-H: control brain MRI at day +96 showed a subtotal resolution of edema (C, E, G: axial FLAIR on basal ganglia level; D, F, H: axial FLAIR on corona radiata level).

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