AUCTORES
Globalize your Research

International Journal of Clinical Case Reports and Reviews
Sven Neubert *

Open Access

Case Report

Successful Treatment of a Relapsed, Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) Patient and Newly Diagnosed Meningeosis Lymphomatosa with CD19 CAR-T Cell Therapy and Intrathecal Chemotherapy: A Case Report

Sven Neubert *, Hermann Einsele, Max S. Topp, Johannes Duell

Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany.

***Corresponding Author:** Sven Neubert, Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany.

Received Date: November 03, 2024 | **Accepted Date:** November 20, 2024 | **Published Date:** November 27, 2024

Citation: Sven Neubert, Hermann Einsele, Max S. Topp, Johannes Duell. (2024), Successful Treatment of a Relapsed, Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) Patient and Newly Diagnosed Meningeosis Lymphomatosa with CD19 CAR-T Cell Therapy and Intrathecal Chemotherapy: A Case Report, *International Journal of Clinical Case Reports and Reviews*, 20(2); **DOI:10.31579/2690-4861/598**

Abstract:

CD19 chimeric antigen receptor-modified (CAR)-T cell therapy can achieve similar response rates in Secondary central nervous system lymphoma (SCNSL) as in patients without central nervous system (CNS) involvement. However, the therapeutic success differs significantly when a distinction is made between parenchymal and meningeal involvement.

A 42-year-old female patient with r/r DLBCL was treated with CD19 CAR-T cell therapy. The patient was diagnosed with meningeosis lymphomatosa six days after the administration of the CAR-T cells. The lumbar puncture was performed because of severe therapy refractory headaches. We additionally administered intrathecal chemotherapy after reaching a Partial Remission (PR) with CAR T cells with Methotrexate, Cytarabine and Dexamethasone. At the time of the report the patient has been in Complete Remission (CR) in the CNS and regarding the peripheral DLBCL manifestations for two months.

To the authors' knowledge, this patient's case is the first case in which intrathecal chemotherapy was used in addition to CAR-T cells to treat clinically progressive meningeosis first diagnosed under CAR-T cell therapy. The follow-up progress so far appears promising, but the long-term course remains to be seen.

Key words: chimeric antigen receptor-modified T cell; diffuse large B-cell lymphoma; meningeosis lymphomatosa; intrathecal chemotherapy; secondary central nervous system lymphoma

Introduction

CD19 targeted CAR-T cell therapy is a very effective method to treat refractory or relapsed DLBCL with patients achieving nearly 50% complete response rates with that kind of therapy [1-2]. It has also already been shown that CAR-T cell therapy achieves similarly good response rates regarding parenchymal SCNSL and that the side effects are also comparable [3]. In case of meningeal involvement, the mean progression-free survival (PFS) after CD19 CAR-T cell therapy is significantly shorter [3]. Two of the most common side effects of CAR T-cell therapy are cytokine release syndrome (CRS) [4-5] and immune effector cell associated neurotoxicity (ICANS) [6-7]. So far, there is no evidence of an increased occurrence of either of those in patients with CNS involvement [3,8] Along with phenomenon of CRS, there is endothelial activation and increased permeability of the blood-brain barrier [9].

Meningeosis lymphomatosa as a secondary CNS manifestation in relapsed DLBCL is generally associated with a very poor prognosis [10]. There is a lack of clear standards of care due to low enrollment on clinical trials and historically limited options in terms of effective and well-tolerated therapies [11]. The prophylactic administration of CNS penetrating substances or prophylactic use of intrathecal chemotherapy has not yet brought any resounding success [11].

Here we report a 42-year-old female with r/r DLBCL who was diagnosed with meningeosis lymphomatosa for the first time six days after receiving CD19 CAR-T cell therapy with Axicabtagen Ciloleucel. With the accumulation of clinical data and increasing reports, we can create

possible therapy optimizations and prognosis-improving therapy concepts.

Case Presentation

A 42-year-old female was diagnosed with stage IVb follicular lymphoma in March 2023. the initial diagnosis and treatment took place externally. Initial manifestation included diffuse lymph node manifestations, diffuse skeletal infiltrations including the spine with intraspinal infiltration. With a Follicular Lymphoma International Prognostic Index of 3 the patient suffered from a high-risk disease. The patient was treated with percutaneous radiotherapy of a paravertebral lesions up to 28gy and systemically with 6 cycles of O-CHOP (Obinutuzumab, Cyclophosphamide, Vincristine, Doxorubicin, Prednisone) [12] until August 2023. With CR in computer tomography, maintenance therapy with Obinutuzumab was initiated. In November 2023 the patient developed obstructive jaundice and massive swelling in her left leg. Histologically, there was transformation of the FL into a germinal center B-cell-like DLBCL in both the bile duct and the left iliacus muscle. The patient was referred to our center, then received one cycle of R-GDP (Rituximab, Gemcitabine, Dexamethasone, Csiplatin) [13] as first line DLBCL treatment and was refractory to this therapy. The patient then was eligible for in lable CD19 CAR-T cell therapy with Axicabtagen Ciloleucel [14]. After Leukapharesis in December 2023 the patient received a bridging therapy with one cycle of R-Pola (Rituximab, Polatuzumab) [15]. In January 2024, the planned lymph-depleting chemotherapy had to be postponed due to a port infection.

At the end of January, the patient presented with recurrent fever episodes. With bland environmental diagnostics and calculated antibiotic therapy with piperacillin/tazobactam [16], the patient appeared fever free and clinically and laboratory analysis showed no evidence of an infection after one week. We then proceeded to start the lymph-depleting chemotherapy with fludarabine (30 mg/m^2) and cyclophosphamide (500 mg/m^2) for 3 days (day −5 to −3) [17]. Subsequently, an amount of 2×106 CD19 CAR-T-cells per kilogram was infused on day (d) 0 (February 1st 2024). In the subsequent phase, the patient developed fever from d1 onwards as part of CRS°I. Because the fever persisted for more than 72 hours with symptomatic therapy and anti-infective therapy, we administered tocilizumab (8mg/kg) and dexamethasone (10mg) a total of three times [18].

On day 6 after the CAR-T-cell-infusion the patient developed severe, treatment-resistant headaches and meningism. The cranial Magnetic resonance imaging (MRI) revealed no groundbreaking findings apart from an empty sella. We performed a diagnostic lumbar puncture on the same day and began calculated meningitis therapy, which was stopped after receiving negative virology and microbiology results. The lumbar puncture revealed infiltration of the cerebrospinal fluid (CSF) by the known DLBCL in the sense of meningeosis lymphomatosa (CD19+, CD38+, CD10+, CD79a+, CD5-) [19]. Detailed lab results are shown in **Table 1**, **Figure 1** and **Table 2**.

	d6	d7	d9	d11	d18	d26	w8	w12
Leu (n/mm^3)	215	174	168	28	1	5	2	2
B-cells %	99	20	1	0	not specified	not available due to low cell counts	not specified	0
T-cells %	1	80	99	40%	48.5 (48.2% CAR-T cells within T cells)	Not available due to low cell counts	96 (2% CAR-T cells within T cells	100 (25% CAR-T cells within T cells)
Pressure (cmH2O)	not done	40	48	12	8	8	22	18

Table 1: CSF laboratory values; Leu, leucocytes; n, number; %, percentage of total lymphocytes in FACS, d, days after CAR-T cell administration; w, weeks after CAR-T cell administration.

s	d7	d14	d19	d26	w8	w12
Leu (n/µl)	400	3800	1200	1700	3700	2100
Lym (n/µl)	not done	160	140	950	670	290
T-cells %	89	65	49	42	63	58
CAR-T cells within T-cells %	20	50	40	25	0,4	0,6

Table 2: Peripheral blood laboratory values; Leu, leucocytes; n, number; Lym, lymphocites; T-cells %, percentage of total lymphocytes in FACS; d, days after CAR-T cell administration; w, weeks after CAR-T cell administration

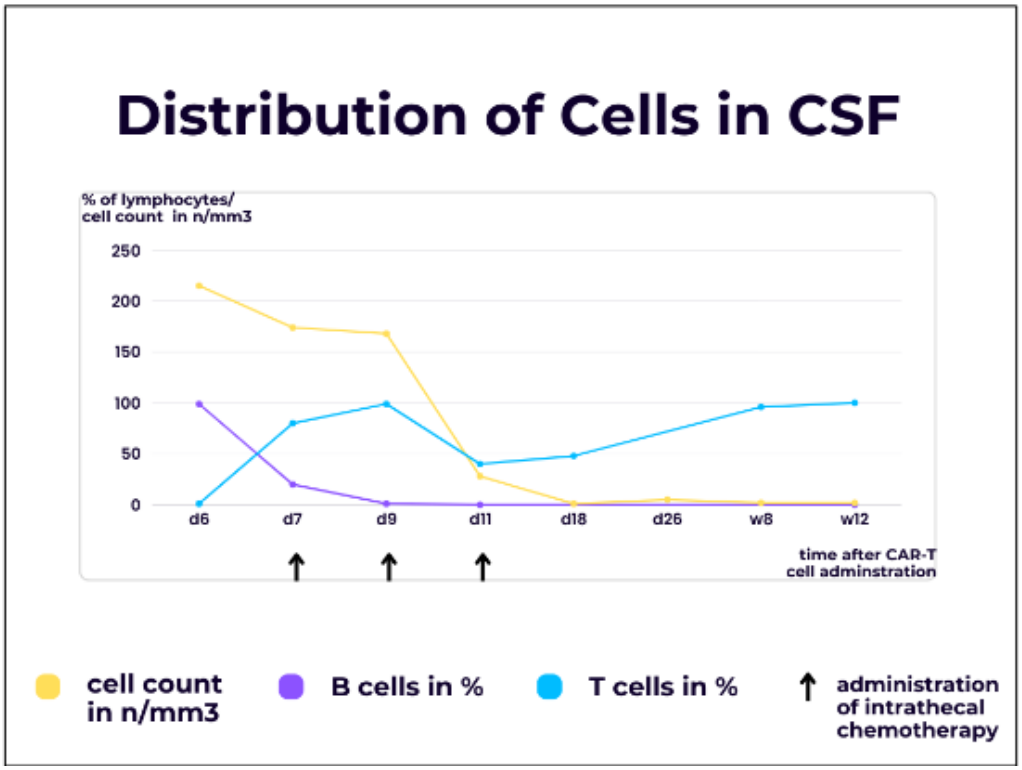

Figure 1: Graphical representation of the CSF cell distributions after CAR-T cell therapy; cell count only referring to Leucocytes, CSF, cerebrospinal fluid; d, day; w, week; n/mm3, Leucocytes per cubic millimeter

The patient had never received a lumbar puncture before and had never suffered from neurological symptoms before. The next day, samples were taken again and, due to newly diagnosed symptomatic meningeosis lymphomatosa, intrathecal triple therapy consisting of methotrexate 15mg, cytarabine 40mg and dexamethasone 4mg was initiated [20]. In addition, due to the increased CSF pressure of 40cmH2O, we drained 40ml of CSF. The patient's headache quickly improved. In the following days, a lumbar puncture with administration of intrathecal triple therapy and pressure measurement was performed every other day. In total, the patient received intrathecal therapy three times (d7, d9, d11). After the second administration, there was a decrease in the number of cells and, as a result, a normal CSF opening pressure.

Between the first and second lumbar puncture, i.e. before the administration of intrathecal therapy, a cell shift took place in the CSF. While on the first day (d6) there was a predominance of malignant B cells due to the lymphoma (99% B cells, 1% T cells), the next day the results showed a predominance of T cells (20% B cells, 80 % T cells) showing a PR through CAR-T cell therapy alone. On d9 fluorescence-activated cell sorting (FACS) showed 1% B cells and 99% T cells. On d11 there was no longer any evidence of persistent lymphoma cells but 40% T cells. The cell shift occurred parallel to the maximum Interleukin-6-level in the peripheral blood and was accompanied by a significant increase in the protein concentration in the CSF as a sign of blood-brain-barrier disruption caused by persisting CRS °I. On d18 we performed another lumbar puncture that showed a normal cell count with 36% of the T-cells being CAR-T cells.
With known CNS infiltration by DLBCL we added a spinal MRI, which showed no evidence of active infiltration by lymphoma.

From d10, the patient received filgrastim [21] for 6 days to stimulate neutrophil granulocytes. There was an adequate increase. Neurotoxicity did not occur throughout treatment. The patient was released in stable general condition on d18 after CAR-T-cell therapy.

At 4 weeks after CAR-T cell therapy a positron emission tomography-computed tomography scan (PET-CT) showed Complete Metabolic Remission of the peripheral DLBCL sites. At week 8 the patient received a CT that found no evidence of recurrence of the lymphoma. The liquor in week 4, 8 and 12 showed normal cell count with a predominance of T cells, persistence of CAR-T cells and no malign cells. At the time of this article, the patient has been in CR for eight months in CNS and peripherally. The patient is in good general condition, apart from recurrent lymphedema in the left leg without persistent clinical symptoms. Laboratory analysis shows mild leukopenia and asymptomatic anemia.

Discussion

In this work, we presented the case of a patient who developed refractory headaches during CAR-T cell therapy, which led to the diagnosis of meningeosis lymphomatosa due to DLBCL. A lumbar puncture had not been performed in advance as the diagnosis was established externally. With a CNS International Prognostic Index for Diffuse Large B-cell Lymphoma (IPI) of 3, the patient was at intermediate risk of CNS recurrence due to the lymphoma [22].

A previously known CNS infiltration by r/r DLBCL would not have changed the therapeutic strategy, as Real-World Results of CAR T-cell therapy have also shown good effectiveness in SCNSL in previous studies with complete response rates of 33% and partial response rates of 33% [23]. A Review compared the results for PCNSL and SCNSL. Similar response rates were found with 37% of the patients in each group maintaining a CR after 6 months [3] However, the type of manifestation significantly affected the PFS with meningeosis patients reaching a median PFS of only 1.1 months in recent real-world data [23]. A single-

center retrospective analysis reported a median PFS of 83 days and a median OS of 129 days in a similar patient collective [24].

To the author`s knowledge there seem to be no reported cases with clinically progressive meningeosis lymphomatosa during CAR-T cell therapy. Since the patient was severely symptomatic, we decided to carry out cytoreductive intrathecal chemotherapy in addition to CAR-T cell therapy. There are a few case reports describing the use of intrathecal chemotherapy for neurotoxicity. There is no evidence of a compromise in the effect of CAR-T cells in these individual case reports [25]. At the time the case report was written, the patient had been in Complete Remission for two months with CAR-T cells still detectable in the CSF, already surpassing the median PFS mentioned in the trial [23].

The case of this patient also illustrates the important role of CRS causing a disruption of the blood-brain barrier, which allows CAR-T cells to flood in the cerebrospinal fluid. This mechanism is a possible explanation for the effectiveness of CAR-T cells in the central nervous system [6]. Nevertheless, CNS involvement is not usually associated with increased neurotoxicity with CAR-T cell therapy [3].

Overall, the data available for the case described is very limited. It remains to be seen how long-term the therapeutic success will be. In principle, the addition of intrathecal therapy in this patient population could represent a possible approach to improving long-term survival. However, well-designed studies are necessary to assess this. A potential negative effect of the intrathecal chemotherapy on the effectiveness of the CAR-T cell therapy cannot be completely ruled out either.

Abbreviations

R/R DLBCL; Relapsed, Refractory Diffuse Large B-Cell Lymphoma; CAR, chimeric antigen receptor-modified; SCNSL, Secondary central nervous system lymphoma; CNS, central nervous system; PR, Partial Remission; CR, Complete Remission; PFS, progression-free survival; CRS, cytokine-release syndrome; ICANS, immune effector cell associated neurotoxicity; d, day; MRI, Magnetic resonance imaging; CSF, cerebrospinal fluid; FACS, fluorescence-activated cell sorting; PET-CT, positron emission tomography-computed tomography scan; IPI, International Prognostic Index for Diffuse Large B-cell Lymphoma

Acknowledgements

Conceptualization: SN, JD, MT. Data curation: SN, JD. Formal analysis: SN. Resources: JD, MT. Supervision: JD, MT. Validation: JD, MT. Writing – original draft: SN. Writing – review & editing: JD, MT, HE. All authors contributed to the article and approved the submitted version.

Ethics Statement

The patient was informed about the intention to scientifically process and publish her case and gave her written consent.

Author Contributions

Conceptualization: SN, JD, MT. Data curation: SN, JD. Formal analysis: SN. Resources: JD, MT. Supervision: JD, MT. Validation: JD, MT. Writing – original draft: SN. Writing – review & editing: JD, MT, HE. All authors contributed to the article and approved the submitted version.

Funding

Not applicable, as no funding was used.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

References

1. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, et al. (2017) Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*.;377(26):2531-44.
2. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, et al. (2019) Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*.;380(1):45-56.
3. Cook MR, Dorris CS, Makambi KH, Luo Y, Munshi PN, et al. (2023) Toxicity and efficacy of CAR T-cell therapy in primary and secondary CNS lymphoma: a meta-analysis of 128 patients. *Blood Adv.;*7(1):32-39.
4. Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, et al. (2018) CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med*.;24(6):731-738.
5. Norelli M, Camisa B, Barbiera G, Falcone L, Purevdorj A, et al. (2018) Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med*.;24(6):739-748.
6. Xiao X, Huang S, Chen S, Wang Y, Sun Q, et al. (2021) Mechanisms of cytokine release syndrome and neurotoxicity of CAR T-cell therapy and associated prevention and management strategies. *J Exp Clin Cancer Res*.;40(1):367.
7. Hirayama AV, Turtle CJ. (2019) Toxicities of CD19 CAR-T cell immunotherapy. *Am J Hematol*.;94(S1):S42-S49.
8. Frigault MJ, Dietrich J, Gallagher K, Roschewski M, Jordan JT, et al. (2022) Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial. *Blood*.;139(15):2306-2315.
9. Gust J, Hay KA, Hanafi LA, Li D, Myerson D, et al. (2017) Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. *Cancer Discov.*;7(12):1404-1419.
10. Tomita N, Kodama F, Kanamori H, Motomura S, Ishigatsubo Y. (2006) Secondary central nervous system lymphoma. *Int J Hematol*.;84(2):128-135.
11. Orellana-Noia V, Abousaud A. (2022) Secondary Central Nervous System Lymphoma: Updates in Treatment and Prophylaxis Strategies. *Curr Treat Options Oncol*.;23(10):1443-1456.
12. Kahl B. (2021) High-risk follicular lymphoma: Treatment options. *Hematol Oncol*.;39 Suppl 1:94-99.
13. Hou Y, Wang HQ, Ba Y. (2012) Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma. *Med Oncol*.;29(4):2409-2416.

14. Papadouli I, Mueller-Berghaus J, Beuneu C, Ali S, Hofner B, et al. (2020) EMA Review of Axicabtagene Ciloleucel (Yescarta) for the Treatment of Diffuse Large B-Cell Lymphoma. *Oncologist*.;25(10):894-902.
15. Argnani L, Broccoli A, Pellegrini C, Fabbri A, Puccini B, et al. (2022) Real-world Outcomes of Relapsed/Refractory Diffuse Large B-cell Lymphoma Treated With Polatuzumab Vedotin-based Therapy. *Hemasphere*.;6(12):e798.
16. Zimmer AJ, Freifeld AG. (2019) Optimal Management of Neutropenic Fever in Patients With Cancer. *J Oncol Pract*.;15(1):19-24.
17. Fabrizio VA, Boelens JJ, Mauguen A, Baggott C, Prabhu S, et al. (2022) Optimal fludarabine lymphodepletion is associated with improved outcomes after CAR T-cell therapy. *Blood Adv*.;6(7):1961-1968.
18. Si S, Teachey DT. (2020) Spotlight on Tocilizumab in the Treatment of CAR-T-Cell-Induced Cytokine Release Syndrome: Clinical Evidence to Date. *Ther Clin Risk Manag*.;16:705-714.
19. Baraniskin A, Schroers R. (2014) Modern cerebrospinal fluid analyses for the diagnosis of diffuse large B-cell lymphoma of the CNS. *CNS Oncol*.;3(1):77-85.
20. Olmos-Jimenez R, Espuny-Miro A, Carceles Rodriguez C, Diaz-Carrasco MS. (2017)Practical aspects of the use of intrathecal chemotherapy. *Farm Hosp*.;41(n01):105-129.
21. Dale DC, Crawford J, Klippel Z, Reiner M, Osslund T, et al. (2018) A systematic literature review of the efficacy, effectiveness, and safety of filgrastim. *Support Care Cancer*. 2018;26(1):7-20.
22. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, et al. (2016) CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *J Clin Oncol*.;34(26):3150-3156.
23. Ayuk F, Gagelmann N, von Tresckow B, Wulf G, Rejeski K, et al. (2023) Real-world results of CAR T-cell therapy for large B-cell lymphoma with CNS involvement: a GLA/DRST study. *Blood Adv*.;7(18):5316-5319.
24. Ahmed G, Hamadani M, Shah NN. (2021) CAR T-cell therapy for secondary CNS DLBCL. *Blood Adv*.;5(24):5626-5630.
25. Shah NN, Johnson BD, Fenske TS, Raj RV, Hari P. (2020) Intrathecal chemotherapy for management of steroid-refractory CAR T-cell-associated neurotoxicity syndrome. *Blood Adv*.;4(10):2119-2122.

DOI:10.31579/2690-4861/598