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# Management of chimeric antigen receptor T-cell-related toxicity of a patient affected by cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, followed by an intestinal perforation: a case report

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## Abstract

**Background** Mantle cell lymphoma is a diverse B-cell lymphoma with varying clinical behaviors. Treating relapsed or refractory mantle cell lymphoma is challenging, with Bruton's tyrosine kinase inhibitors proving effective but not curative. Post-Bruton's tyrosine kinase inhibitor failure, the prognosis remains unfavorable. Brexucabtagene autoleucel, a US Food and Drug and European Medicines Agency-approved anti-CD19 chimeric antigen receptor T-cell therapy, marks a significant breakthrough offering hope in this challenging scenario.

**Case presentation** This article presents an analysis of the management of short-term chimeric antigen receptor T-cell therapy-associated toxicities, focusing on a specific case of a patient with refractory mantle cell lymphoma. The report underscores the complexities of chimeric antigen receptor T-cell treatment and sheds light on strategies employed to mitigate toxic effects. The case involves a white Caucasian 59-year-old male affected by relapsed mantle cell lymphoma who underwent various treatments, including autologous anti-CD19 chimeric antigen receptor T-cell therapy (brexucabtagene autoleucel). The patient experienced immune effector cell-associated hematotoxicity along with cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, necessitating intervention. The management involved a combination of tocilizumab, corticosteroids, and anakinra, which effectively alleviated symptoms. Additionally, the article highlights the patient's case of intestinal perforation following CAR-T therapy. Although there is a correlation between gastrointestinal perforation and interleukin 6 receptor inhibitors, the adverse event was attributed to the patient's preexisting diverticulitis and the immunosuppressive drugs administered leading to cytomegalovirus reactivation. The study emphasizes the evolving landscape of chimeric antigen receptor T-cell therapy and the significance of addressing toxicities associated with this innovative treatment approach. It underscores the value of anakinra as a potential corticosteroid-sparing therapy for immune effector cell-associated neurotoxicity syndrome and raises the need for further research to optimize the management of immune

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effector cell-associated hematotoxicity and associated complications. The potential preventive use of drugs to mitigate toxicities also warrants exploration, albeit with the current dearth of evidence.

**Conclusions** In conclusion, this article offers valuable insights into the challenges of managing chimeric antigen receptor T-cell-related toxicities through a detailed case presentation and highlights the significance of adopting multidisciplinary approaches to enhance patient outcomes and safety. Further research is needed to refine strategies and advance the understanding of these complex treatment-associated toxicities.

**Keywords** CAR-T therapy, Mantle cell lymphoma, Immune effector cell-associated hematotoxicity, Cytokine release syndrome, Immune effector cell-associated neurotoxicity syndrome, Adverse drug reaction, Intestinal perforation, Cytomegalovirus infection, Case report

## Background

Mantle cell lymphoma (MCL) is a mature B-cell lymphoma, with biological and clinical heterogeneity, ranging from indolent cases to highly aggressive ones with limited prognosis. Many prognostic factors are known, including the MCL international prognostic index (MIPI), Ki-67 proliferation index, TP53 aberration, complex karyotype, and disease progression within 24 months of initial treatment (POD24). Treatment for relapsed or refractory (R/R) MCL is still a tough issue and prognosis for R/R MCL post-Bruton's tyrosine kinase inhibitor (BTKi) failure remains unfavorable. Brexucabtagene autoleucel (brexu-cel), an autologous anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy, stands as the first cellular therapy US Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved for R/R MCL, demonstrating high efficacy and long progression-free survival (PFS) in this setting [1]. However, CAR-T cell therapy spreading, imposed the challenge of new toxicities management, such as acute cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), but also longer-term B-cell aplasia, hypogammaglobulinemia, and infections.

CRS is an inflammatory state, onsets with constitutional symptoms, including fever, fatigue, myalgia, and arthralgia. However, it can swiftly escalate to more severe manifestations such as hypotension, tachycardia, tachypnea, and hypoxia, as well as complications such as arrhythmia, capillary leak, coagulopathy, respiratory failure, shock, and multiorgan dysfunction. The CRS management requires interleukin (IL)-6 receptor-blocking antibody tocilizumab and corticosteroids, such as methylprednisolone or dexamethasone, aimed to reduce the cytokine storm.

ICANS can occur at the same time of CRS, after its resolution, or independently. ICANS commonly manifests with impairments in attention and confusion. Early signs included expressive aphasia and alterations in handwriting or attention. However, sometimes it can rapidly evolve to coma, seizures, motor weakness, and cerebral edema. In contrast to CRS, our understanding of the pathophysiology underlying ICANS remains incomplete.

The treatment strategy is tiered based on the severity of ICANS, as graded by established criteria. Management is based on supportive care and close monitoring for mild grade, while on high dose steroids and eventually on anti-interleukin-1 receptor (IL-1R) anakinra, as ICANS progresses to more severe grade.

For patients presenting with high-grade ICANS, admission to the intensive care unit (ICU) becomes necessary [2, 3].

Here we describe a difficult immune effector cell-associated hematotoxicity (ICAHT) case followed by an intestinal perforation episode. The patient suffered from CRS and ICANS and was treated with tocilizumab, corticosteroids and anakinra.

## Case presentation

We present the case of a white Caucasian 59-year-old male patient affected by mantle cell lymphoma. His past medical history was unremarkable, except for hypertension under treatment and diverticulitis, occasionally requiring cycles of antibiotic treatments. He had no major interventions in the past. From the beginning of 2021, he experienced discontinuous diarrhea and significant weight loss. He performed blood exams that revealed mild lymphocytosis and anemia and an abdomen ultrasound scan that was negative, except of mild splenomegaly (17 cm). In April 2021, he performed an exploratory colonoscopy and was diagnosed with cyclin D1 + mantle cell lymphoma by ileoterminal biopsy. He received six cycles of alternated rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and rituximab, cisplatin, cytarabine and dexamethasone (R-DHAP) regimens. After achieving a complete remission, he received an autologous stem cell transplantation (ASCT) in November 2021 after conditioning with the standard regimen of BCNU, etoposide, cytarabine, and melphalan (BEAM). In June 2022, he experienced an early relapse and he initiated ibrutinib, at the standard dose of 560 mg/day, as a second line

treatment. No response was obtained after 6 months of continuous ibrutinib treatment at full dose and therefore he was considered eligible for a third line therapy with brexucabtagene autoleucel according to FDA/EMA/Italian Medicines Agency (AIFA) indications. Ibrutinib was not interrupted during apheresis and CAR-T manufacturing. Standard lymphodepletion was performed with fludarabine 30 mg/m$^2$ and cyclophosphamide 500 mg/sqm for 3 days (days −5, −4, −3) and on the fifth day (day 0) CAR-T were infused (brexu-cel total dose of 154 million of CAR-T lively cells). Two days after CAR-T infusion, he became febrile. Empiric antibiotic therapy with maxipime (2 g three times a day) was initiated concurrently with an extensive diagnostic work-up for infections, according to CAR-T toxicity general management procedures. A cytokine release syndrome grade 1 (CRS1) was diagnosed, according to the Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 of the National Cancer Institute. On day 3, CRS progressed to grade 2, and three doses of tocilizumab 8 mg/kg were given in 24 hours. On day +5, fever was still present and upper limb tremor appeared. Intravenous dexamethasone was initiated at 10 mg every 6 hours and, even if extensive infective diagnostic exams were all negative, antibiotic switch to piperacillin/tazobactam (4.5 g four times a day) was done.

Fever quickly resolved after starting dexamethasone, but ICANS symptoms characterized by handwriting alterations appeared on day 7. The electroencephalogram (EEG) showed evidence of bilateral frontal fundus rhythm slowing, while magnetic resonance imaging (MRI) scan was negative. On day 8, the immune effector cell encephalopathy score (ICE) decreased from 9 to 7 with further deterioration of handwriting, attention capacity, and spatial–temporal orientation. The patient was transferred to the intensive care unit (ICU) and treated with higher doses of dexamethasone 20 mg and anakinra 100 mg every 6 hour with rapid improvement of ICANS. On day 10, the patient was readmitted to the hematology ward given the clinical improvement. Tapering of dexamethasone and anakinra was initiated in hematology ward, and drugs were stopped on day 13. Two days after drug suspension, the patient experienced a novel ICANS episode requiring the quick reintroduction of dexamethasone at a lower dose (10 mg every 6 hours). EEG and brain MRI were repeated and were both unremarkable. Two subsequent attempts to stop dexamethasone on day 22 and 31 were unsuccessful for the recurrence of ICANS. MRI was repeated on day + 23, at second ICANS relapse, but it was not repeated at the last recurrence on day + 33. In all cases the exams were negative for radiological signs of encephalopathy or cerebral edema. No lumbar puncture was performed.

On day 34, the patient complained about acute abdominal pain and he referred to the site where the disease had relapsed. Imaging revealed an acute diverticulitis complicated by perforation and perivisceral collection (Fig. 1). Despite the very low blood cell counts [white blood cell (WBC) count $1.45 \times 10^9$/L, neutrophil granulocyte cell (NGC) $1.19 \times 10^9$/L, platelets $4.3 \times 10^{10}$/L, hemoglobin

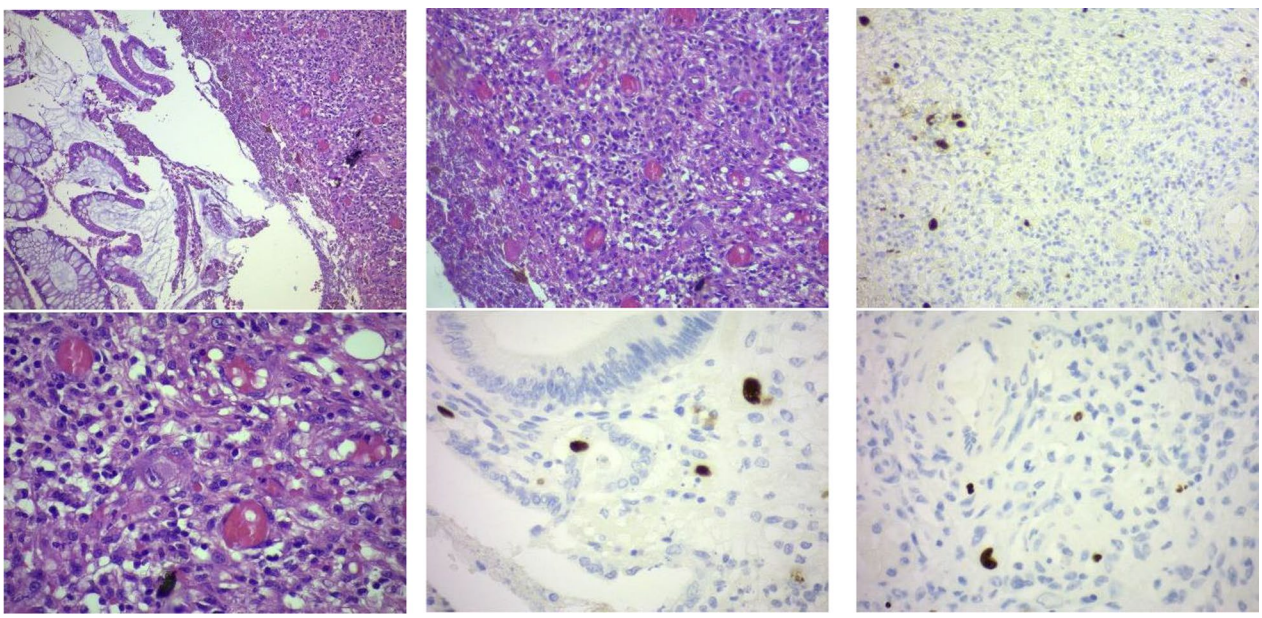

**Fig. 1** Histopathological slide from surgery material: diverticulosis with focal acute diverticolitis with suppurative inflammation and adiponecrosis

7.6 g/dL] and immune suppression status, the patient had to undergo urgent exploratory laparotomy and colic resection with colostomy packing, lavage, and drainage of the cavity. The morphologic and immunohistochemistry analyses ruled out the presence of lymphoma B cells and infiltrating CAR-T, whereas a significant neutrophil infiltration associated with cytomegalovirus (CMV) inclusion was noted. CMV viral load was monitored weekly from the day of brexu-cel infusion. Concurrently to diverticultis, CMV reactivation was documented in the peripheral blood (on day + 32: CMV DNA 1950 copies, on day + 39 CMV DNA 28,160 copies). Anti-CMV treatment with valganciclovir was promptly initiated from day + 39, because of rising DNA copies in peripheral blood, and then continued because CMV inclusions were encountered in the biopsy, with some concern about the hematological tolerance given the incomplete hematological recovery and the lower neutrophil counts. However, the patient was treated valganciclovir for 20 days with occasional neutrophil support with granulocyte colony-stimulating factor (G-CSF). Intravenous immunoglobulin supplementation was done on day + 39 according to CAR-T management indications and to minimize the infection risk.

The positron emission tomography (PET) scan on day + 30 showed complete remission of lymphoma, with a significant reduction of the previous specimen in the right distal external iliac, and complete regression of the findings in the left oropharyngeal and laterocervical sites, which were of a nonspecific locoregional reactive nature, consistent with the resolving power of the method. No other significant pathological elements were identified in the body districts examined.

The patient was discharged on day + 40 with the indication to maintain oral prednisone for 2 more weeks. Prednisone was safely interrupted on day 56 without any ICANS recurrence. Anti-CMV therapy was suspended on day + 59. Full hematological recovery was documented.

Actually, the patient is in complete remission of lymphoma at month 9 PET and computed tomography (CT) scan evaluation, and he underwent surgery for colon anastomosis confection with success.

A summary timeline of the clinical case is depicted below (Fig. 2).

## Discussion and conclusions

CAR-T therapy completely changed the treatment landscape of refractory/relapsed B-cell malignancies. However, this innovative cellular therapy also imposed a distinct toxicity profile. Various challenges arise in treating patients with CAR-T, thus the implementation of optimal strategies to mitigate potential complications is

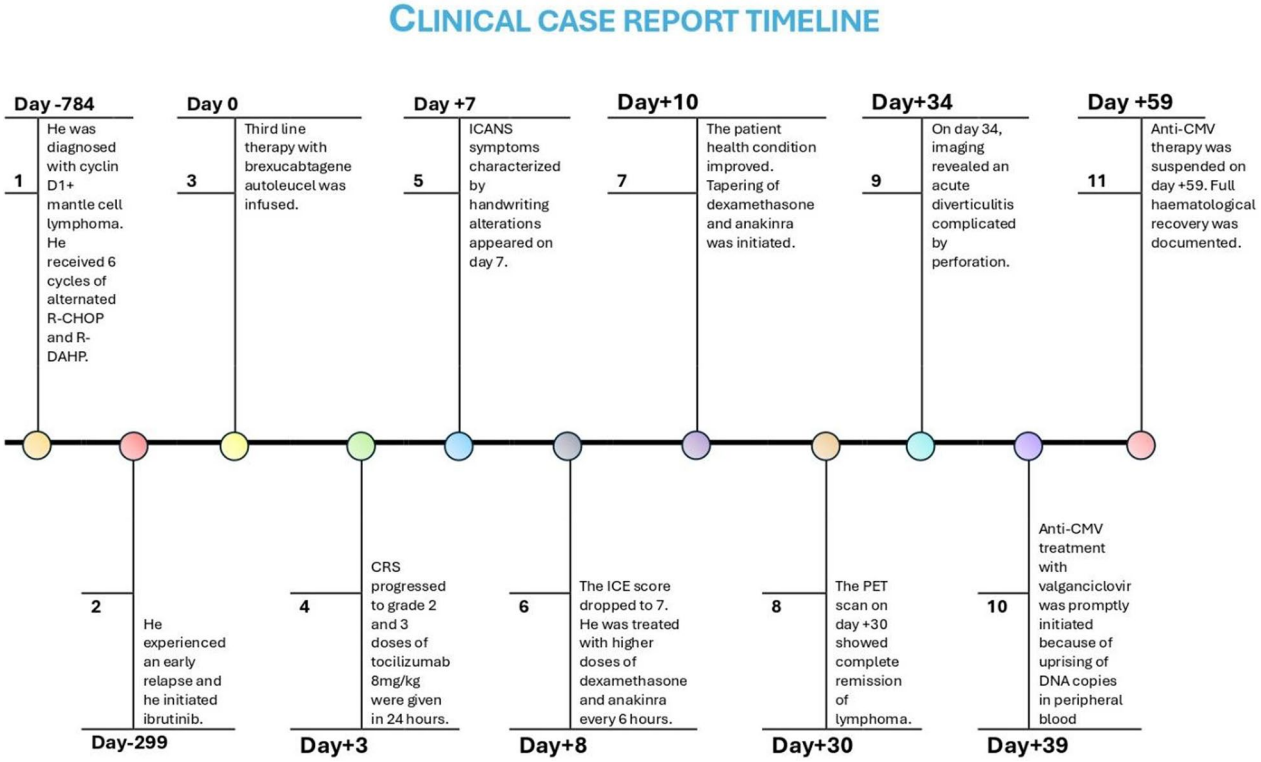


**Fig. 2** Clinical case report timeline

needed. Among the prominent side-effects associated with CAR-T therapy, there are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenia and secondary hypogammaglobulinemia, and B-cell aplasia, with higher risk of infections.

Among them, ICANS is one of the most common toxicities in axicabtageneciloleucel [4] or brexucabtagene autoleucel [4] treated patients, even more than in the tisagenlecleucel [5] treated ones, as the results from the US lymphoma CAR-T consortium and the pivotal CAR-T therapy trials demonstrated [4, 6, 7] (Table 1).

This characteristic has been linked, in part, to the CD28 co-stimulatory domain, compared with 4-1BB. In addition, ICANS may be more severe when targeting CD19, potentially because of the on-target, off-tumor targeting of CD19 on brain mural cells. Even when the target and co-stimulatory domain are identical, kinetics of toxicity may differ between products, which, in turn, affect clinical management [8, 9].

The median onset time of ICANS in axicabtageneciloleucel and brexucabtagene autoleucel-treated patients was 6 and 8 days, respectively, and the median duration was nearly the same.

However, 8% of 154 patients in the brexucabtagene autoleucel population reported ongoing cognitive deficits of varying degrees 90 days after CAR-T administration. In our patient, the highest ICANS grade was reached on the same day of the maximum lymphocyte count, postinfusion (Fig. 3).

ICANS lasted more than 25 days, more than three times of the median duration, but the combined treatment of dexamethasone plus anakinra was very

**Table 1** Rates of immune effector cell-associated neurotoxicity syndrome (ICANS) in pivotal CAR-T therapy

| Drug | Disease | Trial | Any grade neurotoxicity (%) | Grade ≥ 3 neurotoxicity (%) |
|---|---|---|---|---|
| Axicabtageneciloleucel [6, 10] | DLBCL | ZUMA-I | 64 | 28 |
| | FL | ZUMA-5 | 77 | 11 |
| Brexucabtagene autoleucel [1] | MCL | ZUMA-2 | 63 | 31 |
| Tisagenlecleucel [7] | DLBCL | JULIET | 21 | 12 |
| | B-ALL | ELIANA | 40 | 13 |

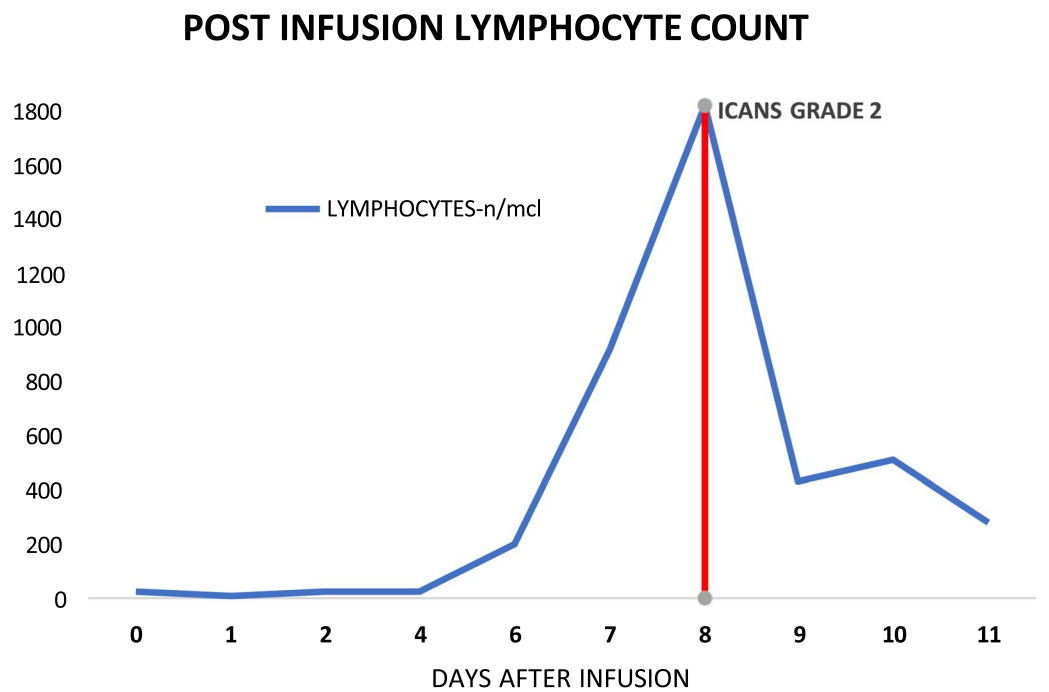


**Fig. 3** Postinfusion lymphocytes count chart. The highest ICANS grade was manifested on the 8th day post infusion at the peak of lymphocytes count

effective, even if at the end a long-term low dose of maintenance steroid was needed to avoid recurrences.

Anakinra, an IL-1R antagonist, has shown an emerging role in refractory CRS/ICANS. Anakinra was administered to treat CRS and/or ICANS in the brexucabtagene autoleucel real-word experience in 17% of patients. The rational of this application has been shown in a humanized mouse model [11] and then confirmed in many clinical reports. The benefit of anakinra administration was also recorded in a single-center experience [12], in which corticosteroid refractory CAR-T-treated patients affected by ICANS were also administered anakinra 100 mg subcutaneously every 6 hours until regression to grade 1. In our case, the patient was already administering the dexamethasone for CRS and we combined anakinra due to the end writing worsening. Other evidence to support the anakinra administration are reported by The University of Texas MD Anderson Cancer Center [3]. The colleagues introduced the dexamethasone median cumulative dose equal to 273 mg (range, 0–1480) before the IL-inhibitor in six patients that received anakinra. Four of the six patients who received anakinra for the management of high-grade ICANS experienced clinical benefit. However, they administered anakinra 100 mg daily for 7 days, and the dose we administered was three times higher than the one they used. Our patient administered 90 mg of dexamethasone before starting anakinra 100 mg and dexamethasone 20 mg, both administered every 6 hours until regression to grade 1, followed by a 6-day steroid tapering. In both the retrospective trials, anakinra was suggested as a corticosteroid sparing therapy, but systematic evaluation is lacking. A phase 2 clinical trial has started recruiting to collect strong evidence of its use in this setting [13]. In this trial, anakinra was started at any grade ICANS or grade $\geq 2$ CRS. The early results based on seven patients demonstrated potential to reduce severe ICANS CAR-T products associated and to reduce corticosteroid use. A corticosteroid-sparing therapy could be helpful to contain secondary side effects, such as the risk of infections. In our patient's case, we did not use anakinra because the patient's recurrent symptoms always responded well to low-dose corticosteroids and because the evidence for the efficacy of anakinra in treating ICANS was less standardized at the time.

However, interleukin inhibitors also seem to have potential side effects. A potential correlation between tocilizumab and adverse gastrointestinal (GI) events, such as ulcer and intestinal perforation among patients with rheumatoid arthritis, has been assumed and observed in clinical trial and post marketing analysis [14]. Intestinal perforation in CAR-T-treated patients are cited in the European Society for Blood and Marrow Transplantation (EBMT) and European Society for Medical Oncology (ESMO) ICAHT management guidelines [15, 16]. Real-word data and post-marketing surveillance reported an increased risk of gastrointestinal perforation in axicabtageneciloleucel-treated patients [17].

To our knowledge, no brexucabtagene autoleucel-related intestinal perforation have been previously reported, and this was the first signal regarding this type of reaction in the Italian pharmacovigilance authority. However, the setting of patients is similar: they are treated with lymphodepletive chemotherapy and receive a strong amount of IL-6 receptor inhibitor and corticosteroids. In our case, the patient used to suffer from diverticulitis, as independent risk factor, and the intestinal segment analyzed after laparotomy did not show mantle cell residual or massive CAR-T lymphocyte infiltration, so a correlation with direct anti-CD19 treatment action should be excluded. In our patient, the adverse event can probably have multifactorial risks: first of all, his prior diverticulitis, the immunosuppressive drugs administered, the large use of corticosteroids and tocilizumab, and the CMV reactivation with intestinal involvement.

This clinical case is intended to describe a real-life experience of managing ICAHT post CAR-T and to validate the use of anakinra in patients with ICANS. The patient benefited from the use of anakinra, and this case report joins the evidence in the literature supporting the use of this drug to treat CRS and ICANS. Systematic evidence must be produced to support the inclusion of this drug in therapy for corticosteroid sparing as well. It also describes a singular case of intestinal perforation in a patient treated with brexucabtagene autoleucel.

It was an acute complication of CAR-T treatment, developed by multifactorial risks: patients' prior diverticulitis, immunosuppressive drugs such as lymphodepletion, steroids and tocilizumab, and CMV reactivation, but also maybe prior bowel lymphoma localization, showing high complexity of these patients and imposing a multidisciplinary management.

Further studies must be conducted in order to reduce the impact of ICAHT in patients receiving CAR-T therapy. Another application could be the preventive use of the drugs, but evidence is still lacking.

**Abbreviations**

| | |
|---|---|
| ASCT | Autologous stem cell transplantation |
| BEAM | Bendamustine, etoposide, cytarabine, melphalan regimen |
| Brexu- cel | Brexucabtagene autoleucel |
| BTKi | Bruton's tyrosine kinase inhibitors |
| CAR-T | Chimeric antigen receptor T-cell |
| CMV | Cytomegalovirus |
| CRS1 | Cytokine release syndrome grade 1 |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse event |
| DLBCL | Diffused large B-cell lymphoma |
| EBMT | European Society for Blood and Marrow Transplantation |
| EEG | Electroencephalogram |
| EMA | European Medicines Agency |

| | |
|---|---|
| ESMO | European Society for Medical Oncology |
| FDA | US Food and Drug Administration |
| FL | Follicular lymphoma |
| ICAHT | Immune effector cell-associated hematotoxicity |
| ICANS | Immune effector cell-associated neurotoxicity syndrome |
| ICE | Immune effector cell encephalopathy score |
| ICU | Intensive care unit |
| MCL | Mantle cell lymphoma |
| MIPI | MCL international prognostic index |
| NGC | Neutrophil granulocyte cell |
| PET | Positron emission tomography |
| POD24 | Disease progression within 24 months of initial treatment |
| R/R | Relapsed or refractory |
| R-CHOP | Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone |
| R-DAHP | Rituximab, cisplatin, cytarabine, and dexamethasone |
| WBC | White cell count |

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**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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